Biochemistry and Biophysics Reports 40 (2024) 101850

Contents lists available at ScienceDirect

Biochemistry and Biophysics Reports

journal homepage: www.elsevier.com/locate/bbrep

Correlation of SNHG7 and BGL3 expression in patients with de novo acute myeloid leukemia; novel insights into lncRNA effect in PI3K signaling context in AML pathogenesis

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ARTICLE INFO

Keywords:
SNHG7
BGL3
AML
PI3K/Akt
PTEN

ABSTRACT

Background: Acute myeloid leukemia (AML) has been identified as a top priority for discovering a reliable biomarker for treatment improvement and patient outcome prediction due to the heterogeneous nature of AML and the obstacle to find an appropriate treatment strategy for this malignancy. Considering the involvement of long noncoding RNA (lncRNA) SNHG7 and BGL3 found in various cancers, the exact expression pattern of these lncRNAs and their clinical implications in acute myeloid leukemia (AML) continue to be elusive. In order to demonstrate a possible mechanism underlying AML pathogenesis, our goal was to examine BGL3 and SNHG7 lncRNA expressions in PI3K pathway.

Methods: This case-control cross-sectional study were conducted on RNA extracted from blood samples of 30 patients diagnosed with AML (Ayatollah-Khansari hospital, Arak, Iran) and 30 (age and gender matched) healthy controls. The expression levels of SNHG7 and BGL3 lncRNAs and their target genes Akt and PTEN, were measured using qRT-PCR. Subsequently, by means of statistical analysis, we determined the plausible correlation between the expressions of the aforementioned genes and lncRNA respectively.

Results: In AML samples, a considerable increase in the expression levels of SNHG7 lncRNA and Akr gene was accompanied by a marked reduction in the expression levels of BGL3 lncRNA and PTEN gene. Nevertheless, No significant relationship between the expression level of the indicated genes/lncRNAs and age and sex was found. The remarkable correlation between the expression of genes/lncRNAs and the blast percentage in patients was the notable point in the result of this study.

Conclusions: As the most straightforward interpretation of our results, we propose that perhaps the association between SNHG7 and BGL3 built through the interaction between Akt and PTEN may play a crucial role in the AML pathogenesis and any element of this axis could be a potential novel target for further profound treatment strategies. Nonetheless, in the context of Hematological Malignancies, particularly AML, more detailed studies are needed in this area to elucidate the precise role played by this interesting testis-specific pathway.

1. Introduction

AML is a disease of the bone marrow, a disorder of hematopoietic stem cells due to genetic variations in blood cell in which precursors lead to overproduction of neoplastic clonal myeloid stem cells [1]. While extramedullary manifestations can occur (e.g., myeloid sarcomas, leukemia cutis), the underlying disease is due to abnormalities in hematologic cellular production [2]. Causative factors, such as prior chemotherapy or some chemical exposures have been identified in a small subset of cases, but the vast majority are due to genetic changes, through chromosomal abnormalities or isolated gene mutations, without obvious causative agents [3]. While approximately fifty percent of affected individuals exhibit chromosomal abnormalities, the remaining half is classified as cytogenetically normal, harboring recurrent somatic mutations in several oncogenes [4]. The exploration of genetic alterations in AML has primarily concentrated on protein-coding

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https://doi.org/10.1016/j.bbrep.2024.101850
Received 6 September 2024; Received in revised form 7 October 2024; Accepted 15 October 2024

genes, aiming to give prognostic tools and elucidate the molecular intricacies inherent to AML [5]. In spite of these discoveries, the heterogeneity of AML has left numerous inquiries regarding the molecular mechanisms that govern development and progression these malignancies unanswered. Advances in high-throughput technologies suggest that up to 90 % of the human genome may be transcribed into noncoding RNAs (lncRNAs) [6]. Although small ncRNAs, including rRNAs, tRNAs, snoRNAs, and miRNAs, have been extensively characterized, profiling efforts have also underscored the significance of lncRNAs. A growing body of evidence suggests that lncRNAs are integral to various cellular events including proliferation, survival, differentiation by modulating different stages of gene expression [7]. The change of lncRNAs levels has been implicated in transformation of normal cells into malignancies and recognized as promising biomarkers across a spectrum of cancers [8]. LncRNAs are RNA molecules with a transcript length of more than 200 nucleotid and a shortage of a protein-coding capacity. Abnormalities in lncRNAs have been confirmed to indicate tumor suppressor or carcinogenic effects and play a significant role in the development of tumors [9]. In addition, recent researches have demonstrated that several lncRNAs play crucial roles in myeloid differentiation and regulate vital signaling pathways including the PI3K axis in AML [10]. Numerous studies suggest that lncRNAs could serve as promising targets for therapy in human cancer and are diagnostic and prognostic markers in certain cancers. However, the information about the role of lncRNAs in AML development, progression, and drug resistance is preliminary and the interest in understanding of the implications of lncRNAs in AML is progressively increasing. As a modulator of biological processes, small nucleolus RNA host gene 7 (SNHG7) located on chromosome 9q34.3 with a length of 2157 bp, was initially found in lymphoblastoid cell lines TK6 and WTK1 in 2013 by Chaudhry [11]. Novel evidence from clinical and fundamental researches suggests that lncRNA SNHG7 is expressed in a broad range of tissues and involved in the occurrence and development of different carcinomas [12]. In other words, it has been reported that this molecule is upregulated and plays significant role in a variety of cancers, namely bladder cancer, breast cancer, colorectal cancer, esophageal cancer, gastric cancer, glioblastoma, hypopharyngeal cancer, lung cancer, osteosarcoma, pancreatic cancer and prostate cancer [13]. Proliferation, Migration and Invasion of Non-Small Cell Lung Cancer Cells are accelerated by Long Noncoding RNA SNHG7 using Suppressing miR-181a-5p Through AKT/mTOR Signaling Pathway [14]. SNHG7 expressions in glioma tissues were enhanced and cell viability, invasion and migration were promoted by upregulation of SNHG7 [15]. BGL3 is a new lncRNA that plays a critical role in various human malignancies. BGL3 was chiefly located in the cytoplasm, where interaction with PTEN and recruitment of OTUD3 increased the de-ubiquitination influence of OTUD3 on PTEN, resulting in increased PTEN protein stability and inactivation of carcinogenic PI3K/AKT signaling [16,17]. The BGL3 lncRNA is a main regulator of BCR-ABL mediated cellular transformation. BGL3 expression is downregulated by BCR-ABL through Myc-dependent DNA methylation *in vitro* [18]. The crucial tumor-inhibiting role of BGL3 in papillary thyroid carcinoma (PTC) is underscored via post-translational regulation of PTEN protein stability, which may serve as a new therapeutic target and prognostic biomarker in human PTC(16). Given the doubts regarding the pathogenic value of SNHG7 lncRNA via the PI3K axis and its downstream targets in AML patients, alongside the significant role of BGL3 lncRNA in adjusting the PI3K pathway through the effect on PTEN gene, a study was carried out [19]. The association between the PI3K signaling pathway and lncRNAs is increasingly recognized as crucial in the realms of cancer initiation, progression, prognostication, and therapeutic intervention. This study was designed to examine both the expression levels of new lncRNA SNHG7 and BGL3 in newly diagnosed AML patients and to explore any possible correlation between the aforementioned lncRNAs in PI3K axis context. To propose a plausible mechanism underlying AML pathogenesis, the aim was to assess the expression of SNHG-7 and BGL3 targets of the Akt/PTEN pathway.

