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Exploring miRNA profile associated with cisplatin resistance in ovarian cancer cells

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ABSTRACT

Ovarian cancer is a common and lethal malignancy among women, whereas chemoresistance is one of the major challenges to its treatment and prognosis. Chemoresistance is a multifactorial phenomenon, involving various mechanisms that collectively modify the cell's response to treatment. Among the changes that arise in cells after acquiring chemoresistance is miRNA dysregulation. Here, this study aimed to identify miRNAs expression changes related to cisplatin resistance in ovarian cancer cells. The miRNA expression profiles of a cisplatin-sensitive A2780 cell line and two cisplatin-resistant cell lines, A2780cis and SK-OV-3, were analyzed using PCR array and qPCR. Accordingly, the miRNAs that were differentially expressed were further investigated to identify their biological functions and the target pathways using Gene Ontology (GO) annotation and KEGG pathway analyses. In order to evaluate the clinical significance of the differentially expressed miRNAs, survival analysis was carried out using expression data for ovarian cancer patients available in the Kaplan-Meier (KM) plotter database. The current work demonstrates that Nine miRNAs were found to be upregulated in cells resistant to cisplatin. Clearly, these miRNAs have functions in cell death/survival related processes and treatment response. They may also target pathways involved in treatment response like PI3K-Akt, pathway in cancer and MAPK. Interestingly, High expression of hsa-miR-133b, hsa-miR-512-are, hsa-miR-200b-3p, and hsa-miR-451a is related to poor overall survival in patients diagnosed with ovarian cancer. Our findings suggest that hsa-miR-133b, hsa-miR-512-5p, hsa-miR-200b-3p, and hsa-miR-451a are good candidates for future studies aimed to establishing functional links and exploring therapeutic interventions to overcome cisplatin resistance.

1. Introduction

Ovarian cancer is one of the most deadly cancers among women worldwide [1]. Primarily, the development of resistance to chemotherapeutic agents hinders ovarian cancer treatment [2]. Cisplatin was the first-line drug recognized for ovarian treatment [3,4]. Cisplatin exerts its cytotoxic effect by inducing DNA damage and triggering apoptosis, eliminating damaged cells [5,6]. However, tumor cells can acquire a complex network of mechanisms to evade cisplatin-induced cell death and survive [7,8]. In this regard, one of the potential mechanisms that might regulate cell fate, and contribute to cisplatin resistance, is epigenetic changes [9–11]. MicroRNAs (miRNAs), which are small non-coding RNAs regulate gene expression by binding to complementary sequences in the untranslated regions or coding regions of target mRNAs, leading to their degradation or translational repression or activation [12]. Remarkably, miRNAs have been implicated in various aspects of cancer biology, including cell proliferation, apoptosis, metastasis, and drug resistance [13]. Moreover, miRNAs can regulate biological pathways that are involved in DNA damage signaling and response to cisplatin [14–17]. However, it's important to acknowledge that miRNA dysregulation alone cannot fully explain the complexity of chemoresistance, given its multifactorial phenomenon involves numerous molecular and cellular mechanisms, including changes in the tumor microenvironment, DNA repair pathways, and immune interactions [18]. Although an analysis of biological pathways regulated by miRNAs identified several potential miRNA-mRNA pairs as possible targets that may contribute to the complex network of cisplatin resistance, establishing a causal link between the identified targets and

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chemoresistance requires functional validation. It is also necessary to generalize the findings using a wide spectrum of cell lines, in addition to in vivo models, to elucidate the role of tumor microenvironments on these potential targets or any immune interactions. Here, the present study is an exploratory and primarily based on in vitro models investigated the miRNA expression changes related to cisplatin in the ovarian cancer cell lines A2780, A2780cis, and SK-OV-3. Moreover, gene ontology and pathway analyses were carried out to identify biological functions of miRNAs that were differentially expressed, and the target genes and pathways that could regulate the cellular tolerance of cisplatin. Additionally, survival analysis was used to validate the possible clinical significance of the identified miRNAs in ovarian cancer patients. Identifying these molecular alterations lays the groundwork for future studies aimed at establishing functional links and exploring therapeutic interventions to overcome resistance.

