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The Role of Autophagy-Associated Genes in the Pathogenesis of Patients with Acute Lymphoblastic Leukemia

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Abstract

Background: Expanding the knowledge of the underlying molecular mechanisms in acute lymphoblastic leukemia (ALL) is of great importance to improving treatment outcomes. Autophagy, a critical and evolutionarily conserved pathway, plays an important role in maintaining cellular homeostasis under stressful conditions. This pathway consists of several sequential steps. The present study aimed to evaluate the expression levels of autophagy-related protein 3 (*ATG3*), autophagy-related protein 5 (*ATG5*), autophagy-related protein 7 (*ATG7*), autophagy-related protein 14 (*ATG14*), and urothelial cancer-associated 1 (*UCA1*) genes in B-ALL patients in order to better comprehend the autophagy pathway in B-ALL.

Materials and Methods: This research is a case-control study. The bone marrow of 50 newly diagnosed patients with B-ALL (mean age = 12.3 years) and 15 healthy controls (mean age = 13.4 years) was evaluated by real-time PCR to analyze the expression of the aforementioned genes. Additionally, morphological, immunophenotypic, and molecular analyses were conducted to examine the phenotypes, genotypes, and percentage of lymphoblasts, respectively.

Results: The findings revealed that B-ALL patients exhibited significantly higher expression of *ATG3*, *ATG5*, *ATG7*, and *ATG14* genes compared to the healthy volunteers ($P < 0.001$). However, there was no significant difference in *UCA1* levels between the two groups ($P > 0.05$). Interestingly, *ATG3*, *ATG5*, *ATG7*, *ATG14*, and *UCA1* had similar mRNA expression levels in the patients with different types of chromosome abnormalities and immunophenotypes.

Conclusion: Based on these results, the substantial increase in the expression of *ATG3*, *ATG5*, *ATG7*, and *ATG14* genes suggests that the autophagy pathway is activated in B-ALL patients. This activation may contribute to tumor growth. Furthermore, the detection of autophagy gene expression could serve as a novel marker to monitor the response of B-ALL patients to treatment.

Keywords: Acute lymphoblastic leukemia (ALL), Autophagy, Autophagy-related proteins (ATG); Gene expression

Introduction

Acute lymphoblastic leukemia (ALL) is a clonal heterogeneous disease affecting both children and adults. It is characterized by the uncontrolled growth of immature lymphocytes and their progenitors, eventually leading to the replacement of bone marrow elements and other lymphoid organs with abnormal cells (1). Although ALL can occur at any age from birth to adulthood, it is the most common in childhood, with a peak diagnosis age from two to ten years (2). The two main ALL subtypes are B-cell ALL (B-ALL) and T-cell ALL (T-ALL). B-ALL accounts for nearly 80% of pediatric ALL and can be further categorized into different genetic subgroups characterized by recurrent structural or numerical chromosomal changes (3). Moreover, B-ALL has been sub-classified into the early pre-B (pro-B) or pre-B subtype based on the expression of antigens related to each stage of B-cell development (4). Advancements in ALL

