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ORIGINAL ARTICLE

MicroRNAs and Their Targets Could Have a Crucial Role in Breast Cancer Drug Resistance: A Bioinformatics Research

MikroRNA'lar ve Hedefleri Meme Kanseri İlaç Direncinde Önemli Bir Role Sahip Olabilir: Biyoinformatik Bir Araştırma

[1]Murat Kaya

[1]Division of Medical Genetics, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Türkiye.

Correspondence

Murat Kaya, Division of Medical Genetics, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Çapa, Fatih/Istanbul, Türkiye.

E-Mail: kmurat@istanbul.edu.tr

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ABSTRACT

Objective: MicroRNAs(miRNAs) have been demonstrated to contribute to cancer development by playing essential roles in processes including proliferation, migration, invasion, and metastasis. One of the most serious issues in breast cancer (BC) is drug resistance. Recent research suggests that miRNAs may play a role in drug resistance. Using diverse datasets and in silico approaches, we focused on the BC/drug resistance/miRNA link in our study.
Material and Methods: GSE73736 and GSE71142 geo datasets (for miRNAs) and GSE162187 geo dataset (for genes) were obtained from the GEO database to detect differently expressed miRNAs and genes using the R software "LIMMA" package. Potential target genes of screened differentially expressed miRNAs (DE-miRNAs) were predicted using miRMap, miRTarbase, and miRNet tools. Differently expressed genes (DE-genes) were filtered and common DE-genes were identified via TCGA data and miRNet. Afterward, Enrichr, and Funrich tools were used to perform GO annotation and KEGG pathway enrichment analysis. KMplot and GEPIA2 web tools were utilized to investigate further hub miRNAs and genes' expression and prognostic effects.
Results: 3 miRNAs that were considerably downregulated and had prognostic significance in BC were identified using the criteria defined in the investigated geo datasets. MiR-586, which is expected to be more closely linked to BC, has been found to have the ability to target 5 genes involved in BC resistance to therapy. GO, KEGG, and survival analysis showed that the probable target genes of miR-586 could be closely connected to BC.
Conclusion: In this study, a comprehensive BC-drug resistance-miRNA-gene network was established and new targets for the treatment and prognosis of BC were revealed using bioinformatics data.

Keywords: Breast Cancer, Drug Resistance, microRNA, Bioinformatics

ÖZ

Amaç: MikroRNA'ların (miRNA'ların) hücre çoğalması, göç, istila ve metastaz gibi süreçlerde önemli roller oynayarak kanser gelişimine katkıda bulunduğu gösterilmiştir. Meme kanserinde (MK) en ciddi sorunlardan biri ilaç direncidir. Son araştırmalar, miRNA'ların ilaç direncinde rol oynayabileceğini öne sürmektedir. Çalışmamızda çeşitli veri setleri ve in silico yaklaşımlar kullanılarak MK/ilaç direnci/miRNA bağlantısı araştırılmıştır.
Gereç ve Yöntem: Geo veritabanından GSE73736 ve GSE71142 veri setleri (miRNA'lar için) ve GSE162187 veri seti (genler için) indirilerek R yazılımı "LIMMA" paketi aracılığıyla farklı şekilde ifade edilen miRNA'lar ve genler tespit edilmiştir. Farklı şekilde eksprese edilen miRNA'ların (DE-miRNA'lar) potansiyel hedef genleri, miRMap, miRTarbase ve miRNet araçları kullanılarak tahmin edildi. İfade düzeyi farklı olan genler (DE-genler) filtrelenmiş olup TCGA verileri ve miRNet'te ortak olan genler belirlenmiştir. Daha sonra GO ve KEGG ilişkilendirme analizleri Enrichr ve Funrich araçlarıyla yapılmıştır. Hub miRNA ve genlerin ekspresyon düzeyleri ve prognostik etkileri KMplot ve GEPIA2 web araçları kullanılarak araştırılmıştır.
Bulgular: MK'da önemli ölçüde ifadesi azalmış ve prognostik önemi olan 3 miRNA tespit edilmiştir. MK ile daha yakından bağlantılı olabileceği düşünülen miR-586'nın, MK'nın tedaviye direncinde rol oynayan 5 geni hedefleme potansiyeline sahip olduğu görülmüştür. GO ve KEGG analizlerinde, miR-586'nın olası hedef genlerinin MK ile yakından ilişkili olabileceği gösterilmiştir.
Sonuç: Bu çalışmada kapsamlı bir MK ilaç direnci-miRNA-gen ağları araştırılmıştır. Çalışmada biyoinformatik veriler kullanılarak MK'nın tedavi ve prognozuna yönelik yeni veriler ortaya çıkarılmıştır.

