DOI: 10.37990/medr.1118392 Med Records 2022;4(3):447-53

MEDICAL RECORDS-International Medical Journal

Research Article

Comparison of Prognostic miRNA Signature in Patients with Acute and Chronic Myeloid Leukemia by Bioinformatic Analysis

Akut ve Kronik Miyeloid Lösemili Hastalarda Prognostik miRNA İmzasının Biyoinformatik Analiz ile Karşılaştırılması

Aynur Karadag Gurel

Usak University, School of Medicine, Department of Medical Biology, Usak, Turkey

Abstract

Aim: In this study, differentially expressed miRNA profiles were determined using high-throughput expression data from samples of AML and CML patients to identify miRNAs involved in the therapeutic response.

Material and Methods: miRNA microarray datasets GSE142699 and GSE90773 were downloaded via the GEO database and analysis was performed with the online analysis tool GEO2R. Data no. GSE142699 was made with 24 control and 24 newly diagnosed AML patients, data no. GSE90773 was made with 8 control and 10 newly diagnosed CML patients. After the analysis, they were grouped according to fold change (FC) values and $p<0.05$. Potential target genes regulated by differentially expressed miRNAs were predicted using the miRDB and TargetScan databases. Target genes enrichment analysis was performed GO function and KEGG pathway analysis using the DAVID program. Then, hub genes were detected using the regulatory network Cytoscape over the target genes.

Results: There were 27 unique miRNAs whose expression increased and 161 decreased in the AML group. In the CML group, 52 unique miRNAs with increased expression and 122 unique miRNAs with decreased expression were found. After clustering analysis between the AML and CML groups, 11 miRNAs with decreased expression and 5 miRNAs with increased expression were found. 7 miRNAs that were similar but differently expressed in the two groups were filtered out. A total of 2525 predicted target genes were found from 7 miRNAs. It was revealed that differently expressed miRNAs affect 22 common signaling pathways, especially the pathways in cancer, MAPK signaling, and PI3K-Akt signaling.

Conclusion: Our findings demonstrated that the same miRNAs are involved as different regulators in human leukemia development. Different miRNA signatures in myeloid development may be candidates for biomarkers for clinical diagnosis and differentiation, prognosis, and treatment of myeloid leukemias.

Keywords: Bioinformatic analyses, GEO, leukemia, AML, CML, miRNA

Öz

Amaç: Bu çalışmada, terapötik yanıtta yer alan miRNA'ları belirlemek için AML ve KML hastalarının örneklerinden alınan yüksek verimli ekspresyon verilerini kullanarak diferansiyel miRNA ekspresyonunu analiz ettik.

Materyal ve Metot: miRNA mikrodizi veri setleri GSE142699 ve GSE90773, GEO veritabanı aracılığıyla indirildi ve çevrimiçi analiz aracı GEO2R ile analizi yapıldı. GSE142699 nolu data, 24 kontrol ve 24 yeni teşhis edilmiş AML hastası, GSE90773 nolu data ise 8 kontrol ve 10 yeni tanı konmuş KML hastası ile yapılmıştır. Analiz sonrası kat değişimi (FC) değerlerine ve $p<0.05$'e göre gruplandırıldı. TargetScan ve miRDB veritabanları, diferansiyel olarak eksprese edilen miRNA'lar tarafından düzenlenen potansiyel hedef genlerini tahmin etmek için kullanıldı. Hedef genler DAVID programı kullanılarak, aday hedef genlerin zenginleştirme analizi GO fonksiyon ve KEGG yolu analizi gerçekleştirildi. Daha sonra hedef genler üzerinden düzenleyici ağ Cytoscape kullanılarak hub genler tesbit edildi.

Bulgular: AML grubunda ekspresyonu artan 27 ve azalan 161 benzersiz miRNA bulundu. KML grubunda ekspresyonu artmış 52 ve ekspresyonu azalmış 122 benzersiz miRNA bulundu. AML ve KML grupları arasında kümeleme analizinden sonra ekspresyonu azalmış 11 miRNA ve ekspresyonu artmış 5 miRNA bulundu. Benzer olan ancak iki grupta farklı eksprese edilen 7 miRNA filtrelenmiştir. 7 miRNA'dan toplam 2525 tahmin edilen hedef gen bulundu. Farklı eksprese edilen miRNA'ların 22 ortak sinyal yolunu, özellikle kanserdeki yolları, PI3K-Akt sinyalini ve MAPK sinyalini etkilediği ortaya çıkmıştır.