2. Methods

2.1. Cell culture

Human ovarian cancer cell lines A2780, cisplatin-resistant variant A2780cis, and SK-OV-3 were purchased from the European Collection of Authenticated Cell Cultures (England). A2780 and A2780cis cell lines were cultured in RPMI-1640 medium supplemented with 10 % FBS, 2 mM L-glutamine, 0.1 mg/ml of penicillin/streptomycin. For A2780cis resistance maintenance, culture media was supplemented with 1 μM of cisplatin (Sigma-Aldrich, USA) every three passages. Whereas SK-OV-3 cell line was grown in McCoy's 5a containing 15 % FBS, 2 mM glutamine, and 0.1 mg/ml of penicillin/streptomycin. Cell cultures were maintained in a humidified atmosphere with 5 % CO_2 at 37 °C (Binder, Germany).

2.2. RNA extraction and cDNA synthesis

Total RNAs, including the miRNAs fraction from A2780, A2780cis and SK-OV-3 cells, were extracted using the miRNA Easy Mini Kit (Qiagen, Germany). cDNA was synthesized from 2 μg total RNA using miScript II RT kit (Qiagen, Germany) for 1 h at 37 °C.

2.3. Gene expression analysis of miRNAs by qRT-PCR

Expression of 96 miRNAs was profiled in A2780 and A2780cis ovarian cancer cells to identify differentially expressed miRNAs related to cisplatin resistance using MiScript miRNA PCR array and qPCR. MiScript miRNA PCR Array (Human Apoptosis miRNA PCR Array: MIHS-114Z, Qiagen, Germany), which profile 84 miRNAs involved in apoptosis—either as anti-apoptotic, pro-apoptotic, or regulators of targets related to apoptosis. The selection of the Human Apoptosis miRNA PCR Array was based on its extensive coverage of miRNAs involved in various pathways that may contribute to resistance mechanisms. This array overlaps with other cancer-related arrays, such as Cancer Pathway Finder array, the cancer stem cell array, and the ovarian cancer array, making it highly comprehensive. The MiScript miRNA array and miScript SYBR® Green PCR Kit (Qiagen, Germany) were used according to the manufacturer's manuals. The assay was run on StepOne plus™ Real-Time PCR System (Applied Biosystems, USA). Then Ct values of studied miRNAs were determined using StepOne software (Applied Biosystems, USA). Ct values of all miRNAs were collected at the same threshold and baseline levels to maintain consistency between samples. Ct values of miRNAs undetermined by the instrument were set up at 40 to use for the statistical analysis. The PCR array data and the relative miRNAs expression were analyzed using the web-based data analysis software by Qiagen (http://pcrdataanalysis.sabiosciences.com/mirna/arrayanalysis.php). Confirmation of the miRNA's expression changes obtained from array experiments was done using quantitative real-time PCR. For each sample, total RNA was extracted and reverse transcribed, as mentioned above. Relative expression fold changes for miRNAs in A2780cis were studied using StepOne™ Real-Time PCRand miScript SYBR® Green PCR Kit. Fold changes were calculated using the ΔΔCt method with SNORD95 as a reference gene. All reactions were run in triplicate.

Furthermore, gene expression of miRNAs that was confirmed to be changed in A2780cis cells were also studied in SK-OV-3 ovarian cancer cell line, which was used as another model for chemoresistance using qPCR as mentioned above. In addition, the expression changes of 12 miRNAs correlated with resistance were in A2780cis cells and SK-OV-3 compared to A2780 using qPCR as mentioned above. Fold changes were calculated using the ΔΔCt method with SNORD95 as a reference gene. All reactions were run in triplicate.

The primers used in confirmation experiments and other qPCR experiments are listed in Table 1.

2.4. Gene ontology analysis

To develop gene ontology for differentially expressed miRNAs in cisplatin-resistant ovarian cancer cells, over-representation analysis in the miEAA software was used [19]. Differentially expressed miRNAs were loaded into miEAA software and were indexed by the statistic generated from DESeq2. Representations of GO were generated for biological processes, and molecular functions.