Anahtar kelimeler: Meme kanseri, İlaç direnci, mikroRNA, Biyoinformatik

Introduction

Breast cancer (BC) is the most frequent malignancy and the main cause of death related to cancer in women worldwide. Chemotherapy, hormonal therapy, and targeted therapy continue to be the first-line treatment options in BC. In clinical trials, some immunotherapeutic drugs showed promising efficacy (1). Nonetheless, drug resistance and the absence of biomarkers for predicting treatment response is a formidable obstacle in the treatment of BC (1). For more successful BC treatment, a deeper understanding of the probable molecular pathways underlying drug resistance is required urgently. MicroRNAs (miRNAs) are non-coding RNAs and they have 18-25 nucleotides in general (2, 3). Many studies showed that they function in a variety of critical biological processes including proliferation, differentiation, migration and metastasis (4, 5). Cross-talk between malignant cells and their surrounding environment is recognized to have a significant impact on tumor formation and resistance to cancer chemotherapy. miRNAs, which have an essential function in the etiology of human malignancies, are among the molecules involved

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in this pathological cross-talk (6). The link between miRNAs and genes is quite complicated. The addition of multiple components such as drug resistance in this intricate structure complicates this process even further. Rapid advances in bioinformatics, particularly in recent years, have made a significant contribution to the understanding of the complicated mechanisms of these biomolecules (7-10).

Using several bioinformatics approaches, this study evaluated miRNAs and genes that may be related to treatment resistance in BC. Following that, the impacts of selected miRNAs and genes on biological processes were uncovered using a variety of in silico tools and literature.

Material and Methods

Identification of Differently Expressed miRNAs Associated with Drug Resistance in Breast Cancer

GSE73736 (miRNA microarray was performed on tissue samples obtained from 10 drug-resistant BC patients and 10 drug-sensitive individuals) and GSE71142 (miRNA microarray was performed using tissue samples from 5 drug-resistant cases and tissue samples from 5 drug-sensitive cases) geo datasets have been obtained from the geo database to find miRNAs (DE-miRs) associated with BC resistance to chemotherapy. GEO2R was used for analyzing differentially expressed miRNAs.

In silico validation of the connection between DE-miRs and BC, as well as a review of the literature

The overlapping miRNAs in the two datasets (GSE73736 and GSE71142) were compared to the BC-related miRNAs in The Cancer Genome Atlas (TCGA) using KMplot (11). Furthermore, the drug resistance link of overlapping DE-miRNAs was investigated in PubMed by entering the words "relevant miRNA name drug, drug resistance, cancer, disease". Next, the kmPlot tool, which was utilized with TCGA data, was used to evaluate the link between overlapping miRNAs and BC overall survival.

Potential target genes of the chosen miRNA were identified in silico.

The selected miRNA's potential target genes were identified using the web tools miRTarbase, miRNet, and miRMap (12).

The Identification of Differently Expressed mRNAs Relevant to Drug Resistance in BC

GSE162187 (22 patients tissues, before and after chemotherapy) geo dataset was obtained from geo database and analyzed using GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/) to find drug resistance-related mRNAs (DE-Genes) in BC.