Sonuç: Bulgularımız, aynı miRNA'ların insan lösemi gelişiminde farklı düzenlenleyiciler olarak rol aldığını göstermiştir. Miyeloid gelişimindeki farklı miRNA imzaları, miyeloid lösemilerin klinik teşhisi ve ayrımı, prognozu ve tedavisi için kullanılabilecek birer biyobelirteç adayı olabilir.

Anahtar Kelimeler: Biyoinformatik analiz, GEO, lösemi, AML, CML, miRNA

Received: 18.05.2022 **Accepted:** 26.07.2022
Corresponding Author: Aynur Karadag Gurel, Usak University, School of Medicine, Department of Medical Biology, Usak, Turkey **E-mail**: aynur.karadag@usak.edu.tr

INTRODUCTION

Over the past decade, it has become clear how important microRNAs (miRNAs) are, both in normal conditions and in disease states. Gene expression, RNA maturation, and protein synthesis are all regulated by miRNAs (1, 2). miRNAs are 18-25 nucleotide long, non-protein-coding RNA fragments. They play a role in various cellular functions such as cell growth, differentiation, and development through post-transcriptional regulation of target genes (3, 4). The microRNA binds to the untranslated region at the 3' end of the target mRNA or the open reading frame region of the target mRNA (5). Many distinct mRNA transcripts, many of which have similar activities, can be inhibited by one miRNA and control multiple signaling pathways (6). In contrast, numerous miRNAs can target the same mRNA transcript (7).

miRNA expression dysregulation has been linked to a variety of diseases and cancers. Nearly half of miRNAs are located near or in cancer-related genes (8). miRNA genes have been determined to be localized in regions of loss of heterozygosity and fragile regions or in regions of common chromosomal breakpoints, which can lead to cancer if damaged (9-10). They are found stably in tissues and body fluids. The unique expression patterns of miRNAs have been proposed as biomarkers for various diseases, making them ideal diagnostic and therapeutic agents (11-13).

miRNAs can acquire oncogenic or tumor suppressor properties depending on the molecular level properties of the mRNA they target. It has been reported that some of the miRNAs inhibit the translation of protooncogenes in normal tissues. Its function is to control the expression of an oncogene. miRNAs are known as "tumor suppressor miRNAs" (TSmir) (14). MiRNAs regulate normal hematopoiesis by regulating myeloid differentiation, cell cycle, proliferation, apoptosis, and gene methylation (15, 16). MiRNA can operate as a tumor suppressor or an oncogene/oncomiR in hematological malignancies originating from hematopoietic stem and progenitor cells (15,17). miRNAs show promise as a biomarker to discriminate between cancers as well as between Chronic myeloid leukemia (CML) and acute myeloid leukemia (AML). Only the K562 cells revealed higher expression of miR-20a in a transcriptome comparison of AML and CML cell lines. This shows that higher levels of miR-20a expression could be used to distinguish CML from AML (18). Other research has found that miR-29a/b is downregulated in both CML and AML patients, and that these two miRNAs play an important regulatory role in myeloid cells (19).

The roles of miRNAs in leukemia pathogenesis are currently being explored, and various studies have proposed miRNA expression profiles as biomarkers for a leukemia diagnosis, prognosis, and response to therapy. The advantage of determining miRNA profiles over mRNA profiles is that miRNAs can classify poorly differentiated cancer types that mRNA profiles cannot distinguish.

This study aimed to discover the function of miRNAs in the pathogenesis of AML and CML patients. As a result, in silico research was performed to better understand the RNA silencing mechanism of miRNAs with similar or dissimilar roles in AML and CML. Target genes of miRNAs and their related biological pathways were explored in this work to determine the therapeutic potential of miRNAs in AML and CML. MiRNA profiles that are similar or dissimilar can be used as prognostic and differential diagnostic markers in AML and CML.

MATERIAL AND METHOD

The study is a bioinformatics study and raw data was used. The database for which we use the data, Gene Expression Omnibus (GEO), is a public database and therefore ethical approval is not required. GEO is a public, functional genomic data repository that supports minimal information about a microarray experiment (MIAME) compliant data submissions where Array and array-based data are accepted (https://www.ncbi.nlm.nih.gov/geo/)

Dataset Collection

The GEO database was used to derive gene expression profiles for datasets GSE142699 and GSE90773. The dataset of GSE142699 was analyzed with GPL19066 and GSE90773 was analyzed with GPL26945. GSE142699 contains 24 controls and 24 newly diagnosed AML patients. GSE90773 includes 4 control and 5 newly diagnosed CML patients containing Lin- CD34+CD38+ and Lin-CD34-CD38- cells isolated from peripheral blood.