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treatment have significantly improved outcomes for children, with a survival rate of approximately 90% over five years (5). However, approximately 20% of children with ALL eventually experience relapse, and prognosis worsens with age. Adult patients with ALL face a poor prognosis, with a 5-year survival rate remaining around 30% (6). Therefore, understanding the pathogenesis of ALL and uncovering the underlying molecular mechanisms of the disease are crucial for enhancing treatment outcomes. The development and evolution of ALL have been attributed to both genetic and epigenetic alterations (7, 8). Autophagy, a critical and evolutionarily well-conserved pathway, plays a key role in the maintenance of cellular homeostasis in response to stressful conditions. It allows ALL cells to survive under harsh circumstances (9). Of particular interest, in B-ALL cells with a translocation between chromosomes 12 and 21 [t (12; 21)], autophagy can activate cell proliferation, enhance survival, and confer resistance to drugs. Conversely, suppression of autophagy using an autophagy inhibitor significantly impairs cell proliferation and survival in these cells (10,11). There is growing evidence that autophagy involves the degradation of misfolded proteins and damaged organelles by lysosomes (12). The autophagy pathway consists of several successive steps, including sequestration of cargo, transport to the lysosome, degradation, and utilization of degradation products. AuTophaGy-related (ATG) proteins play a critical role in this process (13, 14). However, there are also different non-ATG proteins critical for the progression of autophagy (15). At the moment, at least 42 ATG proteins have been identified (16). There are several functional groups for the ATG core proteins, including 1) the ULK kinase complex, which consists of *ULK1* or *ULK2*, *RB1CC1/FIP200*, *ATG13*, and *ATG101*, 2) the PI3K complex containing *VPS15*, *VPS34*, *Beclin1*, and *ATG14L*, 3) the ATG9A trafficking system that includes *WIPI1/2*, *ATG2A*, *ATG2B*, and the transmembrane protein *ATG9A*, 4) the ATG12 conjugation system containing *ATG5*, *ATG7*, *ATG10*, *ATG12*, and *ATG16L1*, and 5) the microtubule-associated protein 1 light chain 3 (LC3) conjugation system including *ATG7*, *ATG3*, *ATG4A/B/C/D*, and *LC3A/B/C* (14, 17). Long noncoding RNAs (lncRNAs) are a class of RNA molecules greater than 200 nucleotides in length. They play roles in various physiological and pathological conditions (18). Although the data on the role of lncRNAs in acute lymphoblastic leukemia (ALL) are scarce, several lncRNAs have been associated with specific ALL lineages (19). Urothelial Carcinoma Associated 1 (UCA1) is an oncogenic lncRNA, which was initially recognized as a sensitive and specific tumor marker for bladder cancer. It is also expressed at high levels in other cancers, including gastric, colorectal, lung, and breast cancers, where it plays an oncogenic role (20, 21). LncRNAs can modify autophagy through regulating the expression of ATG genes and competing endogenous RNAs (22). Despite advances, the role of autophagy in ALL remains underestimated, and further scientific investigation is necessary to enhance therapeutic outcomes, especially in refractory and relapsed cases. This study aims to evaluate the expression levels of *ATG3*, *ATG5*, *ATG7*, and *ATG14*, all of which play roles in different stages of autophagy progression. Additionally, it examines the lncRNA UCA1 gene in patients with B-ALL compared to healthy volunteers. The findings are expected to enhance our understanding of the autophagy pathway in B-ALL, potentially leading to new opportunities for diagnosis, prognosis assessment, targeted therapy, and patient monitoring.

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Materials and Methods

Research population

This research is a case-control study. From 2019 to 2020, bone marrow (BM) samples were collected from 50 newly diagnosed B-ALL patients and 15 healthy controls at Takht-Tavoos Laboratory in Tehran, Iran. The inclusion criteria were untreated patients whose disease diagnosis was made by expert oncologists according to morphology features, CD markers, and type of translocation. The exclusion criterion for the study was patients with ALL who had been treated. As normal controls, BM samples were collected from healthy subjects who were requested for BM analysis but had no evidence of hematologic malignancies and abnormal blood tests. This research was accepted by the Ethics Committee of Alborz University of Medical Sciences (IR.ABZUMS.REC.1399.164). Informed written consent was received from all the B-ALL patients and the normal controls in accordance with the Declaration of Helsinki.

RNA extraction and cDNA synthesis

The BM samples were collected in ethylenediaminetetraacetic acid (EDTA)-containing tubes, and mononuclear cells were separated from the BM specimens by Ficoll-Hypaque density gradient centrifugation (Behringer, Germany). Total RNA was separated from the mononuclear cells of the patients and controls with an RNeasy kit (Qiagen, Germany) according to the manufacturer's procedure. Nanodrop (Thermo Scientific, USA) was used to evaluate the quality and quantity of RNA. The absorbance at 260 nm and 280 nm (the A260/280 ratio) was used to measure the purity of RNA, which indicated high purity (the 260/280 ratio was more than 1.8). In the next step, RNA was reversely transcribed into single-strand cDNA using a cDNA synthesis kit (Thermo Scientific, USA).