In silico verification of DE-Genes and BC relationship

DE-Genes in BC were identified in the TCGA database via the GEPIA2 web tool (13). Then, overlapping genes were identified between GSE162187 DE-Genes and TCGA DE-Genes with the genes shown as potential targets of the selected DE-miR in miRNet 2.0 (14), miRTarbase (15) and miRMap.

Survival analysis of selected DE-Genes

GEPIA2, which was constructed using TCGA data, was used to perform survival analysis regarding the selected genes.

KEGG ve GO analysis

Enrichr (16) and FunRich (17) performed the GO functional annotation and KEGG pathway enrichment evaluation for the selected DE-genes.

Statistical Analysis

Functional enrichment evaluations were carried out using publicly available tools (Enrichr. FunRich and GEPIA2). Overall survival was estimated using the Kaplan-Meier technique, and differences were determined using the log-rank test. P-value<0.05 was established as the statistical cut-off for overall survival evaluation and assessment of enrichment in tools.

Table 1: Overlapping miRNAs between GSE73736 and GSE71142 datasets

miRNAs	GSE73736			GSE71142		
	P-value	LogFC	Regulation	P-value	LogFC	Regulation
hsa-miR-586	0.008114	-2.393	Down	0.00209	-4.589	Down
hsa-miR-587	0.002157	-3.878	Down	0.00446	-4.952	Down
hsa-miR-2681-3p	0.014868	-2.549	Down	0.00724	-3.370	Down
hsa-miR-3927-3p	0.023943	3.732	Up	0.00726	5.449	Up
hsa-miR-4472	0.012622	-1.73	Down	0.00861	-2.294	Down
hsa-miR-4771	0.008397	3.222	Up	0.01585	3.923	Up
hsa-miR-4264	0.02729	3.337	Up	0.01684	4.030	Up
hsa-miR-4277	0.042948	2.952	Up	0.01802	3.064	Up
hsa-miR-620	0.003741	-4.752	Down	0.02168	-4.316	Down
hsa-miR-4633-3p	0.010691	3.808	Up	0.02358	4.804	Up
hsa-miR-619	0.031135	-2.701	Down	0.03378	-4.079	Down
hsa-miR-200c-3p	0.026268	1.702	Up	0.03428	2.660	Up
hsa-miR-4422	0.033616	2.961	Up	0.03776	2.160	Up
hsa-miR-15b-3p	0.04193	-2.935	Down	0.04024	-3.427	Down
hsa-miR-17-3p	0.00929	-2.99	Down	0.04694	-3.187	Down

Results

DE-miRs identification

Between the GSE73736 and GSE71142 datasets, 15 overlapping miRNAs were identified (logFC>1.5 and p<0.05). Among the 15 overlapping miRNAs in the datasets, the miRNAs miR-586, miR-4771, and miR-4422 were found to be present in the TCGA BC data (Figure 1(A) and Table 1).

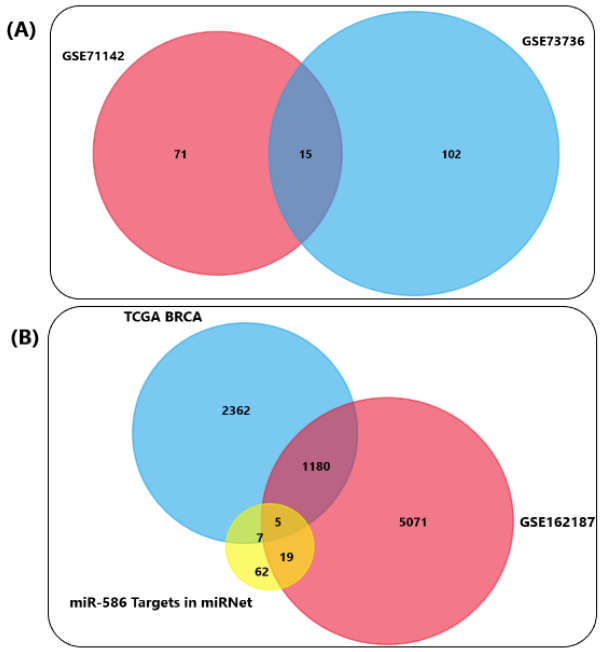

Figure 1: **(A)** Overlapping miRNAs and **(B)** overlapping genes between used datasets in the present study.