Table 1
Primer sequences used for miRNA quantitation using qPCR in this study.

miRNA Name	Seq (5′-3′)
SNORD95	TGATGACCCCAACATGCCATC
hsa-let-7c-3p	CTAGTCGCTGTACAACCTTCTAG
hsa-let-7c-5p	GTCGTGAGGTAGTAGGTTGTATG
hsa-let-7e-5p	GTCTGAGGTAGGAGGTTGTATAGTT
hsa-let-7g-5p	TGGTGAGGTAGTAGTTTGTACAGTT
hsa-miR-122-5p	TGGAGTGTGACAATGGTGTTTG
hsa-miR-1285-3p	TCTGGGCAACAAAGTGAGACCT
hsa-miR-1299	CTTCTGGAATTCTGTGTGAGGGA
hsa-miR-133a-3p	TTTGGTCCCCTTCAACCAGCTG
hsa-miR-133b	TTTGGTCCCCTTCAACCAGCTA
hsa-miR-134-5p	TGTGACTGGTTGACCAGAGGGG
hsa-miR-1-3p	GACTCTGTGGAATGTAAAGAAGTATGTAT
hsa-miR-143-3p	TGAGATGAAGCACTGTAGCTC
hsa-miR-146a-5p	GCTGAGAACTGAATTCCATGGGTT
hsa-miR-15b-5p	ACTAGCAGCACATCATGGTTTAC
hsa-miR-181a-5p	AACATTCAACGCTGTCGGTGAGT
hsa-miR-193a-5p	GGTCTTTGCGGGCGAGATG
hsa-miR-193b-5p	CGGGGTTTTGAGGGCGAGAT
hsa-miR-200a-3p	ATCTAACACTGTCTGGTAACGATGT
hsa-miR-200b-3p	CAGTAATACTGCCTGGTAATGATGA
hsa-miR-200c-3p	ATAATACTGCCGGGTAATGATGGA
hsa-miR-203a-3p	CTGAGTGAAATGTTTAGGACCACTAG
hsa-miR-205-5p	CTTCATTCCACCGGAGTCTG
hsa-miR-20b-3p	ACTGTAGTATGGGCACTTCCAG
hsa-miR-20b-5p	CGCAGGTCAAAGTGCTCATAG
hsa-miR-210-3p	CTGTGCGTGTGACAGCGGCTGA
hsa-miR-212-3p	TAACAGTCTCCAGTCACGGCC
hsa-miR-21-5p	CCTAGCTTATCAGACTGATGTTGA
hsa-miR-23a-3p	ATCACATTGCCAGGGATTTCC
hsa-miR-27a-3p	TTCACAGTGGCTAAGTTCCGC
hsa-miR-29b-3p	GTAGCACCATTTGAAATCAGTGTT
hsa-miR-300	CTATACAAGGGCAGACTCTCTCT
hsa-miR-31-5p	AGGCAAGATGCTGGCATAGCT
hsa-miR-338-3p	GTCCAGCATCAGTGATTTTGTTG
hsa-miR-451a	GCAAACCGTTACCATTACTGAGTT
hsa-miR-491-5p	AGTGGGGAACCCTTCCATGAGG
hsa-miR-497-5p	CAGCAGCACACTGTGGTTTGT
hsa-miR-512-5p	ACTCAGCCTTGAGGGCACTTTC
hsa-miR-625-3p	CAGACTATAGAACTTTCCCCCTCA
hsa-miR-625-5p	CAGGGGGAAAGTTCTATAGTCC
hsa-miR-642a-3p	AGACACATTTGGAGAGGGAACC
hsa-miR-642a-5p	GTCCCTCTCCAAATGTGTCTTG
hsa-miR-708-5p	AAGGAGCTTACAATCTAGCTGGG

2.5. Pathway analysis

To identify the cellular pathways and targets regulated by the differentially expressed miRNAs in cisplatin-resistant ovarian cancer cells, DIANA-miRPath v3.0 program [20] was used. Nine miRNAs that showed significant changes in gene expression were selected as inputs in the DIANA tool, which performs pathway enrichment analysis based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways [21–23].