Quantitative real-time PCR

The Gene Runner software and the NCBI primer blast were used to design specific primers for the target genes (*ATG3*, *ATG5*, *ATG7*, *ATG14*, and *UCA1*) and *GAPDH* as an internal control (IC) reference gene (Table I). The mRNA levels of these genes were measured through a real-time quantitative polymerase chain reaction (qRT-PCR) with LightCycler® 96 real-time PCR System (Roche Diagnostics GmbH, Germany). The qRT-PCR was accomplished using a total volume of 15 µL reaction mixture containing 2 µl of template target cDNA, 1 µL of forward and reverse primer, 7.5 µL of master mix (Amplicon, Denmark), and 4.5 µl nuclease-free water. The amplification reaction comprised a denaturation phase of 1 min at 95°C, then, 35 cycles of denaturation at 95°C for 20 s, 62°C for 15 s for annealing, and final extension at 72°C for 20 s. This was followed by a final cycle of elongation at 72°C for 30 s. The efficiency of the primer for the target genes was assessed based on a standard curve generated with four consecutive 1:10 dilutions of the cDNA sample. The melt curve data were investigated to determine whether a single PCR product was generated for each primer. All the assessments were done in duplicate, and the mRNA expression level for each sample was assessed via the $2^{-\Delta\Delta Ct}$ method.

Statistical analysis

The SPSS software version 24 and the GraphPad Prism 6 software were used to analyze the data. The qRT-PCR data were analyzed by the $2^{-\Delta\Delta CT}$ method. Kolmogorov-Smirnov tests and Shapiro-Wilk served to evaluate the assumption of the normality of expression of the target gene in the ALL patients and the controls. T-student or Mann–Whitney U tests were also used to evaluate the differences between the values of the ALL patients

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and the control group based on the status of normal distribution. For the comparison of the subgroups, t-student or Mann–Whitney U test and one-way ANOVA were used. Moreover, Pearson's correlation test was employed to assess the possible relationship between pairs of variables. The p-values less than 0.05 were considered significant.

Results

Characteristics of the B-ALL patients and the healthy controls

This study evaluated 50 de novo B-ALL patients and 15 healthy volunteers. The healthy control group included seven women and eight men aged 6 to 21 years. The B-ALL patients varied in terms of age, gender, chromosomal abnormality (t (12; 21), t (1; 19), t (4; 11), and t (9; 22)), as well as immunophenotype. B-ALL was sub-classified into two distinct subtypes based on the immunophenotype, including early pre-B cells (or B precursors) and pre-B cells. Early pre-B cells were identified by the expression of CD19, CD22 and CD10, as well as lack of CD20 and cytoplasmic IgM expression, while pre-B cells were defined by the expression of CD19, CD22, CD10 and CD20, as well as cytoplasmic IgM expression. There was no substantial difference of age and gender between the B-ALL patients and the control group ($P > 0.05$). Table II reports some important demographic characteristics of the patients and the control group.

ATG3, *ATG5*, *ATG7*, *ATG14*, and *UCA1* expression in the B-ALL patients and the healthy controls

The mRNA expression levels of *ATG3*, *ATG5*, *ATG7*, *ATG14*, and *UCA1* genes were analyzed for the B-ALL patients and the control group by the qRT-PCR method. The results displayed that the mRNA levels of *ATG3*, *ATG5*, *ATG7*, and *ATG14* genes in the patients were meaningfully higher than those in the control group ($P \leq 0.001$). However, as shown in Fig. 1, the patients and the healthy volunteers were not significantly different in terms of *UCA1* mRNA levels ($P > 0.05$). In the next step, correlation analyses were conducted for the genes. The Pearson correlation analysis indicated no significant correlation between the mRNA levels of *UCA1*, *ATG3*, *ATG5*, *ATG7*, and *ATG14* genes ($P > 0.05$). In addition, the changes in the mRNA levels of these genes were determined for the males and females, as well as the subgroups with different types of chromosome abnormalities and immunophenotypes. This was performed with Mann-Whitney and ANOVA tests. The findings revealed no statistically significant difference in the expression levels of *ATG3*, *ATG5*, *ATG7*, *ATG14*, and *UCA1* genes between these subgroups ($P > 0.05$). Then, the correlations of the expression levels of *UCA1*, *ATG3*, *ATG5*, *ATG7*, and *ATG14* genes with age, gender, chromosomal abnormality and immunophenotype were investigated. The results showed a positive correlation between *ATG3* and age ($\rho = 0.50$, $P = 0.005$) and also between *ATG14* and gender ($\rho = 0.36$, $P = 0.047$). The other evaluated parameters did not have a significant correlation.