Analyzing the Differential Expression of miRNAs

For the analysis of differentially expressed microRNAs, the R-based GEO online tool GEO2R online tool was used. It performs comparisons between sets of samples in the dataset to identify differentially expressed miRNAs (DEMs). $P<0.05$ and $|$ fold change$| \geq 0$ were used as screening thresholds for the GSE142699 and GSE90773 datasets. Comparisons between gr AML and CML groups were first compared with their healthy group and then with each other goups are made by applying log 2 transformation and Benjamini & Hochberg method. MiRNAs and DEMs that were similar and different between groups were obtained using the Venny online tool.

Target Gene Prediction Analysis

The online databases miRDB (http://miRdb.org/) and TargetScan (http://www.targetscan.org/) were used to determine miRNA target genes. The two databases found identical genes in both databases that were used as target genes. Prognostic miRNAs linked to both AML and CML had common target genes.

Functional Analyses of Common Genes

To describe the biological processes involved in common genes, we used DAVID (https://david.ncifcrf.gov/) to apply the Kyoto Encyclopedia of Genes and Genes (KEGG) Pathway enrichment and Gene Ontology (GO) functionality. Pathways with $P<0.05$ and highest gene

counts were considered important pathways, such as enriched KEGG pathways and functional processes of with GO. Gene ontology was investigated in 3 categories as a biological process (BP), cellular component (CC), and molecular function (MF).

PPI Network Construction and Hub Gene Screening

Interactions between common genes were analyzed with the STRING (http://string-db.org) online visualization tool. The PPI network was constructed with common genes with the highest confidence score of 0.9, and then data from the STRING database were analyzed in Cytoscape (version 3.9.2 https://cytoscape.org/) for visualization. Hub genes were identified with the Cytoscape cytoHubba plugin by scoring with MCODE functional modules and using the MCC algorithm. Selection criteria for MCODE functional modules are cutoff degree =2, node score cutoff =0.2, k-core=2, and max. depth=100.

RESULTS

Differentially Expressed miRNAs (DEMs) Analysis

Raw data of AML and CML patients, GSE142699 and GSE28825, were downloaded from the GEO database and analyzed separately with GEO2R. After the analysis, they were grouped according to fold change (FC) values and p<0.05, and and the gene numbers obtained in AML and CML in Venny were compared. Volcanoblot graphs of differently expressed miRNAs belonging to the groups are given in figure 1. There were 27 unique miRNAs whose expression increased and 161 decreased in the AML group. In the CML group, 52 unique miRNAs with increased expression and 122 unique miRNAs with decreased expression were found (Figure 2A-B).

