RESEARCH ARTICLE

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Received: 13.09.2022
Acceptance: 03.12.2022
DOI: 10.18521/ktd.1171549

Konuralp Medical Journal
e-ISSN1309–3878
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www.konuralptipdergi.duzce.edu.tr

Is the *AURKB* Gene Involved in AML Cell Proliferation Since It is Targeted by miR-34a-5p and let-7b-5p?

ABSTRACT

Objective: The production of normal blood cells in the bone marrow is interrupted in AML, which is characterized by the proliferation and accumulation of leukemic blasts. Therefore, patients experience anemia and thrombocytopenia. When gene expression of Aurora kinases, which is reported to be highly expressed in AML, decreases, it may be possible to alleviate the clinical findings in AML. In this study, it was aimed to examine the relationship of *Aurora kinase B (AURKB)* with important miRNAs that have the potential to regulate gene expression

Method: HL60 and NB4 cells were transfected with important tumor suppressor miRNAs miR-34a-5p and let-7b-5p mimics. Then, its effects on proliferation were examined with WST-8 technique and its effects on *AURKB* gene expression were examined with qRT-PCR.

Results: It was determined that these miRNAs negatively regulated proliferation in both AML cell lines and downregulated the expression level of the *AURKB* gene in the miRNA transfected group compared to the control group.

Conclusion: In conclusion, it was determined that miR-34a-5p and let-7b-5p could regulate *AURKB* expression in AML cells. Therefore, it was thought that these miRNAs may have an important potential as a therapeutic biomarker in preventing excessive cell division and poor prognosis in AML.

Keywords: AML, *AURKB*, miR-34a-5p, let-7b-5p.

AURKB Geni miR-34a-5p ve let-7b-5p Tarafından Hedeflenerek AML Hücre Proliferasyonunda Rol Oynayabilir mi?

ÖZET

Amaç: Lösemik blastların çoğalarak birikimiyle karakterize olan AML'de kemik iliğindeki normal kan hücrelerinin üretimi sekteye uğradığından hastalar anemi ve trombositopeni sorunu yaşamaktadır. AML'de yüksek oranda eksprese edildiği bildirilen Aurora kinazların gen ekspresyonu azaldığında AML'deki klinik bulguları hafifletmesi mümkün olabilir. Bu çalışmada, *Aurora kinase B (AURKB)* ile protein ekspresyonunu düzenleme potansiyeli bulunan önemli miRNA'ların ilişkisinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: HL60 ve NB4 hücreleri, önemli tümör supresör miRNA'lardan olan miR-34a-5p ve let-7b-5p mimikleri ile transfekte edilmiştir. Ardından bu miRNA'ların proliferasyona etkisi WST-8 tekniğiyle, *AURKB* gen ifade değişimi üzerindeki etkisi ise qRT-PZR ile incelenmiştir.

Bulgular: Her iki AML hücre hattında da bu miRNA'ların proliferasyonu negatif yönde regüle ettiği ve kontrol grubuna kıyasla miRNA transfekte edilen grupta *AURKB* geninin ifade seviyesini downregüle ettikleri belirlenmiştir.

Sonuç: Sonuç olarak miR-34a-5p ve let-7b-5p'nin AML hücrelerinde *AURKB* ifadesini düzenleyebileceği tespit edilmiştir. Bu nedenle, AML'deki aşırı hücre bölünmesi ve kötü prognozun engellenebilmesinde bu miRNA'ların terapötik bir biyomarker olarak önemli bir potansiyeli olabileceği düşünülmüştür.

Anahtar Kelimeler: AML, *AURKB*, miR-34a-5p, let-7b-5p.

INTRODUCTION

Acute myeloid leukemia (AML) is an important hematopoietic disease in which clonal proliferation of myeloid cells is seen due to various genetic and epigenetic alterations (1). Even though several inductions and remission therapies are now available for AML, survival rates are still poor. So, it is important to identify new diagnostic and therapeutic biomarkers for AML, which constitutes the vast majority of leukemias (2).