2. Materials and methods

2.1. Patients and controls samples

From January 2023 to March 2024, peripheral blood samples were collected from 30 de-novo AML patients and 30 healthy controls. The samples were obtained from Ayatollah-Khansari Hospital, Markazi Province, Arak, Iran. The research protocol got approval by the Research Ethics Committee at the arak University of Medical Sciences (ID number: IR.ARAKMU.REC.1402.026) and all participants signed informed

Table 1
The clinical characteristics of de novo acute myeloid leukemia patients.

No.	FAB	RBC × 10^6	WBC × 10^3	Hb (g/dL)	Hct (%)	Plt × 10^3	Blast (%)
1	AML-M3	4.21	17.4	12.3	37.1	72	41
2	AML-M4	3.12	31.1	10.2	31.1	176	32
3	AML-M1	3.12	86.4	9.5	28.1	78	65
4	AML-M0	3.98	15.1	12.2	37.6	135	33
5	AML-M2	3.82	19.8	11.4	34.6	106	43
6	AML-M2	4.13	21.6	11.8	33.7	253	28
7	AML-M1	2.91	16.7	9.7	28.1	117	53
8	AML-M3	3.68	22.1	9.9	29.4	73	28
9	AML-M2	3.63	53.4	11.3	34.1	153	41
10	AML-M2	4.01	27.3	12.1	36.2	96	43
11	AML-M5	2.93	21.1	10.2	30.4	156	49
12	AML-M1	4.83	15.9	12.3	37.1	126	37
13	AML-M3	3.14	43.1	12.3	37.6	139	42
14	AML-M6	3.04	23.4	11.6	33.4	183	51
15	AML-M2	4.17	26.1	12.5	37.2	110	48
16	AML-M3	4.03	21.5	11.9	34.7	89	64
17	AML-M5	2.93	36.1	8.2	25.6	101	54
18	AML-M4	3.56	34.7	11.8	34.2	103	49
19	AML-M2	4.06	16.8	13.1	38.2	155	29
20	AML-M4	3.63	43.2	10.8	31.7	103	48
21	AML-M5	3.08	41.4	9.2	27.6	93	53
22	AML-M3	3.83	43.2	10.1	30.4	86	43
23	AML-M2	4.34	10.8	12.7	38.1	183	29
24	AML-M4	3.31	53.2	10.4	31.7	98	48
25	AML-M1	4.21	18.7	12.6	37.8	121	43
26	AML-M2	4.82	19.3	13.4	39.1	145	29
27	AML-M3	2.98	54.1	9.2	27.9	53	72
28	AML-M4	3.68	25.1	9.6	28.4	93	52
29	AML-M1	4.36	19.3	12.3	37.2	83	36
30	AML-M2	3.89	43.1	10.1	31.4	88	38

consent document in agreement with the statement of Helsinki. The clinical characteristics of participants with de novo AML are demonstrated in Table 1. Patients were diagnosed based on French-American-British (FAB) classification, which categorizes AML subtypes according to morphologic characteristics of malignant cells. Among all collected samples, 83.4 % were diagnosed as non-M3 AML and 16.6 % were classified as AML-M3. The mean age of the patients at the time of diagnosis was ~59 years. It is worth noticing that 58 % of the samples (18 out of 30) were collected from male and 42 % of the samples (12 out of 30) were obtained from female patients.

2.2. RNA Extraction and Preparation of cDNA

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

2.3. Quantitative real-time PCR

Target lncRNA-specific primers (SNHG7 and FER1L4) and genes-specific primer (Akt and PTEN) were used, in conjunction with GAPDH as a reference gene, by means of GeneRunner software (details in Table 2). Alterations in lncRNAs expression levels were identified by SYBR green-based real-time quantitative polymerase chain reaction (qRT-PCR) (Roche, LightCycler® 96, Germany). A 15 μL reaction which contained 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 efficiency was assessed from a standard curve utilizing four consecutives 1:10 dilutions of the cDNA sample for each target gene. All tests were performed in triplicate and fold changes in the expressions of each mRNA were estimated by means of the Livak method ($2^{-\Delta\Delta CT}$) [20].