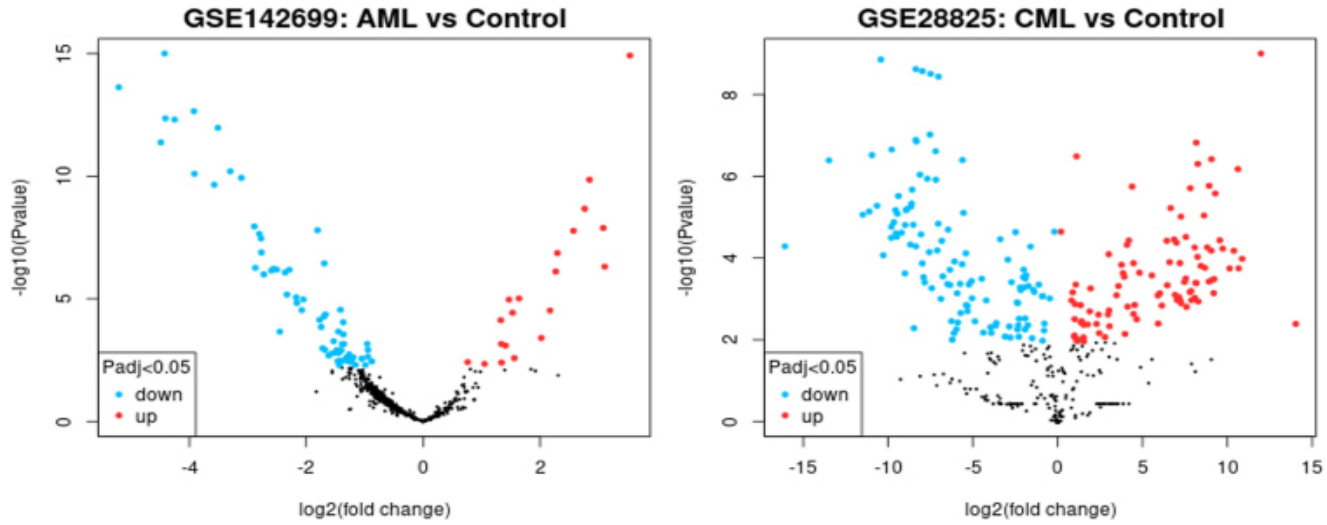
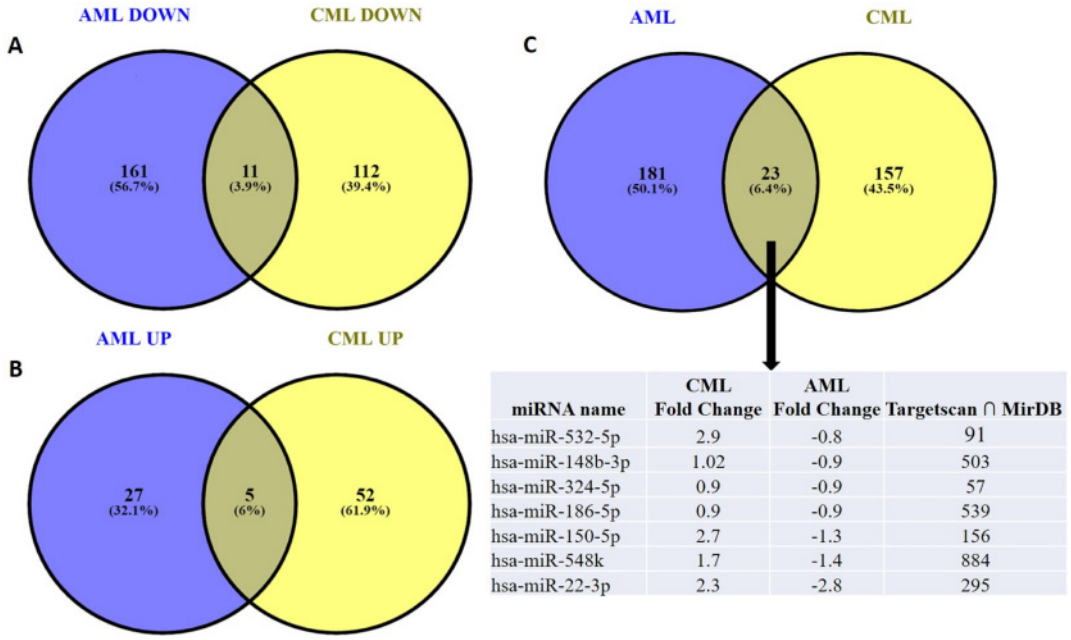


Figure 1. Volcano plot of differentially expressed genes based on GSE142699 and GSE28825, respectively



miRNA name	CML Fold Change	AML Fold Change	Targetscan ∩ MirDB
hsa-miR-532-5p	2.9	-0.8	91
hsa-miR-148b-3p	1.02	-0.9	503
hsa-miR-324-5p	0.9	-0.9	57
hsa-miR-186-5p	0.9	-0.9	539
hsa-miR-150-5p	2.7	-1.3	156
hsa-miR-548k	1.7	-1.4	884
hsa-miR-22-3p	2.3	-2.8	295

Figure 2. Using the Venny to obtain common miRNAs in AML and CML. A. Common downregulated miRNAs in AML and CML B. Common upregulated miRNAs in AML and CML C. Different expressions of miRNAs in AML and CML

A total of 23 common mirnas were found between the two groups (Figure 2C). After clustering analysis between the AML and CML groups, 11 miRNAs with decreased expression and 5 miRNAs with increased expression were found. 7 MiRNAs that were similar but differently expressed in the two groups were filtered out. 7 MiRNAs were found to be the same in the two groups but expressed differently, that is, increased in CML and decreased in AML (hsa-miR-532-5p, hsa-miR-186-5p, hsa-miR-148b-3p, hsa-miR-324-5p, hsa-miR-150-5p, hsa-miR-548k, hsa-miR-22-3p) (Figure 2C).