Aurora is a family of serine/threonine kinases whose importance has been reported in the stages of chromosome distribution and cytokinesis in cell division (3, 4). Studies are needed to understand the mechanisms by which members of this kinase family contribute to cancer processes. It has been reported that the expression of Aurora A and *AURKB* is increased in a wide variety of solid tumors compared to normal tissue, and elevated Aurora expression levels have been reported in association with tumor recurrence and the advanced stages of the disease (5, 6). In the literature, abnormally increased expression of Aurora A and B kinases has been reported in hematological malignancies, including acute myeloid leukemia. It has been reported that ZM447439, which is an inhibitor of AuroraA and B kinase, increases the tendency to apoptosis by reducing cell growth in leukemia cells (7). The MLN8054 is another Aurora kinase inhibitor that has been reported to suppress tumorigenesis in lung cancer xenograft experiments (8).

Despite the use of all these Aurora kinase inhibitors, the need for more effective agents against Aurora kinases brings to mind microRNAs (miRNAs). MiRNAs are small non-coding RNAs that regulate gene expression. It is possible to group miRNAs according to the characteristics of the gene that are silenced via miRNAs. For example, if a miRNA plays a role by suppressing an oncogenic gene in the regulation of gene expression, it is called tumor suppressor miRNA (Ts-miR), whereas if it plays a role by suppressing a tumor suppressor gene, it is called oncogenic miRNA (onco-miR). MiRNAs that are important for many cancers, including AML, have been reported in the literature. In AML, miR-9 (9) and miR-139 (10) are reported as Ts-miR, while miR-155 (11) is reported as an onco-miR. miR-34a-5p and let-7b-5p, whose in vitro function was investigated in this study using AML cell lines, are among the important miRNAs reported as Ts-miR for many cancers in the literature. Like Aurora kinase inhibitors reported in the literature, it may be possible to suppress gene expression by targeting Aurora kinases through miRNAs and thus reduce their contribution to cancer formation. Based on this, in our study, the relationship between *AURKB* gene and the 2 important Ts-miRs was investigated in HL60 and NB4 AML cell lines.

MATERIAL AND METHODS

In Silico Detection of the *AURKB* Gene as a Target of miR-34a-5p and let-7b-5p: The expression of *AURKB* in various cytogenetic anomalies associated with AML was determined by the bloodspot tool (12). The hub proteins directly related to the *AURKB* gene were found using the Enrichr database. The relationship between *AURKB* and hub proteins was visualized by String (13). The *AURKB* gene has been shown to be highly expressed in AML. Thus TsmiRs whose expression is reduced in AML were identified first. The TsmiR miRNAs associated with AML in the literature were identified by reviewing the (14, 15) studies. The miRNet tool was used to determine whether the identified TsmiRs could potentially target the *AURKB* gene (16). miRDB (17), Targetscan (18) miRWalk (19) were utilized for confirmation. Following a review of the literature, 2 miRNA was selected for in vitro study and the complementarity of miR-34a-5p and let-7b-5p with *AURKB* 3'UTR is checked via STarMirDB tool (20).

HL60 and NB4 Cell Culture and Transfection of miRNA Mimics: HL60 and NB4 AML cell lines were used in this study. Cells were seeded and cultured under the 37°C and 5% CO2 incubator condition and 10% FBS-1% antibiotic added RPMI-1640 medium condition. According to the manufacturer's procedure, transfection of 30 pmol miR-34a-5p, let-7b-5p and non-targeting (nt) control) mimics (Thermo Fisher Sci. Inc.) were performed on cells using the lipofectamine-mediated method (Lipofectamin 2000, Thermo Fisher Sci. Inc.).

miR-34a-5p and let-7b-5p Effect on Cell Proliferation: The WST-8 technique, which provides information about viability colorimetrically, was used to examine whether the selected miRNAs have an effect on cell proliferation. For this purpose, $5x10^3$ cells were inoculated on a culture plate (96-well plate) in three wells for each miRNA mimics and nt control mimic. Using the CVDK-8 kit (EcoTech Biotechnology) protocol cell proliferation was determined by measuring absorbance at 450 nm with the MultiScan FC microplate reader (Thermo) at 48 and 96 hours. Cells were also observed with an inverted fluorescent microscope (Nikon ECLIPSE 80i).