2.4. Statistical analysis

Statistical analyses were done utilizing SPSS software (version 20.0), and graphs were created using the GraphPad Prism 6 software. The Kolmogorov Smirnov test was used to test the normality of all continuous variables. For comparing patients with the control group, independent student or Mann Whitney U tests were utilized. Pearson's correlation test was used to assess the potential connection of indicated lncRNA with genes. It was considered statistically important that the probability level was below 0.05.

3. Results

3.1. The expression level of SNHG7 and BGL3 in AML samples

In numerous human solid tumors, the prognostic value of SNHG7 and BGL3 has been reported; nevertheless, it is not yet known whether it is associated with human leukemia [21,22]. Peripheral blood of 30 AML patients (58 % male and 42 % female) with the median age of 59 years old were collected for quantitative real-time PCR analysis in order to evaluate the expression level of SNHG7 and BGL3 lncRNA in AML and explore its probable contributory role in leukemogenesis as well. Moreover, in order to provide a more accurate outlook for gene expression pattern changes, 30 common cases were included as a control group as well. We discovered that the elevated expression of SNHG7 lncRNA in AML samples was combined with the depletion in BGL3 lncRNA (Fig. 1B). The expression level of both SNHG7 and BGL3 was different in AML patients and healthy individuals based on the results. It was particularly important to assess whether there was any association between age and gender with changes in the expression pattern of these genes, however, a significant relationship was observed with the percentage of blast in patients (Table 3).

3.2. The expression level of Akt and PTEN in AML patients as compared to healthy counterparts

The inverse correlation between PTEN and AKT represents a significant characteristic observed in numerous cancers. In many cancer types, there is often an upregulation of AKT expression, which contributes to increased cell proliferation and survival. Conversely, PTEN expression is commonly diminished; cancer cells frequently employ several strategies to downregulate PTEN, resulting in the hyperactivation of the PI3K/AKT signaling pathway and the facilitation of oncogenic activities [23]. A cross-talk between PTEN downregulation and Akt expression in malignant cell has been demonstrated in previous studies [24]. Given this and based on our results, we intended to examine the expression level of PTEN and Akt in AML patients as well. The qRT-PCR analysis indicated that the expression level of PTEN gene was considerably reduced in comparison to healthy individuals (Fig. 1A), suggesting an inhibitory effect of PTEN on the leukemogenesis process. Consequently, the qRT-PCR analysis revealed an increased expression level of Akt in AML samples as compared to its expression in the healthy volunteers (Fig. 1A). We also found that, using the Livak method, there was no significant correlation between the mRNA expression patterns of these genes and age and gender (Table 4), but there was a particular relationship between the percentages of blast in patients (Table 4).

3.3. Correlation between Akt, PTEN, SNHG7, and BGL3 expression levels in the studied groups

Having established that there was an important difference between the expression levels of the indicated genes and lncRNA among AML patients and healthy counterparts, in order to assess whether there is a strong correlation between gene expression levels and lncRNA in the patient group, we applied a statistical correlation analysis. Our results displayed that there is a no significant correlation between SNHG7 and BGL3 gene expression levels ($r = -0.281$, $P > 0.05$), But a significant and important relationship was found between genes and lncRNA, Akt and PTEN ($r = -0.417$, $P < 0.05$), Akt and SNHG7 ($r = 0.662$, $P < 0.01$), Akt and BGL3 ($r = -0.361$, $P < 0.05$), PTEN and SNHG7 ($r = -0.494$, $P < 0.05$), and PTEN and BGL3($r = 0.475$, $P < 0.05$) (Fig. 2);

Table 2
Nucleotide Sequences of the primers used for real-time RT-PCR

Gene	Forward Primer (5′-3′)	Reverse Primer (5′-3′)	Size
GAPDH	GACAGTCAGCCGCATCTTCT	GCGCCCAATACGACCAAATC	104
AKT	TCCTCCTCAAGAATGATGGCA	GTGCGTTCGATGACAGTGGT	181
PTEN	TGTAAAGCTGGAAAGGGACGA	GGAATAGTTACTCCCTTTTTGTCTC	137
SNHG7	TTTCTAACTCTCGCGCTGGG	CGTACCTCACCTGACCTGAC	141
BGL3	ATGAGACGTGCAGCACATGA	GTCTGGCACAGGCTTGATCT	130