Prediction of Target Genes with DEMs

The target genes of the DEMs common to AML and CML were found using the targetscan and mirDB databases. Using both tools, common target genes were selected and analyzes were continued with these genes. A total of 2525 predicted target genes were found from 7 overlapping miRNAs.

GO ve KEGG Enrichment Analysis of Target Genes

Gene ontology and KEGG pathway analyzes were performed using the DAVID database for data enrichment on predicted target genes. It was revealed that differently expressed miRNAs affect 22 common signaling pathways, especially the pathways in cancer (108 genes), PI3K-Akt signaling (76 genes) and MAPK signaling (61 genes) (Table 1).

In GO analysis, 660 overlapping genes involved in many biological processes (BP) such as protein phosphorylation, cell division and regulation of transcription are involved. In molecular function (MF), 891 genes were found to be involved in RNA polymerase II transcription factor activity, metal ion binding, ATP binding, sequence-specific DNA binding, and sequence-specific double-stranded DNA binding processes. In terms of cellular components (CC), 290 is enriched in chromatin, receptor complex, RNA polymerase II transcription factor complex, and ribonucleoprotein complex processes. Other enriched processes are shown in Figure 3.

Construction of PPI Network

Target genes predicted by differentially expressed miRNAs were generated by the STRING database, and hub genes were selected using the network analyzer and MCODE interfaces of Cytoscape software to generate the target gene network map from the results from STRING. Genes with degree >25 TP53, EP300, MAPK1, SMAD3, PIK3CA, HDAC2, STAT3, KRAS, ESR1, CREBBP, NRAS, SOS1, MAPK14, ITGAV, FYN, PTEN, UBE2D1, HIF1A, NCOR1, CREB1, EIF4E, MTOR, emerged as important genes (Figure 4). Modules and genes with scores >4 after MCODE cluster analysis are given in the table (Table 3). As it is mostly associated with disease pathogenesis, nodes formed by hub genes in biological networks contain very important proteins.

Table 1. Major KEGG pathways related to miRNAs differentially expressed in AML and CML

	KEGG PATHWAYS	Count	PValue
1	hsa05200:Pathways in cancer	108	1.18E-09
2	hsa04151:PI3K-Akt signaling pathway	76	5.07E-08
3	hsa04010:MAPK signaling pathway	61	4.17E-06
4	hsa05206:MicroRNAs in cancer	57	2.95E-04
5	hsa04014:Ras signaling pathway	50	1.22E-05
6	hsa04510:Focal adhesion	45	1.32E-05
7	hsa04550:Signaling pathways regulating pluripotency of stem cells	37	2.99E-06
8	hsa04150:mTOR signaling pathway	35	1.37E-04
9	hsa04068:FoxO signaling pathway	34	7.57E-06
10	hsa04140:Autophagy - animal	32	2.25E-04
11	hsa04390:Hippo signaling pathway	31	0.003064
12	hsa04310:Wnt signaling pathway	29	0.02364
13	hsa01521:EGFR tyrosine kinase inhibitor resistance	28	7.43E-08
14	hsa04066:HIF-1 signaling pathway	28	6.88E-05
15	hsa04012:ErbB signaling pathway	25	1.73E-05
16	hsa04350:TGF-beta signaling pathway	24	2.83E-04
17	hsa05220:Chronic myeloid leukemia	23	2.52E-05
18	hsa04512:ECM-receptor interaction	23	2.75E-04
19	hsa04110:Cell cycle	23	0.027655
20	hsa05235:PD-L1 expression and PD-1 checkpoint pathway in cancer	21	0.002123
21	hsa05221:Acute myeloid leukemia	17	0.003
22	hsa04115:p53 signaling pathway	15	0.035079

Table 2. Hub genes resulting from the MCODE score for predicted target genes of DEMs.