Identifying the link between DE-miRs and BC

The literature analysis revealed that there was very little knowledge available on miR-4771 and miR-4422, which are found in the GSE73736-GSE71142 datasets and the TCGA BC data. The associations of miR-587, miR-4277, miR-620, and miR-619 miRNAs with various tumors have been confirmed, and these miRNAs have been linked to drug resistance in several cancers (Table 2).

Table 2. PubMed research results of overlapping miRNAs between GSE73736-GSE71142 datasets and drug resistance relations. (Four miRNAs have been associated with drug resistance)

MiRNA	Drug	Target	Disease	Reference
hsa-miR-587	5-fluorouracil	PPP2R1B	Colorectal Ca	(36)
miR-4277	Sorafenib	CYP3A4	HCC	(37)
miR-620	Gemcitabine	DCTD	BC (TNBC)	(38)
miR-619	Cisplatin	ATXN3	OSCC	(39)

Selected miRNA and Potential Target Genes

The screening to identify the possible target genes of miR-586, one of the DE-miRs, revealed that miR-586 may target 93 genes (Figure 2).

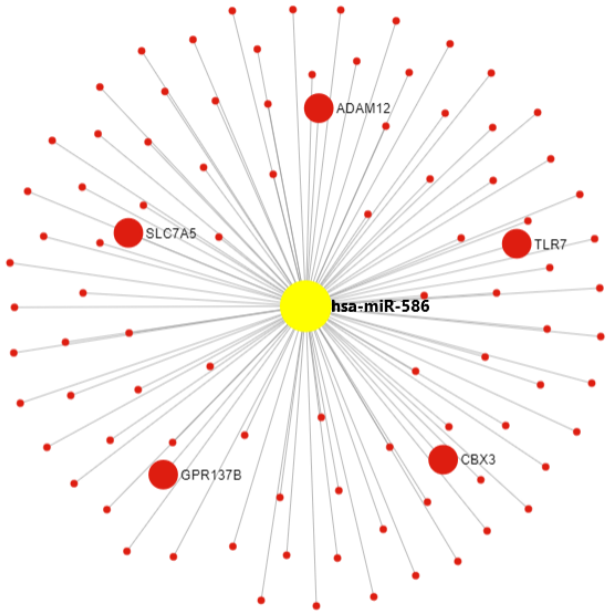

Figure 2: miR-586 and its 93 potential targets including *GPR137B, ADAM12, SLC7A5, TLR7* and *CBX3* in miRTarbase and miRNet. (Red circles represent genes and yellow circles represent miR-586)

DE-Genes Identification

In the GSE162187 geo dataset, 6275 genes matched the logFC>0.4 and p<0.05 criterion. It was found that 3554 genes in TCGA BC samples met the logFC>2 and p<0.05 criterion as seen in Figure 1(B). It was found that 12 genes overlapped between miR-586's targets and TCGA BC data. It was assumed that because miR-586 was observed to be downregulated in the GSE73736 and GSE71142 datasets, its target genes should be overexpressed in BC. As a result, because 7 of the 12 possible miR-586 target genes were downregulated in TCGA, they were eliminated from the analysis (Table 3). It was determined that there were five common genes (GPR137B, ADAM12, SLC7A5, TLR7, CBX3) among possible in silico target genes of miR-586, GSE162187 dataset, and TCGA BC data (and these five genes were overexpressed in BC). These genes are subjected to enrichment analysis (Figure 3, Figure 4).