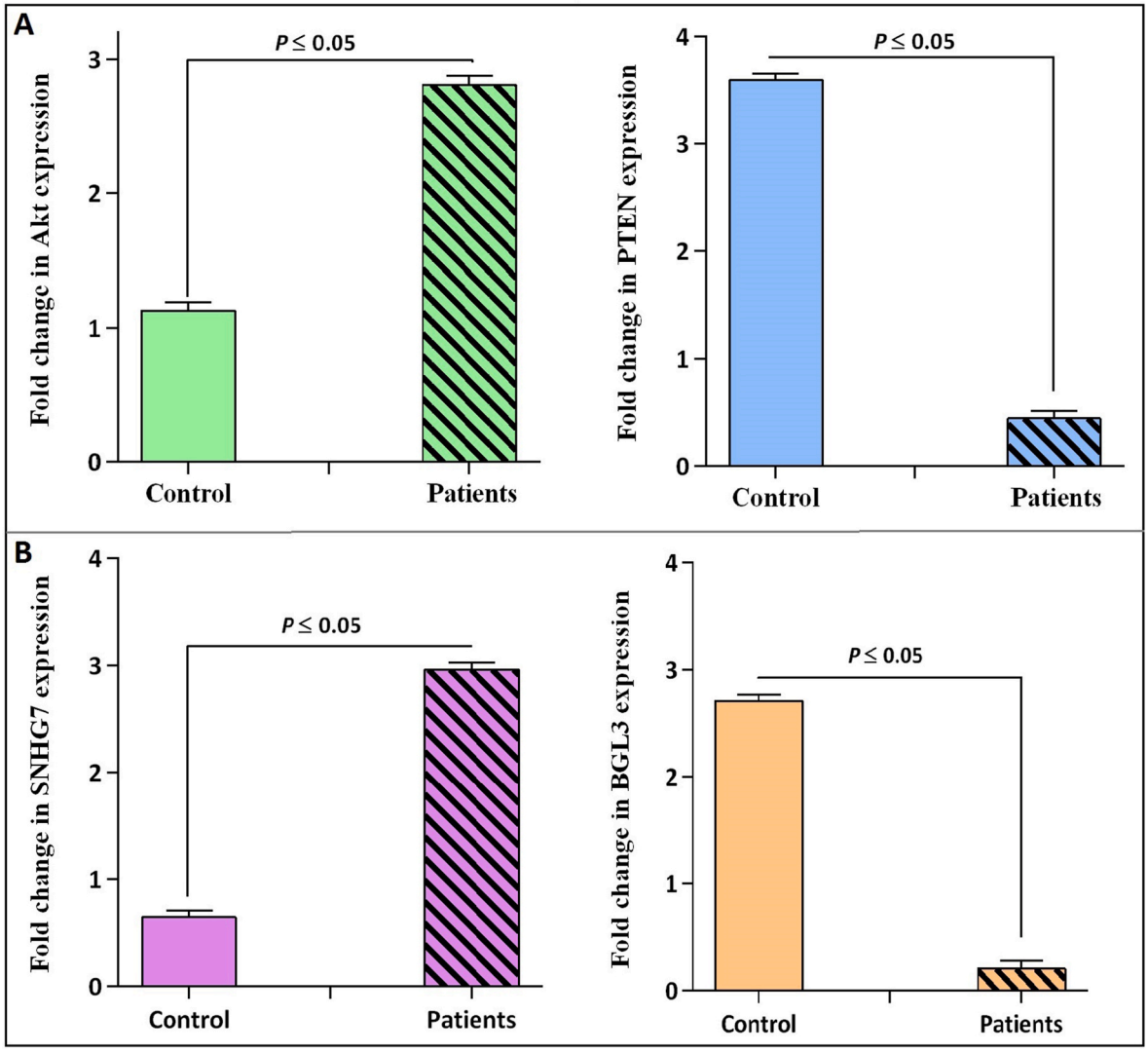

Fig. 1. A, While the expression levels of Akt gene in leukemic patients were significantly higher than the control group, the gene expression level of PTEN significantly decreased. **B**, there was a significant elevation in the expression levels of SNHG7and significand lower expression level lncRNA in leukemia patients as compared with control group. Values are given as mean ± standard deviation of three independent experiments.

Table 3
The Evaluation of the lncRNA Expression of SNHG7 and BGL3 in AML Patients[a,b].

Clinical Variables	Total Patients, 30	Evaluable Patients			Evaluable Patients		
	(100)	**SNHG7 (↑)**	**SNHG7 (↓)**	**P Value**	**BGL3 (↑)**	**BGL3 (↓)**	**P Value**
Age, year	59, 22 - 81			0.435			0.652
n < 60	20 (66.6)	15 (50)	5 (16.6)		6 [20]	14 (46.6)	
n ≥ 60	10 (33.3)	8 (26.6)	2(6.6)		3 [10]	7 (23.3)	
Sex				0.511			0.4402
Male	18 (58)	11 (36.6)	7 (23.3)		6 [20]	12 (40)	
Female	12(42)	9 [30]	3 [10]		3 [10]	9 [30]	
Percentage of blast				0.042			0.038
n < 40	18 (58)	11 (36.6)	7 (23.3)		5 (16.6)	13 (43.3)	
n ≥ 40	12 (42)	6 [20]	6(20)		4 (13.3)	8 (26.6)	
AML subtype				0.381			0.320
M3	6 [20]	3 [10]	3 [10]		2 [6]	4 (13.3)	
Non-M3	24 (80)	16 (53.3)	8 (26.6)		14 (46.6)	10 (33.3)	

Abbreviation: AML, acute myeloid leukemia.
[a] Values are expressed as No. (%) or median, range.
[b] Statistically significant values: P < 0.05.

Table 4
The Evaluation of the gene expression of Akt and PTEN in AML patients[a,b].

Clinical Variables	Total Patients, 30	Evaluable Patients		Evaluable Patients			
	(100)	**Akt (↑)**	**Akt (↓)**	**P Value**	**PTEN (↑)**	**PTEN (↓)**	**P Value**
Age, year	59, 22 - 81			0.535			0.334
n < 60	20 (66.6)	16 (53.3)	4(13.3)		3 [10]	17 (56.6)	
n ≥ 60	10 (33.3)	8 (26.6)	2 [6]		4(13.3)	6(20)	
Sex				0.641			0.214
Male	18 (58)	12 (40)	6 [20]		5 (16.36)	13 (43.3)	
Female	12(42)	8 (26.6)	4 (13.3)		3 [10]	9 [30]	
Percentage of blast				0.029			0.048
n < 40	18 (58)	15 (50)	3 [10]		2(6)	16 (53.3)	
n ≥ 40	12 (42)	8 (26.6)	4(13.3)		4 (13.3)	8(26.6)	
AML subtype				0.022			0.326
M3	6 [20]	4(13.3)	2 [6]		3 [10]	3 [10]	
Non-M3	24 (80)	21 (70)	3 [10]		18(60)	8 (26.6)	

Abbreviation: AML, acute myeloid leukemia.
[a] Values are expressed as No. (%) or median, range.
[b] Statistically significant values: $P < 0.05$.

demonstrating the important role played by this axis in pathogenesis of AML.