2.6. Kaplan-Meier survival analysis

To evaluate the clinical significance of the identified miRNAs in ovarian cancer patients, survival analyses were performed using data for patients diagnosed with ovarian cancer available in the KMplot database [24]. The overall survival (OS) was analyzed for 486 patients after samples were categorized based on the expression (high vs. low) for each miRNA identified in this study. Thus, Kaplan-Meier survival curves were created with hazard ratios (HR), confidence intervals (CI), and log-rank *p*-values. HR values greater than 1 indicate poor outcome and hazard increase while HR values below 1 indicate good outcome and hazard reduction, whereas HR values equal to 1 indicate no differences in hazard between groups. *p*-values <0.05 were considered statistically significant.

2.7. Statistics

GraphPad Prism (GraphPad Software, USA) was used for graphical figure generation and statistical analysis. Data are presented as the mean ± SD. Statistical significance was indicated as follows: * = $P \leq 0.05$, ** = $P \leq 0.01$, *** = $P \leq 0.001$.

3. Results

3.1. Identification of differentially expressed miRNAs in cisplatin-resistant ovarian cancer cells

In this study we used three ovarian cancer cell lines; A2780, A2780cis and SK-OV-3 cell lines which are commonly used as models for ovarian cancer: A2780 cells are considered a cisplatin sensitive cell line (IC_{50} = 5 μg/ml), whereas A2780cis and SK-OV-3 (IC_{50} = 30, 40 μg/ml) cell lines were more resistant to cisplatin compared with A2780 cells as previously reported [25].

MiScript miRNA PCR Arrays were used to analyze 84 miRNAs expression in the cell lines A2780, and A2780cis. Results revealed that a total of 30 miRNAs showed a difference in their expression levels between A2780 and A2780cis cell lines (Supplementary File 1). The changes were considered when the fold change values were greater than or equal to 2 or less than 0.5. The expression changes of the 30 miRNAs selected from array experiment were studied to confirm changes in A2780cis and investigated in the cisplatin-resistant cell line SK-OV-3 relative to A2780 cells using qPCR. Only 7 miRNAs had similar patterns of significant expression changes in the cisplatin-resistant A2780cis, and SK-OV-3 cell lines in comparison to sensitive cell line A2780 (Supplementary File 2). The miRNAs and their fold changes in the resistant cells were: hsa-miR-133b (10.53 and 3.695), hsa-miR-203a-3p (5.805 and 8.665), hsa-miR-512-5p (15.87 and 5.7), hsa-miR-21-5p (2.25 and 30.8), hsa-miR-708-5p (3.54 and 3.885), hsa-miR-451a (6.5 and 5.5) and hsa-miR-15b-5p (5.5 and 9.5) in A2780cis and SK-OV-3 cells, respectively. In addition, the relative expression changes of 12 miRNAs correlated with resistance were also studied using qPCR in A2780cis and SK-OV-3 cells compared to A2780 (Supplementary File 3). The results showed that only hsa-miR-200b-3p and hsa-miR-625-5p were co-expressed and significantly upregulated in resistant cell lines A2780cis and SK-OV-3. The expression fold change of the hsa-miR-200b-3p was 3.457 and 6.975 in the resistant cells A2780cis and SK-OV-3, respectively, compared to the sensitive cell line A2780. Similarly, the expression of hsa-miR-625-5p was upregulated by 8.95 and 10.5 fold in A2780cis and SK-OV-3, respectively, compared to the sensitive cell line A2780. The results of all significant changes from miRNA expression studies in the resistant A2780cis and SK-OV-3 cells are displayed in Fig. 1.

3.2. Gene Ontology Enrichment Analysis of Differentially Expressed miRNAs

To understand the probable functions of differentially expressed miRNAs in the development of cisplatin resistance in ovarian cancer cells, Gene Ontology enrichment analysis was performed. The results shown in Fig. 2, indicated that the most significantly enriched GO terms in the biological process category included stress activated signaling cascades (Stress Activated MAPK Signaling Cascade and Stress Activated Protein Kinase Signaling Cascade), Apoptosis Regulation (Regulation of Intrinsic Apoptotic Signaling Pathway, Negative Regulation of Intrinsic Apoptotic Signaling Pathway, Intrinsic Apoptotic Signaling Pathway, Apoptotic Signaling Pathway, Negative Regulation of Apoptotic Process), DNA Damage Response and Cell Signaling. In the molecular function category, the most significant enrichments were found in kinase binding, purine ribonucleotide binding, and signaling receptor binding.