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Table I: Real-time RT-PCR oligonucleotide primers

Gene	Forward primer (5′-3′)	Reverse primer (5′ − 3)	Product length
ATG3	GATGGCGGATGGGTAGATACA	TCTTCACATAGTGCTGAGCAATC	125
ATG5	TTCAGCTCTTCCTTGGAACATCAC	CCCATCCAGAGTTGCTTGTGATC	189
ATG7	AGCGGCGGCAAGAAATAATG	GTCCTTGGGAGCTTCATCCAGC	155
ATG14	CCATCATGGCGTCTCCCAGT	TCTTGTCGATAAACCTCTCCCG	240
UCA1	AAATCGGATCTCCTCGGCTTAGTG	GCTGGGAATCCTCCACCGTAAGAG	118
GAPDH	ACAACTTTGGTATCGTGGAAGG	GCCATCACGCCACAGTTTC	101

Table II: Demographic characteristics of the B-ALL patients and the control group

Variables	Study group (n = 50)	Healthy volunteers (n = 15)
Age (year)		
Mean	12.3	13.4
Median	9.5	11.2
Range	4-22	6-21
< 10	25 (50%)	7 (47%)
≥ 10	25 (50%)	8 (53%)
Gender		
Male	28 (56%)	8 (53%)
Female	22 (44%)	7 (47%)
Leukocyte count		
Mean	22500	13400
Range	6100-45000	5200-19300
Blast count		
Mean	94%	NA
Range	80-100%	NA
Chromosomal abnormality		
t(12, 21)	7 (14%)	NA
t(1, 19)	2 (4%)	NA
t(4, 11)	0	NA
t(9, 22)	3 (6 %)	NA
No translocation	38 (74%)	NA
Immunophenotype		
Early pre-B cell	25 (50%)	NA
Pre-B cell	25 (50%)	NA

NA: Not applicable.