4. Discussion

In spite of the dramatic therapeutic advances in recent years, the minimal overall survival (OS) for AML patients ascertained the importance of the identification of the novel biomarkers in order to provide a more accurate outlook of the disease pathogenesis [25]. Intense interest has been aroused in this factor for the purpose of assessing its association with the development or prognosis of AML following the results of genetic and molecular studies showing that aberrancy in the expression or lncRNA is common in many types of cancer [26]. Some of these lncRNAs, in particular AML, have been identified as promising tools for detecting and predicting hematological cancer and have attracted considerable attention in the field [27]. Nevertheless, there is still a lack of information on the expression of particular lncRNAs in AML patients and their association with clinicopathologic classification. In the current study, we detected an increased expression level of SNHG7 lncRNA in AML samples, but we could not find a strong correlation between its expression and the age or gender differences. In agreement, accumulating evidence also indicated that the high expression level of Akt in the neoplastic myeloid cells could be an important criterion for the development of the disease and the induction of drug-resistance in AML patients [28]. Analysis of the critical role of the PI3K aberrancy and more precisely the over-expression of Akt, as the chief downstream component of the PI3K axis, in chronic lymphoid leukemia (CLL) currently resulted in the application of the PI3K inhibitors in the therapeutic approaches of this malignancy, which in turn led to an elevated tendency to study the role of this axis in the other types of hematologic malignancies [29]. Several studies suggested that in various types of AML, AML-M3 (APL) which is notorious for the translocation of PML-RARα shows a superior amount of over-activated Akt [30]. In the current study, we discovered that in AML patients either diagnosed as M3 or non-M3, the expression level of Akt was more than healthy counterparts, which was in accord with the increased SNHG7 in these patients; further highlighting the fact that the activation of the PI3K/Akt through SNHG7 lncRNA may be a probable event participating in AML pathogenesis. Studies have been done in the field of the activity of PI3K axis and SNHG7, which have shown that SNHG7 expression outlines in malignancies tissues and metastatic malignant cell lines. SNHG7 promotes malignant progression both *in vitro* and *in vivo* in colorectal cancer although high SNHG7 levels associate with hostile tumor characteristics such as size, lymphatic metastasis, distant metastasis, tumor stage, and overall survival [31]. SNHG7 interacts with miR-34a, reducing its expression through a ceRNA mechanism. Consequently, the downstream acetylglucosaminyltransferase GALNT7 is upregulated, causing abnormal O-glycosylation and activating mTOR, thereby initiating the PI3K/Akt pathway [32]. The results of our research showed that there is a significant difference in the expression of Akt gene in M3 and Non-M3 AML patients, while other studies have shown that the expression of Akt gene can be caused by specific genetic mutations in AML patients although our limitations in this study, which included the lack of access to patients' cytogenetics, did not allow further investigation of this relationship. In malignant cells, several mediators have been shown to play a role in regulating the PI3K/Akt axis and among them PTEN has been identified as one of the most significant proteins that regulates the activity of Akt axis [33]. In previous studies, modulation of PTEN expression by lncRNA BGL-3 has been shown to inhibit cell growth. lncRNA BGL3 has been demonstrated to impair cell proliferation and influence the cycle of cells in endometrial carcinoma, using PTEN as a target [19,34]. The PTEN gene is a major tumor suppressor, which has therapeutic implications for the prognosis of cancer. Through its lipid phosphatase activity, it negatively affects the PI3K/Akt/mTOR axis [35]. While BGL-3 has the potential to increase PTEN expression levels in tumor cells, the restoration of BGL3 expression in cancer cells with firstly low levels may not merely lead to decrease PTEN expression but also induce the phosphoridylated Akt level [36]. In addition, the reduction of BGL3 expression is associated with a reduced level of PTEN in cancer according to findings from colon cancer, consistent with our findings in AML [18,37]. This study mainly focuses on the role of BGL3 in regulating the biological activity of AML cells, perhaps through its effect on PTEN and subsequent Akt signaling pathways, even though the regulatory mechanism between BGL3 and PTEN has been investigated in other types of cancer. In a study conducted by Gau and her colleagues, they addressed mechanism of how lncRNA-BGL3 is regulated in the leukemic cells and showed that Bcr-Abl repressed lncRNA-BGL3 expression through c-Myc-dependent DNA methylation. Taken together, their results disclose that Bcr-Abl-mediated cellular transformation critically requires silence of tumor-suppressor lncRNA-BGL3 and recommend a possible approach for the treatment of Bcr-Abl-positive leukemia [38,39]. Our results confirmed that an increase in Akt expression levels was observed in AML patients with a low regulated B-3GL and PTEN profile. In addition, we observed an increase of SNHG-7 expression in AML patients in comparison to controls. There is still no clear understanding of the role played by SNHG7 and BGL3 in AML pathogenesis, and this study for the first time proposed that this lncRNA may be a missing point in SNHG7/BGL3's ability to regulate Akt/PTEN expression level (Fig. 3).