3.3. Differentially expressed miRNAs may modulate multiple signaling pathways in cancer

The involvement of the miRNAs related to cisplatin resistance in the studied ovarian cancer cell lines in the biological pathways was analyzed with a specific focus on pathways involved in cancer development and progression. Hsa-miR-133b, hsa-miR-203a-3p, hsa-miR-512-5p, hsa-miR-21-5p, hsa-miR-708-5p, hsa-miR-451a, hsa-miR-15b-5p, hsa-miR-200b-3p and hsa-miR-625-5p were used as input in DIANA-miRNAPath tool. The miRNA targets were pooled together and linked to KEGG to identify the enrichment of these targets in various biological pathways. The analysis showed 41 cellular pathways regulated by the candidate miRNAs as factors influencing resistance (Supplementary File 3). Supplementary File 3 demonstrates all the target cellular pathways and the number of genes for each miRNA target. The pathways that were affected by all candidate miRNAs and involved in cancer development and progression included the TGF-beta signaling pathway, Proteoglycans in cancer, PI3K-Akt signaling pathway, AMPK signaling pathway, FoxO signaling pathway, MAPK signaling pathway, Pathways in cancer, ErbB signaling pathway, and Focal adhesion, respectively according to p-values. Table 2 shows these target cellular pathways, and the number of genes targeted in them and p-values. The Pathways in cancer was the pathway that was affected by all miRNAs and had the most significant number of genes targeted by these miRNAs (97 mRNAs) with a p-value of 0.001192, followed by the PI3K-Akt signaling pathway and MAPK signaling pathway which were targeted by candidate miRNAs with 93 and 70 mRNAs genes and p-values of 0.000118 and 0.001058, respectively.

When studying the role of miRNAs targets as influencing factors in resistance in Pathways in cancer (KEGG), which are 97 mRNAs (Fig. 3), the candidate targets, such as *AKT3*, *MAPK8*, *TGFBR2*, *CCND2,* etc., were found that interfere in pathways that may determine cellular resistance to cisplatin because they are key genes in signaling pathways, such as the cell cycle, p53 signaling pathway, MAPK signaling pathway, TGF-β signaling pathway, and the PI3K-Akt signaling pathway. These pathways regulate essential cellular functions such as apoptosis, proliferation, differentiation, migration, and metastasis formation, which makes this pathway a significant influence on chemoresistance development. Moreover, PI3K-Akt signaling pathway was found to be regulated by miRNAs that were identified to be correlated to cisplatin resistance in ovarian cancer cells. 93 mRNAs were found as candidate