RNA Extraction: After transfection, total RNAs of the study group and control group AML cells were extracted according to the TRIzol reagent (Invitrogen, Carlsbad, CA, USA) as stated in the procedure instruction. RNA purity and concentrations were determined spectrophotometrically with NanoDrop 2000 device (Thermo Fisher Scientific, Madrid, Spain).

qRT-PCR Process for miRNA Transfection Verification: For the determination of miR-34a-5p and let-7b-5p quantify in miRNA

mimic transfected cells, selected miRNA and RNU43 (control miRNA) specific TaqMan primer-probes were commercially purchased. cDNA was synthesized with a total of 30 ng RNA using TaqMan primers (Thermo Fisher) and TaqMan MicroRNA reverse transcriptase kit (Applied Bio., Foster City, CA, USA). Then, qRT-PCR was performed with TaqMan probes (Thermo Fisher) and TaqMan Universal Master Mix (Thermo Fisher).

Expression Analysis of *AURKB* Kinase: cDNA synthesis (SCRIPT kit, Jena Bioscience) was performed using RNAs extracted from miRNA mimic and nt mimic transfected cells. For this purpose, a total of 1000 ng RNA was used, and then expression analysis was performed by a qRT-PCR technique using SybrMaster reagent (Jena Bioscience) and F/ R primers of the *AURKB* gene (Forward-5′-ATTGCTGACTTCGGCTGGT-3′, Reverse-5′-GTCCAGGGTGCCACACAT-3′) (21). Forward-5'-GCCTCGCCTTTGCCGATC-3' and Reverse-5'-CCCACGATGGAGGGGAAG-3' primers specific to the *β-Actin* gene were used as a housekeeping control (22).

Statistical Analysis: The experiments were performed in duplicate for qRT-PCR analysis and for in triplicate for WST-8 assay. The relative quantitation method ($2^{-\Delta\Delta Ct}$ method) was used for the evaluation of the expression levels. The data were analyzed by SPSS 28 program and stated as mean ± standard deviation (SD). $p<0.05$ value was considered statistically significant and the figures were drafted using GraphPad Prism 9.3 software.

RESULT

In Silico Analysis Data: The expression of *AURKB* in various cytogenetic anomalies associated with AML is shown in Figure 1. As a result of PPI analysis, it was determined that *AURKB* was directly related to 9 hub proteins (Figure 2). Following a review of the literature, 30 miRNAs were identified as acting as TsmiR in AML (Figure 3). Six of these miRNAs were determined to have the potential to target *AURKB* (Figure 4 and Figure 5). After the confirmation of the findings with miRWalk, miRDB, and Targetscan, as well as a deeper investigation of the literature, miR-34a-5p, and let-7b-5p, which are assumed to be more connected to *AURKB*, were used in an in vitro study. The complementarity of miR-34a-5p, let-7b-5p with *AURKB* 3'UTR is shown in Figure 6.

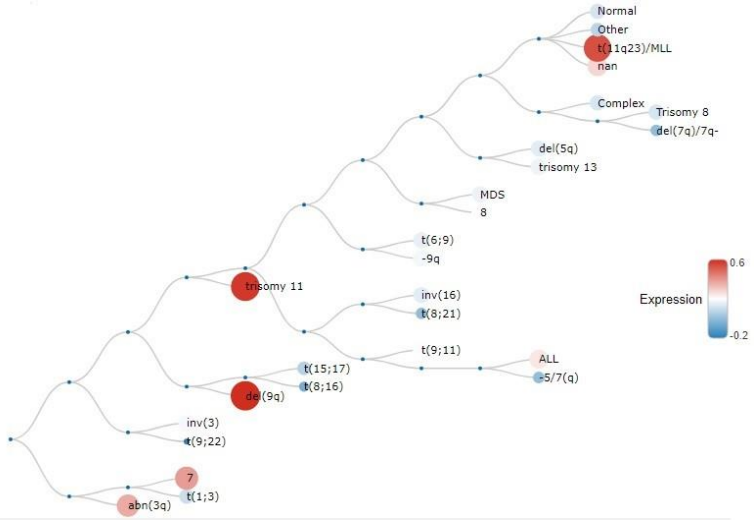

Figure 1. The expression states of the *AURKB* gene in various cytogenetic abnormality groups. Data was obtained using the 'bloodspot' tool (37). 'BloodPool: AML samples versus normal' was selected as the dataset. The selected dataset includes GSE13159, GSE15434, GSE61804, GSE14468 and TCGA.