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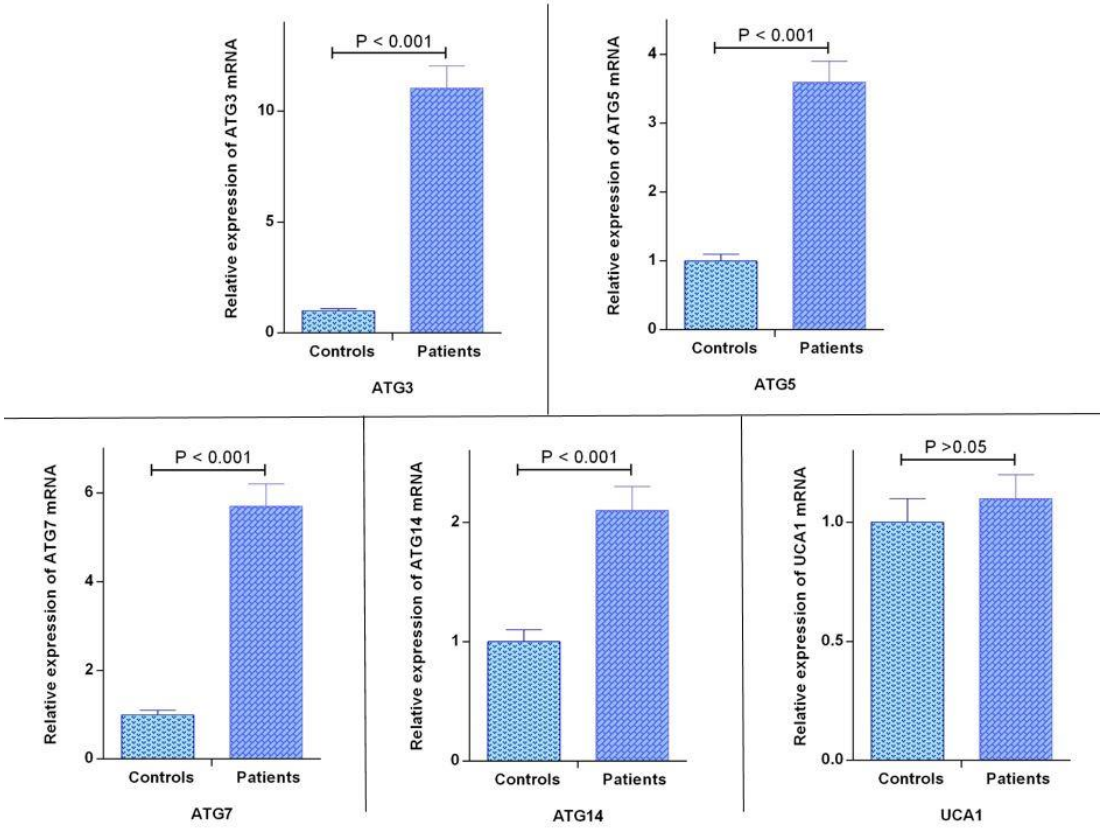

Figure 1. **The expression of *ATG3*, *ATG5*, *ATG7*, *ATG14*, and *UCA1* genes in the B-ALL patients and the healthy controls:** The results demonstrated that the expression levels of *ATG3*, *ATG5*, *ATG7*, and *ATG14* genes were significantly higher in the patients than in the control group ($p \leq 0.001$). However, as represented in Fig. 1, the mRNA expression level of the *UCA1* gene showed no significant difference between the two groups ($p > 0.05$).

Discussion

Despite therapeutic improvements in recent years, relapse of the disease remains a challenge for patients with acute lymphoblastic leukemia, particularly in developing countries (23). The identification of new molecules or pathways may aid in improving disease diagnosis and delivering successful cancer treatment. Autophagy has a key role in cellular homeostasis by damaged organelles and proteins (24). Evaluation of the alterations in the expression of autophagy-related genes can be useful in the diagnosis, prognosis, treatment, and monitoring of the disease. However, in malignant cells, autophagy plays a dual role, leading to controversy about whether autophagy prevents or promotes cancer growth, initiation, and development (25). Nevertheless, a growing body of evidence supports the role of autophagy in tumor promotion and survival, as it recycles the degraded products to produce energy for anabolic pathways (26). Autophagy supports malignant cells to adapt to unfavorable situations related to hypoxia, nutrient starvation, and chemotherapy; for example, the omission of Beclin-1, an essential mediator of autophagy, suppresses autophagy and improves cellular death (27). Moreover, a recent study indicated that alantolactone can have anti-cancer activity by inhibiting autophagy in ALL, suggesting a potential therapeutic approach for the treatment of