Cluster	Score	Nodes	Edges	Hub Genes
1	10	10	45	CYCS, PPP3CA, PPP1R12A, WDR82, PPP1CC, PPP1R15B, PPP1R9B, PPP1CB, PPP3CB, PPP4R2
2	9.9	21	99	UBE2D1, HDAC2, SCML2, UBE2W, PHC1, PHC3, UBE2Q2, UBE2N, UBAP2L, UBE2E1, UBE2R2, UBE2B, PCGF5, COMMD3-BMI1, UBE2A, UBA6, BMI1, UBE2D3, SUZ12, UBE2J1, UBE2K
3	7	7	21	ADAMTS18, ADAMTS5, ADAMTS19, ADAMTS15, ADAMTS1, THSD7A, POFUT2
4	6	6	15	KLHL9, GAN, KBTBD8, KLHL3, KLHL13, ENC1
5	5.964	56	164	INO80D, ITGB8, NRIP1, IL6ST, CD28, CUL4A, YIPF6, YY1, PICALM, ITGAV, IKZF3, POU2F1, COPS5, TFRC, NUP35, ZEB1, NECAP1, DICER1, NRAS, IL6R, RORC, NUP107, SUMO2, IL2, PIK3C2A, RAN, SNX2, DDX6, RORA, KRAS, YWHAQ, CEBPD, KITLG, CPD, DCP2, PDGFA, HDAC4, GAB1, CREB1, NUP153, SORT1, SP1, MAPK14, ESR1, YWHAB, KIT, COPS7B, IGF1, ITGA11, ITGA5, EP300, ITGB6, INO80, SOS1, INO80E, AP4E1
6	5.6	6	14	CERS6, UGT8, UGCG, CERK, SGMS2, SGPP2
7	5.6	6	14	SNAP25, LIN7A, CASK, SYT1, RIMS1, LIN7C
8	4.8	6	12	WNT1, FZD3, WNT10B, FZD7, WNT5A, WNT4
9	4.5	5	9	PDS5A, NIPBL, PDS5B, STAG2, SMC3
10	4.444	28	60	DCP1A, TNRC6C, AR, RRAGD, MECP2, CREBBP, DYNC1I1, CNOT7, GTF2B, NCOA1, CNOT6L, MAX, CNOT6, PRKAA2, TOB1, UPF1, PRKAA1, DYNC1I2, PABPC1, TNRC6B, PRKAG2, CPEB3, DYNLL2, AGO4, EDC3, CNOT11, AGO1, KMT2A
11	4	4	6	CDK8, MED28, MED6, CDK19
12	4	4	6	TCP1, BBS2, BBS1, BBS7
13	4	4	6	ARMC8, RMND5A, WDR26, GID8