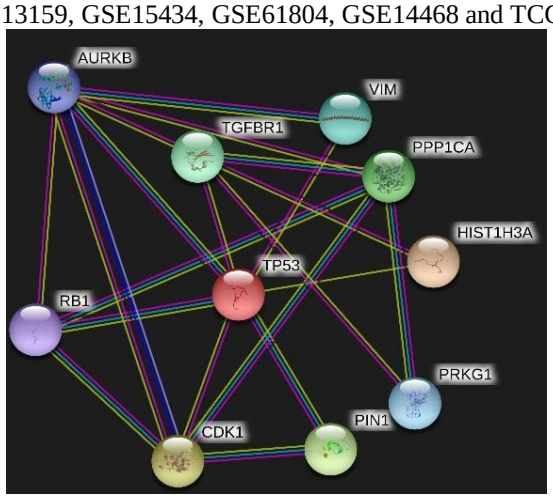

Figure 2. The relation between *AURKB* gene and its 9 hub proteins. The hub proteins were obtained using enrichr. *AURKB* and the hub genes' association was created via String (38).

Figure 3. AML associated 30 TsmiRs (14, 15).

Figure 4. *AURKB* and potantial target miRNAs acording to miRNet (39). Six of the 46 miRNAs contained here have been reported as TsmiR in AML. The six miRNAs are shown in yellow.

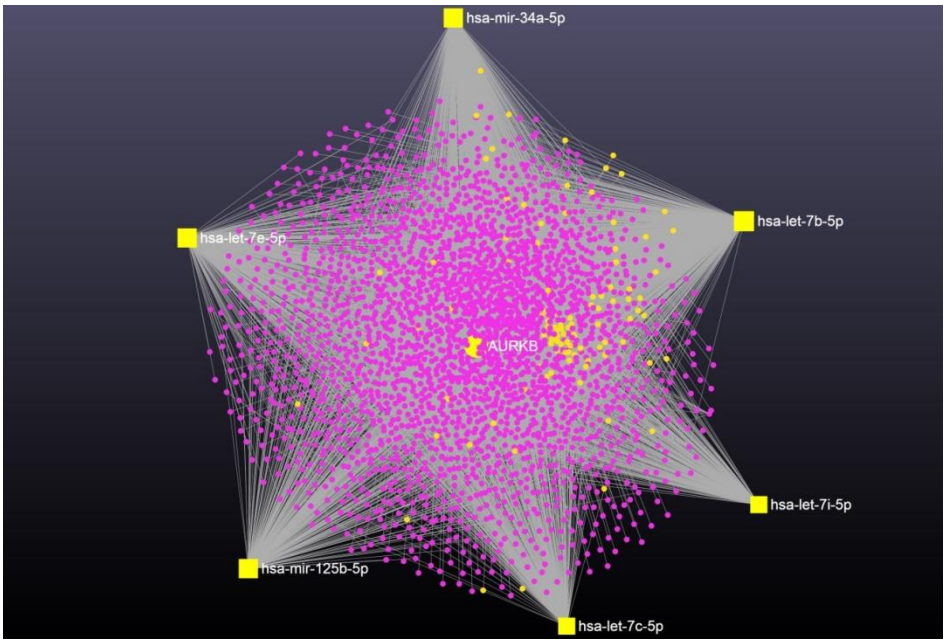

Figure 5. The connections of miRNAs and genes in leukemia. The six TsmiRs may regulate the expression of hundreds of genes, including *AURKB* (39).