Enrichment Analysis Results

Selected potential target genes of miR-586 were associated with many cancers, including BC (Figure 5).

Effect of Overlapping miRNAs on BC Overall Survival

Among the 15 overlapping miRNAs between GSE73736 and GSE71142 datasets, miR-586, miR-4771, and miR-4422 miRNAs were observed to affect overall survival of BC TNBC (Figure 6).

Effect of selected genes on BC overall survival

Although it was observed that GPR137B, ADAM12, TLR7, and CBX3 gene had no significant effect on BC overall survival, SLC7A5 had a significant effect on BC overall survival (Figure 7).

Table 3: Overlapping genes between the potential targets of miR-586 found miRNet and TCGA BC data

Gene name	Description	Regulation In TCGA
ACSL4	acyl-CoA synthetase long chain family member 4	Down
MYC	MYC proto-oncogene, bHLH transcription factor	Down
PLP1	proteolipid protein 1	Down
GPR137B	G protein-coupled receptor 137B	Overexp.
TNS1	Tensin 1	Down
ZFP36	ZFP36 ring finger protein	Down
ADAM12	ADAM metallopeptidase domain 12	Overexp.
SLC7A5	solute carrier family 7 member 5	Overexp.
CBX3	chromobox 3	Overexp.
TLR7	toll like receptor 7	Overexp.
ERRFI1	ERBB receptor feedback inhibitor 1	Down
ITIH5	inter-alpha-trypsin inhibitor heavy chain 5	Down

Down: Down-regulation, Overexp.: Overexpression

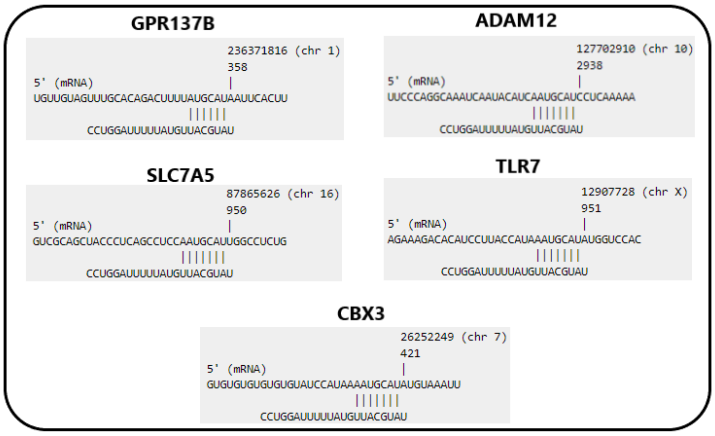

Figure 3: Sequence matching of miR-586 and selected target genes.

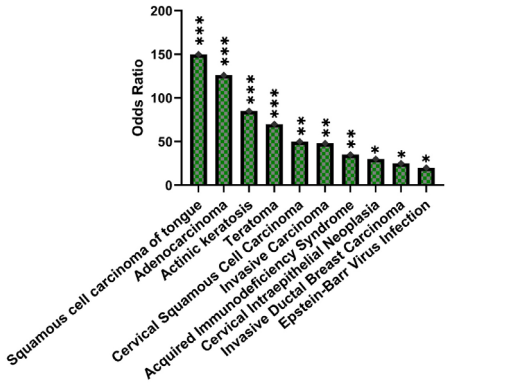

Figure 5: The relation between selected miR-586 potential targets and diseases. Selected genes have been associated with many cancers including BC (***: p<0.0001, **: p<0.001, *: p<0.01).