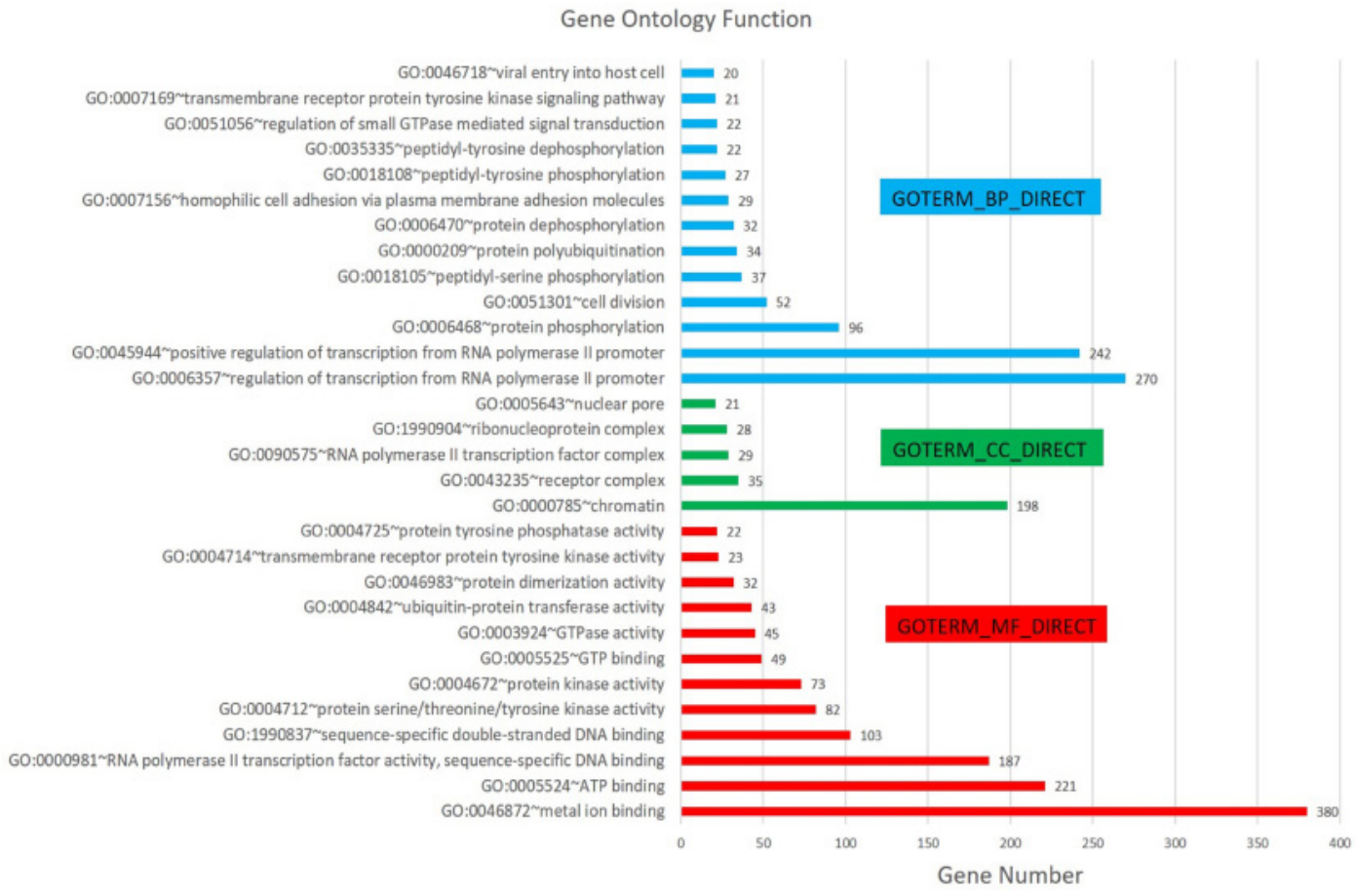


Figure 3. GO terms of down- and upregulated target genes of miRNAs, including BP, CC and MF

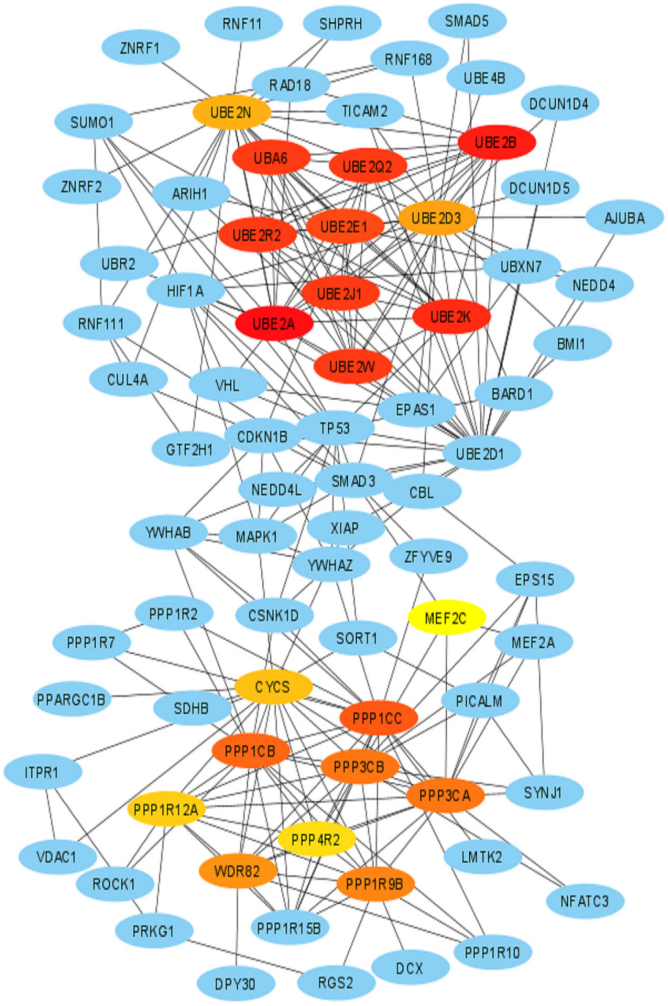


Figure 4. Cytoscape plug-ins cytoHubba analysis of hub genes after PPI analysis

DISCUSSION

Leukemia is a clonal malignant hematopoietic stem cell disease that affects both blood and bone marrow. Excessive cell proliferation of immature blood cells characterizes this disorder. Leukemia is the sixth most common disease and accounts for 4% of all cancers, according to research. Despite the scarcity of remedies, current therapeutic techniques have some drawbacks. As a result, new therapeutic alternatives must be discovered and developed. The identification of distinct cellular and molecular pathways involved in the etiology of leukemia is a crucial step in the quest for new treatment medicines (20).