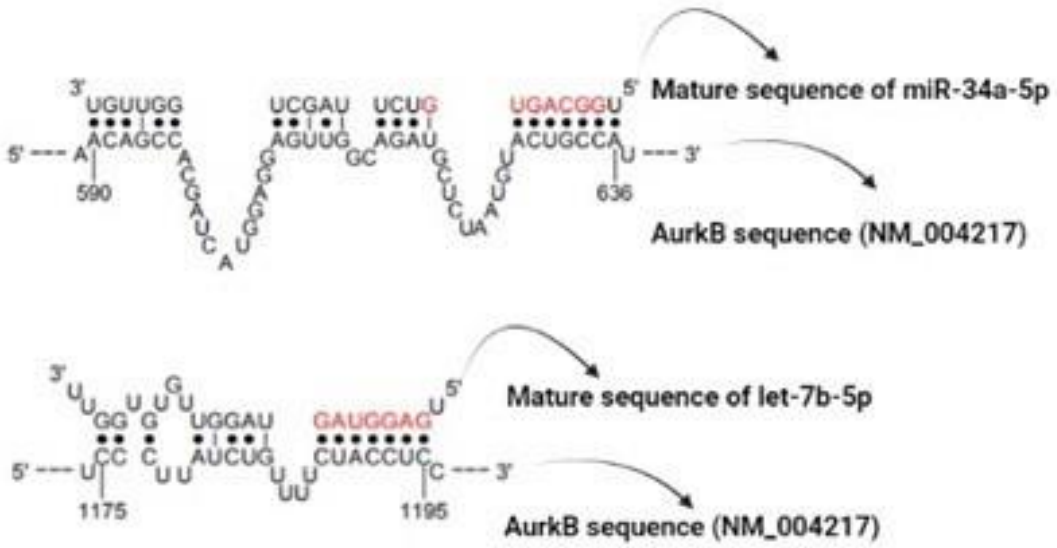

Figure 6. *AURKB* 3'UTR region complementarity with selected miRNAs (40).

Selected TsmiRs Repress the AML Cell Proliferation: In both HL60 and NB4 cells, 2 selected miRNAs were found to have a statistically significant effect on reducing cell proliferation in the study group compared to the control group (miR-34a-5p mimic transfected HL60 cell proliferation at 48 hour p<0,001, fold change= 1,27; at 96 hour p<0,001, fold change= 1,3), (miR-34a-5p mimic transfected NB4 cell proliferation at 48 hour p<0,05, fold change= 1,23; at 96 hour p<0,001, fold change= 1,41), (let-7b-5p mimic transfected HL60 cell proliferation at 48 hour p<0,001, fold change=1,3; at 96 hour p<0,001, fold change= 1,37) and (let-7b-5p mimic transfected NB4 cell proliferation at 48 hour p<0,05, fold change= 1,1; at 96 hour: p<0,001, fold change= 1,2) (Figure 7-8).

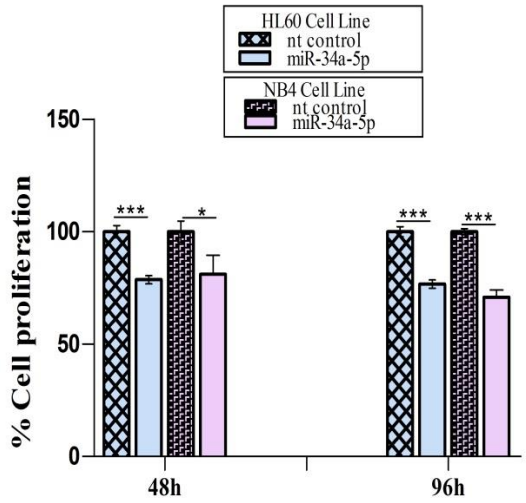

Figure 7. Effect of miR-34a-5p on cell proliferation (*p<0,05; ***p<0,001).