5. Conclusions

Overall and as the most straightforward interpretation of our results, we suggested that any component of this axis could serve as a potential

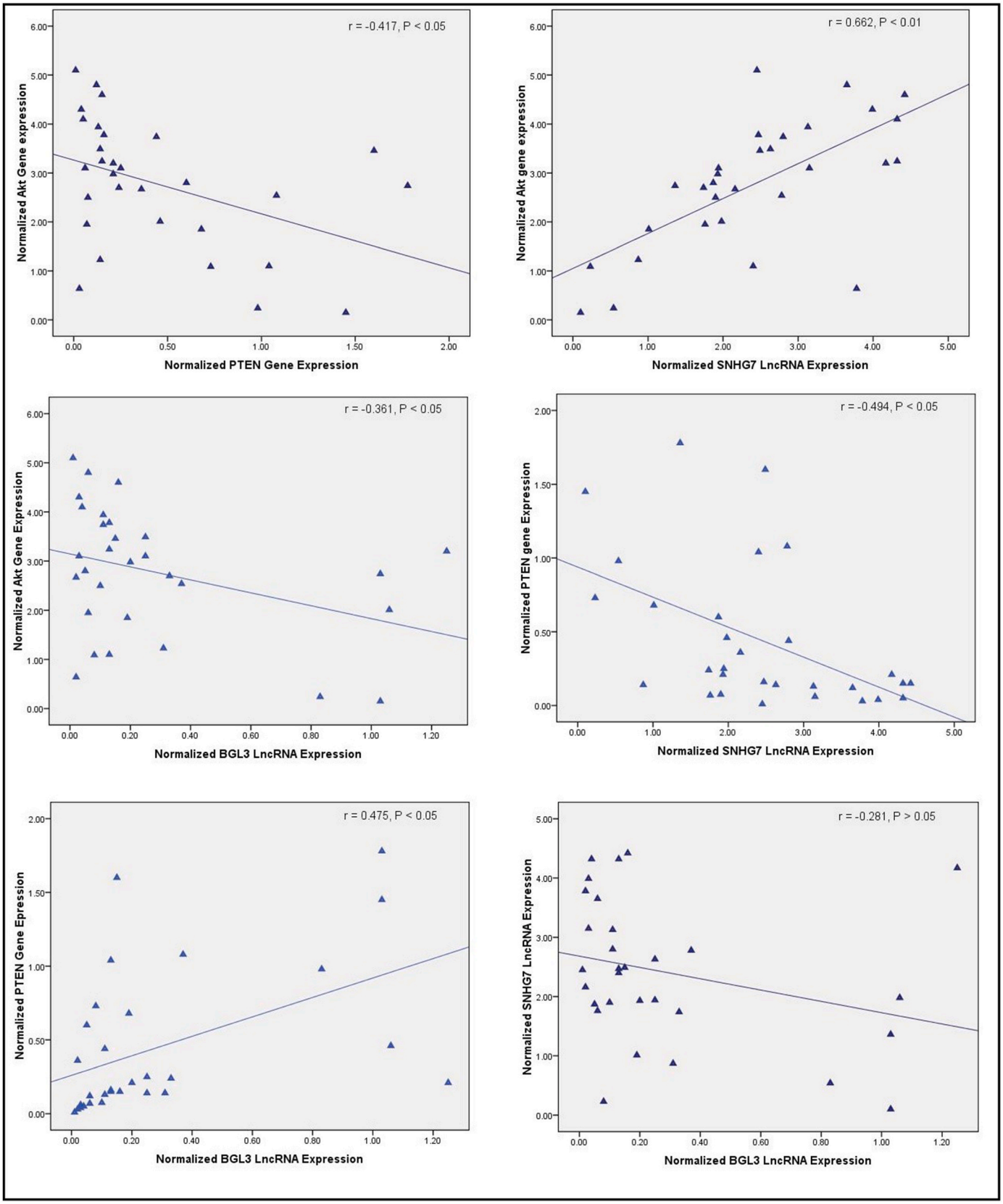

Fig. 2. A, correlation between Akt, PTEN, SNHG7, and BGL3 was determined in 30 AML patients. Values are given as mean ± standard deviation of three independent experiments.