MiRNAs have emerged as essential participants in the etiology of leukemia among numerous cellular and molecular targets. These molecules are epigenetic regulators that function as tumor suppressors or oncogenes in a variety of cancers, including leukemia. As a result, they can be used as diagnostic, prognostic, and therapeutic biomarkers at various stages of leukemia. Furthermore, growing evidence suggests that miRNAs could be used as markers in diagnosis and treatment in the early stages of the disease or following chemotherapy (21,22).

Using bioinformatics analyses, we identified several miRNAs that could be used as new differential therapeutic targets in the treatment of AML, and CML. MiRNAs have the potential to be used as therapeutic candidates in the treatment of leukemia patients. Creating novel miRNAs for AML, and CML to aid in diagnosis and prognosis, and also open the path for the creation of new treatment platforms for leukemia patients.

In this study, miRNAs between the two leukemia types were compared using AML, and CML data numbered GSE142699 and GSE28825. In the AML group, 161 unique miRNAs were found, 27 of which were increased in expression. In the CML group, 122 unique miRNAs were found with increased expression and 52 decreased expression. In common between AML and CML, 11 miRNAs with decreased expression and 5 miRNAs with increased expression were found. Interestingly, apart from these miRNAs that act as regulators between AML, and CML, 7 miRNAs that were similar but differently expressed in the two groups were detected. 7 differentially expressed miRNAs (hsa-miR-532-5p, hsa-miR-186-5p, hsa-miR-148b-3p, hsa-miR-324-5p, hsa-miR-150-5p, hsa-miR-548k, hsa-miR-22-3p) increased in CML and decreased in AML. GO and KEGG analyses of target genes of these miRNAs were found to be enriched in pathways in cancer, PI3K-Akt signaling, MAPK signaling, and miRNAs in cancer pathways.

miR-148 was associated with poor prognosis in previous studies (23), but it was emphasized that miR-148 inhibited proliferation of AML cells by disrupting CDK expression in AML and targeting miR-148 could be used in the effective treatment of AML (24). While miR-150 was associated with a good prognosis in both, it was found to be expressed differently in our study (23). While studies have shown increased expression of miR-532-5p in AML, it has not been previously identified in CML (25).

According to our findings, the level of miR-186 expression in AML was significantly lower than in normal controls and predicted a poor prognosis in AML patients. In CML cells, however, EAD box polypeptide 43 (DDX43) is overexpressed and DDX43 upregulates long non-coding RNA-H19, increasing cell proliferation and inhibiting apoptosis. miR-186 functions as a negative regulator of DDX43 in CML (26). It has an increased expression in our study and is used as a differential marker between AML and CML, associated with poor prognosis. The miR-548k and miR22-3p miRNAs have not previously been associated with AML and CML and can be suggested as a diagnostic and prognostic marker for AML and CML.

The predicted target genes of 2550 genes were found by 7 miRNAs that were differentially expressed between the two groups. After PPI analysis with these genes, TP53, EP300, MAPK1, SMAD3, PIK3CA, HDAC2, STAT3, KRAS, ESR1, CREBBP, NRAS, SOS1, MAPK14, ITGAV, FYN, PTEN, UBE2D1, HIF1A, NCOR1, CREB1, EIF4E, MTOR, 20 key

genes, including the NOTCH1 gene, emerged as important genes. These key genes, which include many tumor suppressors and oncogenes, show that they regulate biological mechanisms by DEMs in AML and CML.

CONCLUSION

In this study, we analyzed differential miRNA expression using high-throughput expression data from samples of AML and CML patients to identify miRNAs involved in therapeutic response. Our findings will be used to investigate the role of microRNAs in human malignant transformation and hematopoietic development in the future. Different miRNA signatures could also be possibilities for myeloid leukemia clinical diagnosis, prediction, and treatment. Differentially expressed miRNAs representing these two forms of myeloid leukemia will provide insights into CML and AML differentiation and myogenic regulatory control. The results revealed that the same miRNAs have different effects in AML and CML. The miRNAs and their target genes identified in this study are associated with various biological pathways, suggesting that they can serve as distinctive biomarkers in the diagnosis and treatment of the two types of leukemia.

Financial disclosures: *The authors declared that this study hasn't received no financial support.*

Conflict of interest: *The authors declare that they have no competing interest.*

Ethical approval: *The study was conducted with the decision of the local ethics center of Sivas Cumhuriyet University Non-Interventional Research Ethics Committee dated on 10.03.2021 and decision number 2021-03/27.*

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