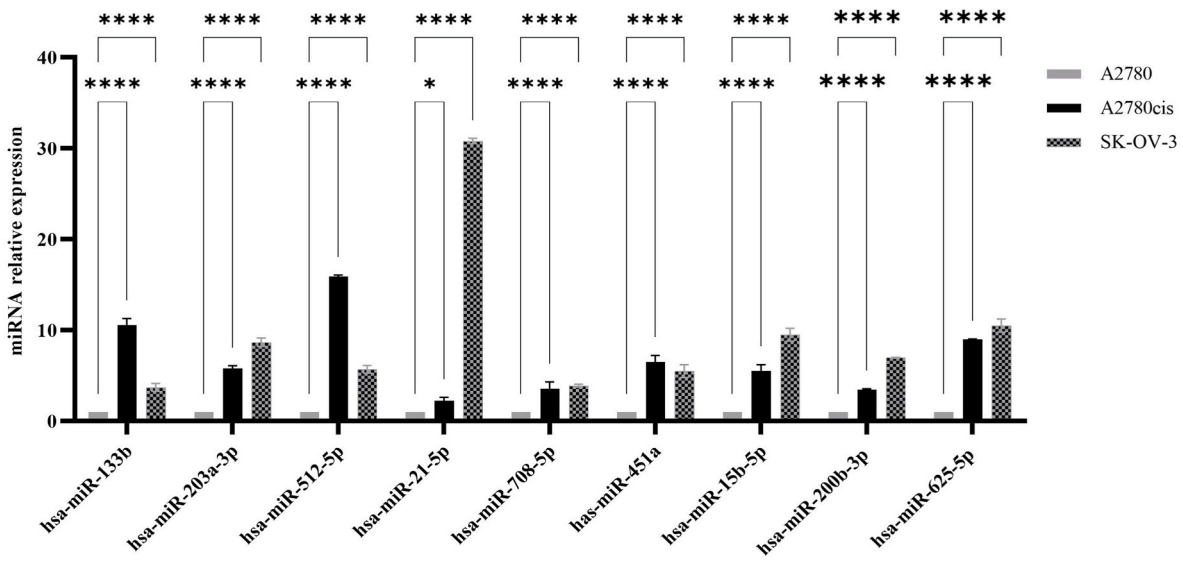


Fig. 1. miRNA expression changes in cisplatin-resistant cell lines A2780cis and SK-OV-3, compared with the sensitive cell line A2780 using qPCR. The cisplatin-resistant A2780cis and SK-OV-3 cells had significantly higher expression of seven miRNAs compared to the cisplatin-sensitive A2780 cell line. The expression levels were normalized to SNORD95 and relative to A2780 cells.

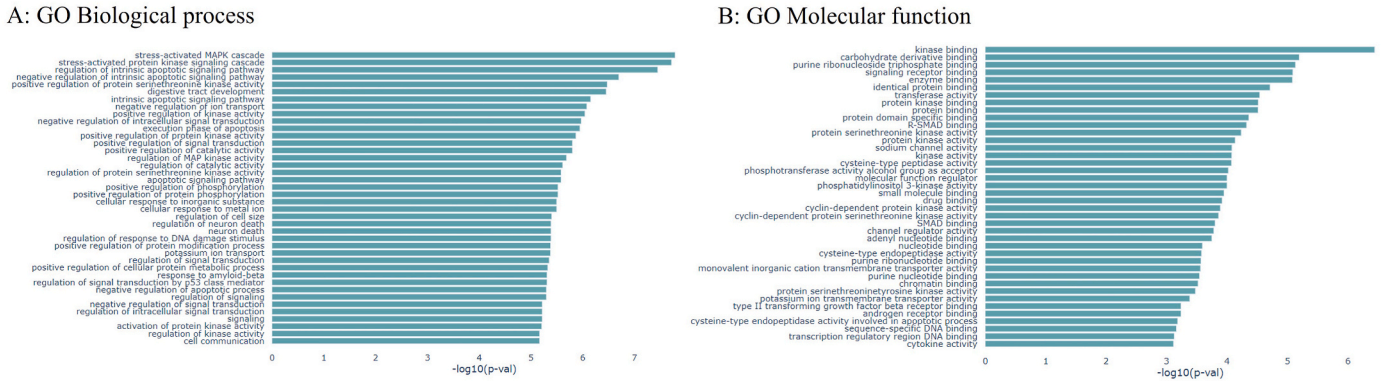


Fig. 2. Gene Ontology Enrichment Analysis of Differentially Expressed miRNAs in cisplatin-resistant cell lines. A: Top twenty enriched GO terms in the biological process category. B: Top twenty enriched GO terms in the molecular function category.

Table 2
KEGG pathways affected by differentially expressed miRNAs.

KEGG pathway	log p-value	#Genes
TGF-beta signaling pathway	5.77E-08	31
Proteoglycans in cancer	2.68E-05	62
PI3K-Akt signaling pathway	0.000118	93
AMPK signaling pathway	0.000637	40
FoxO signaling pathway	0.000809	43
MAPK signaling pathway	0.001058	70
Pathways in cancer	0.001192	97
ErbB signaling pathway	0.004919	28
Focal adhesion	0.013715	54

targets and were key genes in this pathway, such as *AKT3*, *MAP2K1*, *EIF4B*, *IKBKB*, *CDK6,* etc., which regulated the cell cycle, apoptosis, cell proliferation, NFκB signaling pathway, p53 signaling pathway (Fig. 4). Moreover, the influence of miRNAs on the MAPK signaling pathway was examined, and 70 target mRNAs were predicted and found to be key genes in this pathway, such as *AKT3*, *CRK*, *MAP3K1*, and *MAPK8,* respectively, etc. (Fig. 5). These targets may play crucial roles and affect the cell cycle, apoptosis, cell proliferation, and p53 signaling pathway. These findings suggest that differentially expressed miRNAs may contribute to cisplatin resistance in ovarian cancer cells.