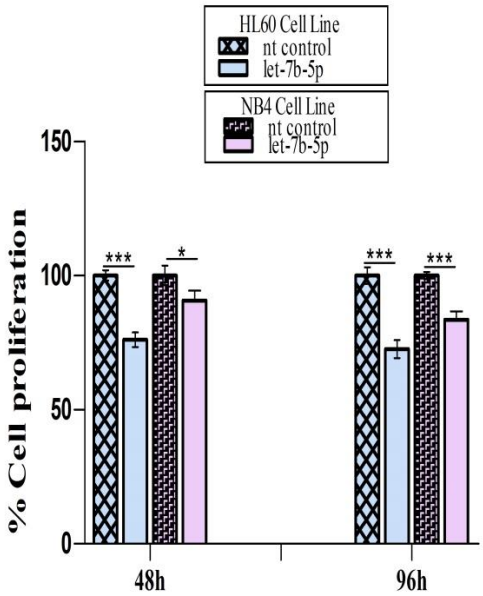

Figure 8. Effect of let-7b-5p on cell proliferation (*p<0,05; ***p<0,001).

***AURKB* Gene Expression was Negatively Regulated via Selected TsmiRs:** *AURKB* gene was found to be statistically less expressed in HL60 and NB4 cells transfected with selected miRNA mimics compared to control groups (miR-34a-5p mimic transfected HL60 cells p<0,05 ; fold change= 4); (let-7b-5p mimic transfected HL60 cells p<0,01 ; fold change= 2,32), (miR-34a-5p mimic transfected NB4 cells p<0,01 ; fold change= 1,6) and (let-7b-5p mimic transfected NB4 cells p<0,01 ; fold change= 5) (Figure 9-10). This result indicates that miR-34a-5p and let-7b-5p may play a role in regulating the expression of the *AURKB* gene as a negative regulators in HL60 and NB4 cells.

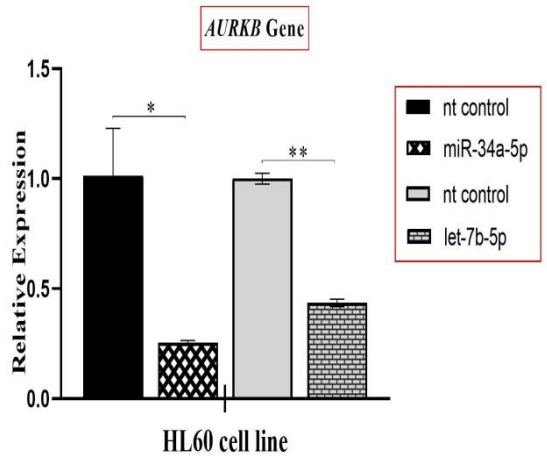

Figure 9. The expression level of *AURKB* gene in HL60 cells transfected with selected miRNA mimic and nt mimic (*p<0,05; **p<0,01).

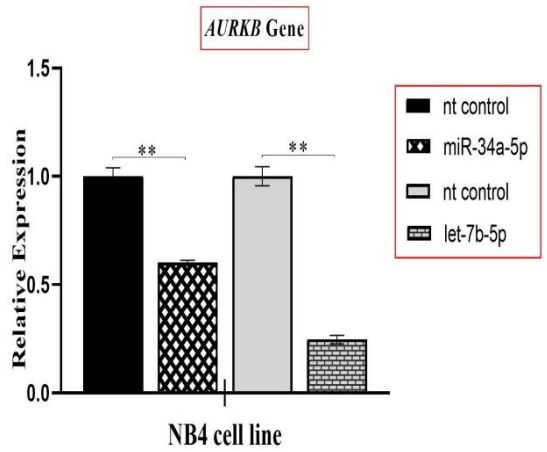

Figure 10. The expression level of *AURKB* gene in NB4 cells transfected with selected miRNA mimic and nt mimic(**p<0,01).