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ALL (28). In the present study, the important function of autophagy in the development and progression of malignancy in acute lymphoblastic leukemia was shown by evaluating the expression of *ATG3*, *ATG5*, *ATG7*, *ATG14*, and *UCA1* using RT-PCR in newly diagnosed B-ALL cases. The results revealed the higher expression of *ATG3*, *ATG5*, *ATG7*, and *ATG14* in the B-ALL patients compared to their healthy matched controls. These findings suggest a hypothesis that autophagy genes can play a protective role for tumor growth. In support of the results obtained, Ibrahim et al. (2021) indicated that *ATG5* expression was significantly higher in patients with ALL than in controls; it was associated with B-ALL phenotype, lower hemoglobin, and lower platelet count (29). Notably, a previous study presented that high levels of *ATG5* contribute to poor clinical outcomes in acute myeloid leukemia (AML), proposing that autophagy inhibition might be a beneficial approach for improving AML treatments (30). Nevertheless, Liu et al. (31) indicated that *ATG5*-mediated autophagy may be involved in AML development, but it does not involve the maintenance of malignant AML or its sensitivity to chemotherapeutic agents. *ATG5* is essential in both canonical and non-canonical autophagy pathways and has the potential to halt the extrinsic pathway of apoptosis through binding to FADD and interrupting the FADD-DISC interaction (14, 32). Growing evidence indicates autophagy alterations in malignancies treated with chemotherapy and radiotherapy, concluding that the overexpression of autophagy genes results in resistance to treatment. Therefore, attempts have been made to attenuate autophagy to improve treatment outcomes (33, 34). There is also evidence that the results obtained are not necessarily correct. As studies (34, 35) demonstrated, the expression of several *ATG* genes including *FIP200*, *BECN1*, *ULK1*, *ATG3*, *ATG5*, *ATG7*, *ATG4B*, *ATG4D*, and *ATG14*, which act at diverse stages of biosynthesis of autophagosome, was significantly lower in AML than in healthy granulocytes. Regarding AML, another study also showed significant downregulation in the *ATG7* and *LC3* genes of the patients compared to the controls, suggesting that the autophagy gene reduction in AML is essential to initiate leukemogenesis (36). Several studies propose that *UCA1* can regulate autophagy in both solid tumors and hematologic malignancies (37). For instance, in colorectal cancer (CRC) cells, UCA1 acts as an endogenous miRNA sponge by interacting with miR-185-5p and reducing its expression. This reversal of miRNA inhibition contributes to the growth of CRC cells (38). However, based on the present study, no significant difference was found in the *UCA1* level in the ALL patients in comparison to the healthy volunteers. Contrary to the results obtained, Sun et al. (39) indicated a higher level of lncRNA *UCA1* in human myelogenous leukemia (ML) K562 and HL60 cell lines. They also showed that the knockdown of this lncRNA inhibits cell migration, viability, and invasion provoking the apoptosis of these cells in vitro. Furthermore, a recent study indicated that *UCA1* promotes AML cell proliferation by acting as a miR-96-5p sponge and upregulating its target, *ATG7*, thereby inducing autophagy (37). Nevertheless, no correlation was found between the expressions of the *UCA1* gene and *ATG* genes. It seems reasonable to assume that the discrepancy in findings is partly due to the exclusive molecular mechanism responsible for the pathogenesis of AML compared to ALL. According to the present research findings, the expression of *ATG3*, *ATG5*, *ATG7*, *ATG14*, and *UCA1* genes is not

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significantly related to gender, different types of chromosome abnormality, and immunophenotype. This suggests that alterations in autophagy may be an underlying mechanism, with increased expression associated with leukemogenesis but not sufficient to cause ALL on its own.

Conclusion

Identifying the novel pathways involved in the pathogenesis of acute lymphoblastic leukemia (ALL) can significantly improve diagnosis, prognosis, and treatment strategies, particularly in relapsed cases. The role of autophagy in cancer is highly context-dependent, varying by cancer type and clinical setting. This study revealed a marked increase in the expression of autophagy-related *ATG3*, *ATG5*, *ATG7*, and *ATG14* genes in patients with B-ALL, suggesting that autophagy is actively involved in this malignancy and may contribute to tumor progression. These findings highlight the potential of autophagy-related gene expression as a biomarker for monitoring treatment responses in B-ALL patients. However, further research is needed to fully elucidate the mechanistic role of autophagy in B-ALL and explore its therapeutic implications.

Ethical Considerations

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Authors' Contributions

Conceptualization: M.M., Design: M.M., Selection of patients: E.S.S., Laboratory practices: M.M. and E.S.S., Data collection: M.M., E.S.S., and H.M., Data analysis: M.M., Literature review: M.M. and E.S.S., Writing the manuscript: M.M., E.S.S., and H.M.

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Conflict of Interest

The manuscript was read and approved by all the authors. The authors declare that they have no conflict of interests regarding this research.

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