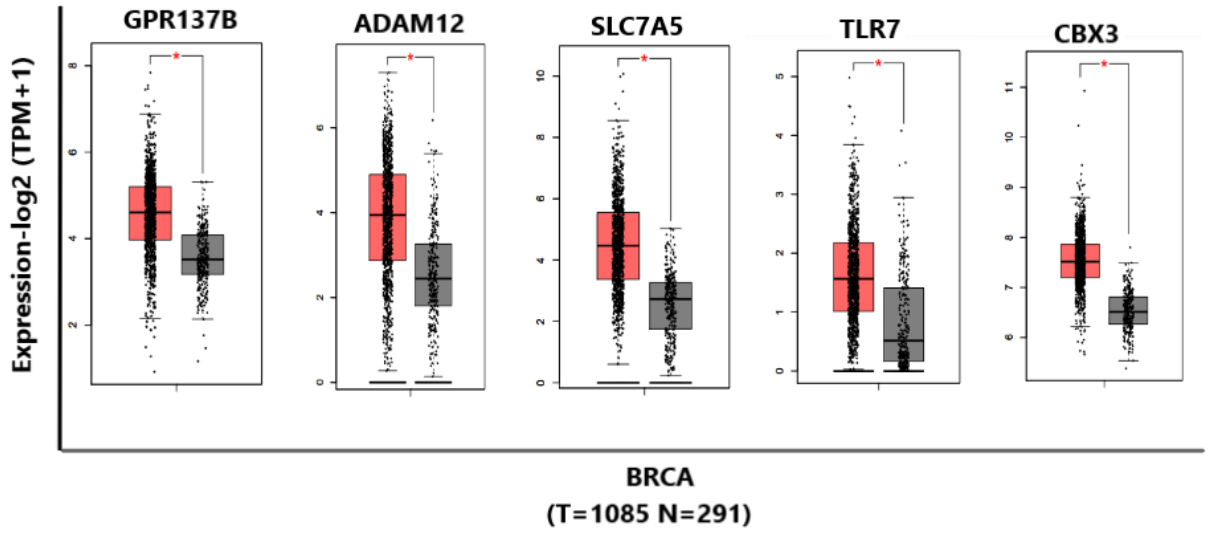

Figure 4: Expression levels of 5 selected target genes of miR-586 in TCGA BC patient samples. (T: tumor, N: Normal, TPM: Transcript Per Million)

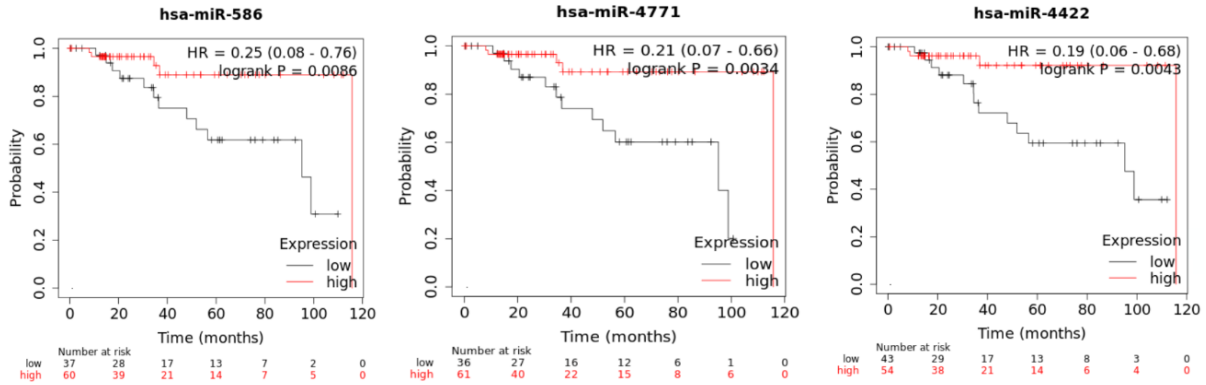

Figure 6: Survival effects of overlapping miRNAs in triple-negative breast cancer (TNBC). (based on 300 patients in TCGA) (HR: Hazard Ratio)