3.4. Kaplan-Meier survival analysis

To determine the clinical significance of the identified miRNAs in patients with ovarian cancer, Kaplan-Meier survival curves for ovarian cancer patients was generated using the KM plotter database. Fig. 6 shows Kaplan-Meier survival curves with HR values for hsa-miR-133b, hsa-miR-512, hsa-miR-200b, and hsa-miR-451a. Results indicate that patients with elevated expression levels of hsa-miR-133b, hsa-miR-512, hsa-miR-200b, and hsa-miR-451a have shorter survival times compared to patients with lower expression levels. These findings suggested that high expression of these four miRNAs correlated with poor overall survival of ovarian cancer patients. In contrast, survival data for hsa-miR-15b and hsa-miR-625 showed that high expression of these two miRNAs correlates with better overall survival of ovarian cancer patients (Fig. 7). For hsa-miR-708, hsa-miR-21 and hsa-miR-203a, no statistically significant differences in overall survival were found between groups with different expression levels (Fig. 7). Kaplan-Meier survival data suggested that hsa-miR-133b, hsa-miR-512, hsa-miR-200b, and hsa-miR-451a are possible prognostic biomarkers and may have influence the treatment response and progression of ovarian cancer patients.

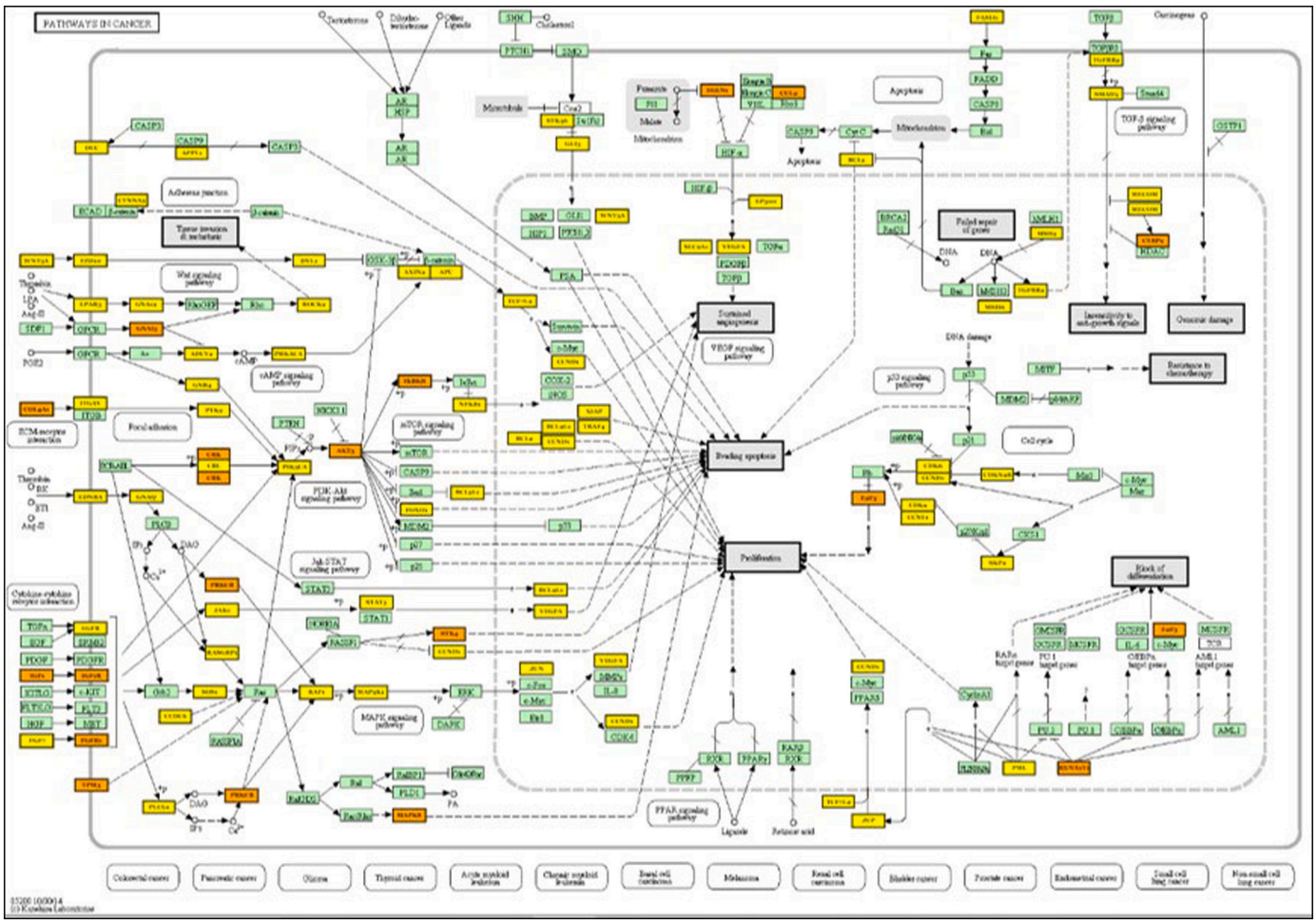


Fig. 3. Effect of differentially expressed miRNAs related to cisplatin resistance on Pathways in cancer. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis was used to identify nine differentially expressed miRNAs' putative targets (highlighted by different colors). The yellow color indicates the target genes that are targeted by one of the miRNAs, the orange color indicates the target genes that are targeted by more than one miRNA, and the green color indicates the rest of the pathway genes that are not targeted by the studied miRNAs.

4. Discussion

Cisplatin is widely used for the treatment of many types of cancer, including ovarian cancer [3,4]. However, a major challenge that limits its clinical efficacy is the development of chemoresistance [26]. Cancer cells develop complex mechanisms to evade cisplatin-induced cytotoxicity. This can lead to alteration of treatment response pathways and can it can also dysregulate the expression of miRNAs [27,28]. Moreover, several studies investigated the expression of miRNAs and linked the expression changes with resistance to chemotherapy [29–32]. Previous research