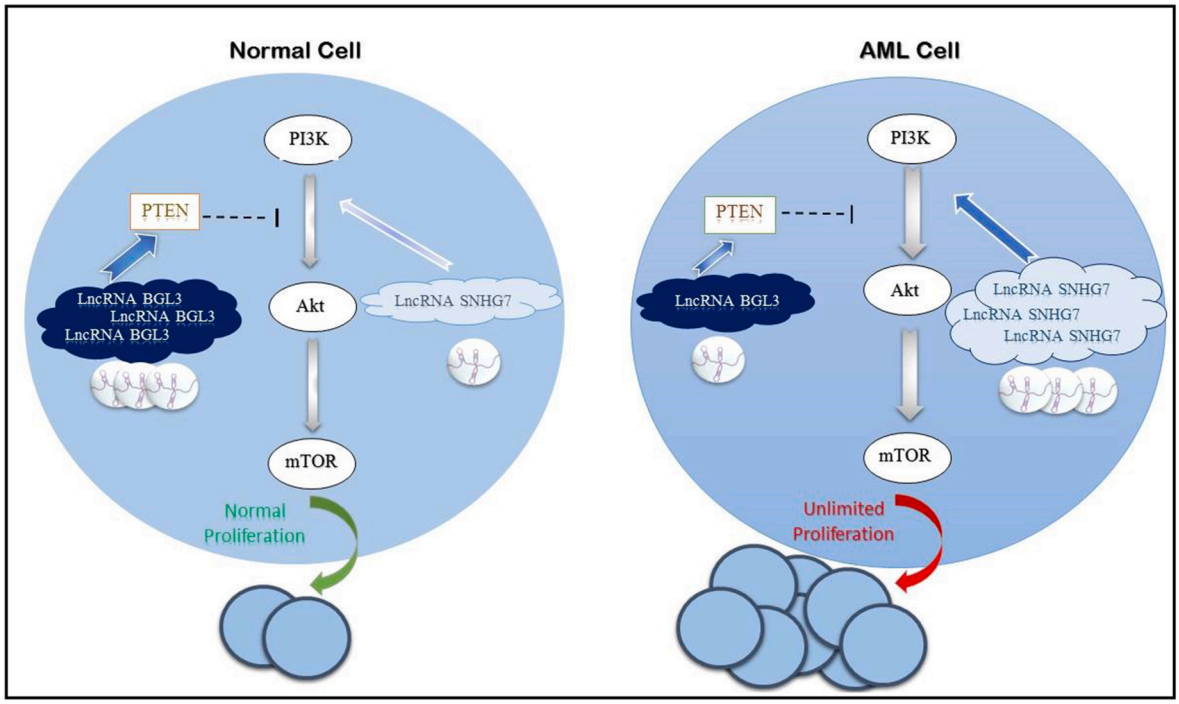

Fig. 3. Schematic illustration proposed for the probable role of PI3K axis in AML cells. Through aberrant over-expression of SNHG7 activation, subsequently leads to over activation PI3K signaling pathway in AML cells. Upon BGL3 downregulation and this defective loop may be responsible for providing a chance for AML cells to proliferate more strongly.

novel target to interfere in novel therapy strategies, and the association between SNHG7/Akt and BGL3/PTEN might play a key role in AML pathogenesis. Nonetheless, the precise role of this interesting pathway in the context of hematological malignancies, particularly AML, requires more detailed investigations in this field.

CRediT authorship contribution statement

Saeed Hassani: Validation, Methodology, Investigation, Data curation. **Parsa Rostami:** Methodology, Investigation, Data curation, Conceptualization. **Meshkat Pourtavakol:** Writing – original draft, Investigation, Data curation. **Amirhossein Karamashtiani:** Software, Data curation. **Mohammad Sayyadi:** Writing – review & editing, Writing – original draft, Supervision, Software, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to appreciate Arak University of Medical Science for supporting and providing research facilities for this study.

Data availability

Data will be made available on request.

References

[1] L.F. Newell, R.J. Cook, Advances in acute myeloid leukemia, Bmj 375 (2021).
[2] H. Kantarjian, T. Kadia, C. DiNardo, N. Daver, G. Borthakur, E. Jabbour, et al., Acute myeloid leukemia: current progress and future directions, Blood Cancer J. 11 (2) (2021) 41.
[3] S. Shimony, M. Stahl, R.M. Stone, Acute myeloid leukemia: 2023 update on diagnosis, risk-stratification, and management, Am. J. Hematol. 98 (3) (2023) 502–526.
[4] S.S. Lam, S.P. Tsui, C. Fung, N.Y. Saw, A. Javed, A.H. Ip, et al., Distinct karyotypic and mutational landscape in trisomy AML, Br. J. Haematol. 204 (3) (2024) 939–944.
[5] D. Macečková, L. Vaňková, M. Holubová, P. Jindra, R. Klieber, E. Jandová, P. Pitule, Current knowledge about FLT3 gene mutations, exploring the isoforms, and protein importance in AML, Mol. Biol. Rep. 51 (1) (2024) 1–11.
[6] Y. Solomon, A. Berhan, A. Almaw, T. Ersino, S. Damtie, T. Kiros, et al., Long non-coding RNA as potential diagnostic markers for acute myeloid leukemia: a systematic review and meta-analysis, Cancer Med. 13 (11) (2024) e7376.
[7] M. Coan, S. Haefliger, S. Ounzain, R. Johnson, Targeting and engineering long non-coding RNAs for cancer therapy, Nat. Rev. Genet. (2024) 1–18.
[8] K. Grillone, G. Caridà, F. Luciano, A. Cordua, M.T. Di Martino, P. Tagliaferri, P. Tassone, A systematic review of non-coding RNA therapeutics in early clinical trials: a new perspective against cancer, J. Transl. Med. 22 (1) (2024) 731.
[9] A.B. Herman, D. Tsitsipatis, M. Gorospe, Integrated lncRNA function upon genomic and epigenomic regulation, Mol. Cell 82 (12) (2022) 2252–2266.
[10] P. Li, J. Li, F. Wen, Y. Cao, Z. Luo, J. Zuo, et al., A novel cuproptosis-related LncRNA signature: prognostic and therapeutic value for acute myeloid leukemia, Front. Oncol. 12 (2022) 966920.
[11] F. Malakoti, F. Alemi, S.J. Yeganeh, F. Hosseini, N. Shabestani, S. Samemaleki, et al., Long noncoding RNA SNHG7-miRNA-mRNA axes crosstalk with oncogenic signaling pathways in human cancers, Chem. Biol. Drug Des. 101 (5) (2023) 1151–1161.
[12] R. Liao, Q. Han, L. Zhang, Long non-coding RNA SNHG7 serves as a diagnostic biomarker for acute coronary syndrome and its predictive value for the clinical outcome after percutaneous coronary intervention, J. Cardiothorac. Surg. 19 (1) (2024) 450.
[13] K. She, S. He, X. Lu, S. Yu, M. Li, W. Xiong, M. Zhou, LncRNA SNHG7 promotes non-small cell lung cancer progression and cisplatin resistance by inducing autophagic activity, J. Thorac. Dis. 15 (1) (2023) 155.
[14] K. Chen, A. Abuduwufuer, H. Zhang, L. Luo, M. Suotesiyali, Y. Zou, SNHG7 mediates cisplatin-resistance in non-small cell lung cancer by activating PI3K/AKT pathway, Eur. Rev. Med. Pharmacol. Sci. 23 (16) (2019).
[15] Y. Deng, L. Cheng, Z. Lv, H. Zhu, X. Meng, lncRNA SNHG7 promotes cell proliferation in glioma by acting as a competing endogenous RNA and sponging miR-138-5p to regulate EZH2 expression, Oncol. Lett. 22 (1) (2021) 1–9.
[16] M. Zhao, F. Yang, C. Sang, C. Yan, Z. Wang, BGL3 inhibits papillary thyroid carcinoma progression via regulating PTEN stability, J. Endocrinol. Invest. (2021) 1–10.
[17] L. Benetatos, A. Benetatou, G. Vartholomatos, Long non-coding RNAs and MYC association in hematological malignancies, Ann. Hematol. 99 (10) (2020) 2231–2242.