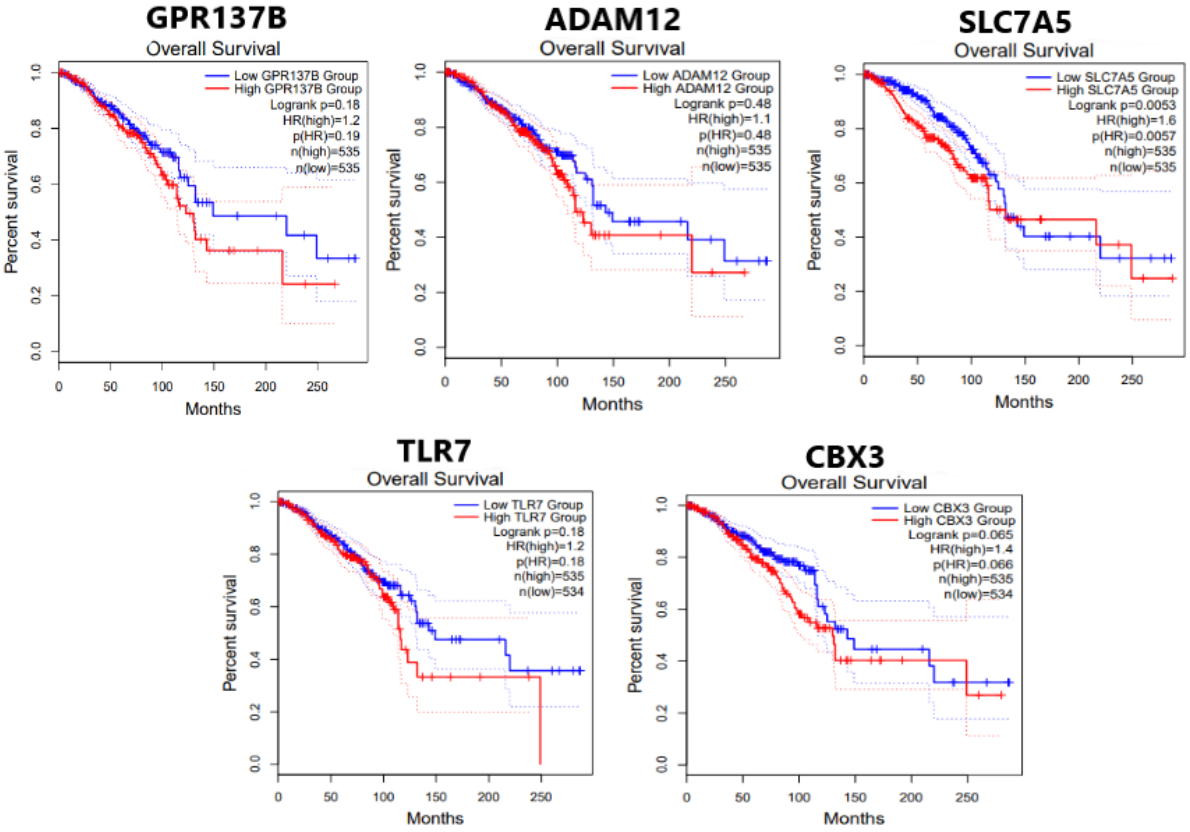

Figure 7: Overall survival analysis of selected genes according to TCGA BC data

Discussion

Cancer drug resistance is a well-known condition that occurs when cancer becomes resistant to pharmaceutical therapy. Anticancer drug resistance is caused by a range of causes, including mutations in DNA and/or epigenetic modifications and several other molecular variations. Resistance to drugs and the insufficient efficacy of therapy with drugs are the causes of up to 90% of cancer-related deaths (18). Unfortunately, many traditional chemotherapy drugs are not targeted to cancer cells and have considerable toxicity. Targeted drug therapies have contributed to great progress in the fight against cancer in recent years. However, while such drugs have impressive results during early treatment, drug resistance may pose a significant challenge in completely eliminating cancer (19). Therefore, identifying molecules related to resistance to drugs and elucidating the underlying pathways is critical.