DISCUSSION

Acute myeloid leukemia (AML) is a hematological malignancy in which a boost in myeloid stem cells is seen in the bone marrow under the influence of various genetic-epigenetic and/or environmental factors (1). Although a wide variety of cytogenetic and molecular genetic changes such as t(8;21), inv(16), t(15;17), and *FLT3* mutation are used in the rapid diagnosis and prognosis of AML, there is still a need to identify novel molecules that may be useful for early diagnosis and treatment (23). As an example of the research used for AML and the treatments on which studies are still ongoing; immunotherapy, development of gene-specific inhibitors against various gene mutations (*FLT3*, *TP53*, *IDH1/2*, checkpoint inhibitors, etc), antibody-based studies, CART cells treatments could be shown (24). One of the inhibitor treatment is using Aurora kinase inhibitor in AML. Aurora kinases, which are important molecules in cellular mitosis and cytokinesis, have been reported to have increased expression levels in many cancers (25). Since problems with mitosis in cell division are known to increase genomic instability, it is essential to control the amount of Aurora kinase protein molecules which involved in mitosis (26). Therefore, several inhibitors have been developed for members of this protein kinase family and some of them have received FDA approval (27). In t(8;21) AML cells, inhibition of the cell cycle and proliferation has been reported through inhibition of *AURKA* (inhibitor Alisertib) and *AURKB* (inhibitör Barasertib) (28). In addition, various molecules such as ZM447439, AZD2811 and AZD1152 have been developed as Aurora kinase inhibitors in leukemias including AML (29) and It has been proposed that utilizing these compounds in combination with certain chemotherapeutics can boost their efficiency and also it has been suggested that use of the FDA-approved *FLT3* inhibitor "Gilteritinib" with *AURKB* inhibitors may be beneficial prior to relapse in AML (30). It has been reported in the literature that *AURKB* is a more essential protein than other Aurora kinases for the proliferation and survival of AML cells (31). Due to this reason, in our study, we focused on alternative *AURKB* targeting strategies. In recent years, studies have brought up the idea of miRNA-mediated suppression of the expression of Aurora kinase genes, and miRNA researches are increasing as an alternative to Aurora kinase inhibitors. MiR-34a-5p and let-7b-5p, whose relationship with *AURKB* we examined in this study, are very important TsmiRs known to play a role in suppressing tumor growth and progression in many cancer types including AML (32, 33). It is expected that by increasing the amount of these TsmiRs in the cell, they can suppress their targeted oncogenes more effectively, thereby reducing processes such as cell proliferation, metastasis and cancer progression. To the best of our knowledge, there is no study investigating the relationship between *AURKB* and miR-34a-5p and let-7b-5p in AML, and also there are limited studies on this subject in other cancers as well.. It has been reported in the literature that in some cancers, due to decreased levels of some miRNAs including miR-34a, the gene expression of the *FOX* family up-regulated, which indirectly increases the expression of genes such as *CCNB1*, *AURKB*, *MYC*, leading to poor prognosis (34). In a study investigating the let-7b/*AURKB* relationship in HeLa and HCT-116 cells, it was reported that increased *AURKB* expression is seen in many cancers and this situation causes poor prognosis in patients. In the same study, let-7b was found to contribute to the reduction of genomic instability by targeting *AURKB*, which is an important protein for the mitosis stage (21). In addition, there are some studies reporting that let-7b reduces drug resistance of gastric cancer cells (35) and it could be

associated with resistance in K562 chronic leukemia cells (36) by targeting *AURKB*.

In our study first, we conducted a literature review and used various in silico tools to identify miRNAs that could regulate *AURKB* expression. Following in vitro study, we revealed that miR-34a-5p and let-7b-5p miRNAs play a role in decreasing HL60 and NB4 cell proliferation and suppressing *AURKB* expression statistically significantly. Among the limitations of our study, we examined the effect of miR-34a-5p and let-7b-5p only on AML cell proliferation and on *AURKB* gene expression in AML cells. Another limitation is that we have not yet confirmed the accuracy of our data in AML patients. Therefore, this study must be investigated in terms of its effect on protein and miRNA-gene interaction using advanced techniques in both AML cell lines and bone marrow samples from individuals with AML.

CONCLUSION

Mortality rates are still quite high in AML, which is a rare type of cancer compared to many diseases. Therefore, it may be a good alternative to discover miRNA-Aurora kinases relationships both for early diagnosis and for the development of new treatments.

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