[18] Z. Hu, S. Mi, T. Zhao, C. Peng, Y. Peng, L. Chen, et al., BGL3 lncRNA mediates retention of the BRCA1/BARD1 complex at DNA damage sites, EMBO J. 39 (12) (2020) e104133.
[19] J. Liu, Y. Pan, Y. Liu, W. Wei, X. Hu, W. Xin, N. Chen, The regulation of PTEN: novel insights into functions as cancer biomarkers and therapeutic targets, J. Cell. Physiol. 238 (8) (2023) 1693–1715.
[20] K.J. Livak, T.D. Schmittgen, Analysis of relative gene expression data using real-time quantitative PCR and the 2− ΔΔCT method, methods 25 (4) (2001) 402–408.
[21] P. Yi, W. Zhang, M. Yang, Q. Lu, H. Wu, LncRNA SNHG7 serves as a potential biomarker on the prognosis of human solid tumors: a meta-analysis, Curr. Pharmaceut. Biotechnol. 22 (11) (2021) 1501–1510.
[22] S. Dahariya, A. Velidandi, D.K. Gautam, R.K. Gutti, I. Paddibhatla, lncRNAs in Leukemia. Hematopoiesis, Apple Academic Press, 2024, pp. 193–228.
[23] W.H. Almalki, LncRNAs and PTEN/PI3K signaling: a symphony of regulation in cancer biology, Pathol. Res. Pract. (2023) 154764.
[24] D. Bashash, M. Sayyadi, A. Safaroghli-Azar, N. Sheikh-Zeineddini, N. Riyahi, M. Momeny, Small molecule inhibitor of c-Myc 10058-F4 inhibits proliferation and induces apoptosis in acute leukemia cells, irrespective of PTEN status, Int. J. Biochem. Cell Biol. 108 (2019) 7–16.
[25] D. Killock, Newly diagnosed AML: quizartinib improves OS, Nat. Rev. Clin. Oncol. 20 (8) (2023) 504.
[26] M. Aprile, V. Costa, A. Cimmino, G.A. Calin, Emerging role of oncogenic long noncoding RNA as cancer biomarkers, Int. J. Cancer 152 (5) (2023) 822–834.
[27] J. Gao, F. Wang, P. Wu, Y. Chen, Y. Jia, Aberrant LncRNA expression in leukemia, J. Cancer 11 (14) (2020) 4284.
[28] M. Sayyadi, A. Safaroghli-Azar, M. Safa, H. Abolghasemi, M. Momeny, D. Bashash, NF-κB-dependent mechanism of action of c-Myc inhibitor 10058-F4: highlighting a promising effect of c-Myc inhibition in leukemia cells, irrespective of p53 status, Iran. J. Pharm. Res. (IJPR): IJPR 19 (1) (2020) 153.
[29] N. Bou Zeid, V. Yazbeck, PI3k inhibitors in NHL and CLL: an unfulfilled promise, Blood Lymphatic Cancer Targets Ther. (2023) 1–12.
[30] Y. Chen, X. Tong, R. Lu, Z. Zhang, T. Ma, All-trans retinoic acid in hematologic disorders: not just acute promyelocytic leukemia, Front. Pharmacol. 15 (2024) 1404092.
[31] Y. Li, C. Zeng, J. Hu, Y. Pan, Y. Shan, B. Liu, L. Jia, Long non-coding RNA-SNHG7 acts as a target of miR-34a to increase GALNT7 level and regulate PI3K/Akt/mTOR pathway in colorectal cancer progression, J. Hematol. Oncol. 11 (2018) 1–17.
[32] Z. Bian, W. Ji, B. Xu, W. Huang, J. Jiao, J. Shao, X. Zhang, The role of long noncoding RNA SNHG7 in human cancers, Molecular and Clinical Oncology 13 (5) (2020) 1.
[33] A. Glaviano, A.S. Foo, H.Y. Lam, K.C. Yap, W. Jacot, R.H. Jones, et al., PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer, Mol. Cancer 22 (1) (2023) 138.
[34] V. Gasic, T. Karan-Djurasevic, D. Pavlovic, B. Zukic, S. Pavlovic, N. Tosic, Diagnostic and therapeutic implications of long non-coding rnas in leukemia, Life 12 (11) (2022) 1770.
[35] R. Nussinov, M. Zhang, C.-J. Tsai, H. Jang, Phosphorylation and driver mutations in PI3Kα and PTEN autoinhibition, Mol. Cancer Res. 19 (4) (2021) 543–548.
[36] W. Li, T. Zhang, L. Guo, L. Huang, Regulation of PTEN expression by noncoding RNAs, J. Exp. Clin. Cancer Res. 37 (2018) 1–12.
[37] W. Li, Z. Li, Z. Deng, J. Zhai, S. Han, X. Liu, Proximity RNA labeling reveals functions of lncRNA in DNA damage response, Genome Instability & Disease 4 (3) (2023) 176–180.
[38] G. Guo, Q. Kang, X. Zhu, Q. Chen, X. Wang, Y. Chen, et al., A long noncoding RNA critically regulates Bcr-Abl-mediated cellular transformation by acting as a competitive endogenous RNA, Oncogene 34 (14) (2015) 1768–1779.
[39] M.N. Peiris, F. Li, D.J. Donoghue, BCR: a promiscuous fusion partner in hematopoietic disorders, Oncotarget 10 (28) (2019) 2738.