Using bioinformatics data, this study found many miRNAs and genes that may be related to drugs resistance in BC. Among them, miR-587, miR-4277, miR-620, miR-619 have been shown as a part of the drug resistance mechanism in several cancers (Table 2). Although there is little knowledge about miR-4277 in the literature, the other three miRNAs have been

linked to a variety of malignancies, including BC. For example, miR-587 was identified as having a role in the initiation and progression of TNBC, a subtype of BC in a study using a bioinformatics approach by A et al. (20). MiR-620 has been observed to promote tumor radioresistance by targeting HPGD (21). Tumor-derived exosomal miR-619 has been reported to promote tumor angiogenesis and metastasis via RCAN1.4 (22).

According to the present study findings, another miRNA that we consider to be associated with drug resistance in BC is miR-586. The miRNAs miR-586, miR-4771, and miR-4422 were found effective in the overall survival of TNBC patients in survival analysis (Figure 6). To our knowledge, there is only one study in PubMed regarding the relationship between miR-4771 and cancer. In the relevant study, it was shown that the rs3737589 polymorphism in the TP73-AS1 gene may be associated with the colorectal cancer process by affecting the binding of miR-4771 (23). miR-586 has been reported to be implicated in cancer processes via multiple genes in tumors ranging from BC to gastric cancer (24, 25). According to our results, there are five genes (GPR137B, ADAM12, SLC7A5, TLR7, and CBX3) that are distinctive in resistance to drugs in BC. These five genes, which are putative miR-586 target genes, have also been linked to a variety of malignancies, including BC: For instance, in a study it has been demonstrated that knockdown of GPR137 in HepG2 cells leads to cell cycle arrest in the G0/G1 phase and G2/M phase and induces cell apoptosis (26). The ADAM12 gene has been reported to be a prognostic factor in ER-positive BC (27). According to the study of Wang et al. (28) it was underlined that selective ADAM12-L suppression could optimize the 5-FU-based treatment of BC, hence minimizing BC recurrence in patients. The SLC7A5 gene has also been associated with BC in many studies (29, 30). For example, a study highlighted that SLC7A5 is a potential prognostic biomarker and may be a valuable therapeutic target in BC patients (31). The SLC7A5 gene has also been associated with resistance to various chemotherapeutics. For example, in Retinoblastoma, SLC7A5 has been found to increase chemosensitivity by directly inhibiting it through the tumor suppressor miR-184 (32). In a study conducted using BC patient's tissues and cell lines, it has been evaluated that the LAT1 (SLC7A5) gene plays a role in drug resistance and may be a new therapeutic target against chemotherapy resistance in luminal-type BC (33). TLR 7/8 agonists have been found to reverse oxaliplatin drug resistance in colorectal cancer by directing myeloid-derived suppressor cells to tumor-killing M1 macrophages (34). CBX3, another possible target gene of miR-586, is also one of the important genes associated with drug resistance. For instance, Sang et al. (35) showed that the CBX3 (HP1γ) gene contributes to cervical cancer cells being sensitive to cisplatin via UBE2L3.

Conclusion

In our study, many miRNAs and genes that might be associated with drug resistance in BC were identified using bioinformatics data. Prominent miRNAs are miR-587, miR-4277, miR-620, miR-619 and miR-586. Notable genes in this regard are GPR137B, ADAM12, SLC7A5, TLR7, and CBX3, among the potential target genes of miR-586. Our study results may guide new studies using in vitro and in vivo methods.

Ethics Committee Approval: Open Geo Datasets were used to conduct the study. Ethics committee approval is not necessary since these data are from bioinformatics analysis and no clinical or experimental study has been performed.

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

Acknowledgments: None declared by the authors.

Author Contributions: All parts of the study prepared by MK

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