has studied the role of miRNAs in ovarian cancer, focused on their association with acquired therapy resistance, or to correlate or predict treatment outcome in ovarian cancer. Moghbeli et al. comprehensively reviewed and categorized numerous studies, summarizing their findings based on the molecular mechanisms by which miRNAs modulate treatment response [28]. A lot of research has employed experimental models particularly A2780, A2780DDP, and SKOV3 to investigate the impact of specific miRNAs on cisplatin treatment response. For instance, overexpression studies demonstrated that miR-519d, miR-155, miR-708, miR-34c, miR-200b, miR-200c, miR-29, and miR-1305 increase cisplatin cytotoxicity in A2780 or SKOV3 cells [33–39]. These studies identified gene targets for each miRNA, providing mechanistic insights into their role in chemoresistance. Another major approach to study miRNAs' role in cisplatin treatment response is comparing specific miRNA expression between cisplatin-sensitive and cisplatin-resistant variants of ovarian cancer cell lines using qPCR. MiRNAs such as miR-449a, miR-152, miR-185, miR-186, miR-497, miR-34c, miR-130a, miR-770-5p, miR-338-3p, miR-454, and miR-34a-5p have been identified as dysregulated miRNAs in resistant cell lines, including SKOV3/DDP and A2780/DDP, compared to their parental counterparts [40–49]. Manipulating the expression of these miRNAs was shown to alter cisplatin sensitivity, often through validation of their mRNA targets related to apoptosis, cell proliferation, or drug efflux pathways. Additionally, wide profiling studies have provided a broader view of miRNA dysregulation in cisplatin resistance by using microarray platforms miRNAs and chips LNA technology. These profiling efforts often highlighted miRNAs as part of larger networks, further advancing the understanding of their contribution to treatment response. Collectively, these studies lay the foundation for investigating miRNAs as potential biomarkers or therapeutic targets. Kumar et al. performed miRNA profiling for 1500 known miRNAs, using LNA technology on just two cell lines: A2780 and its cisplatin resistant variant cell line A2780/CP70, identifying 11 dysregulated miRNAs. Only 5 miRNAs were validated using qPCR and were further analyzed for putative targets using KEGG and IPA pathway analysis. The study highlighted miRNAs hsa-miR-193b, hsa-miR-642, hsa-miR-625, hsa-miR-20b, and hsa-let-7c as possible regulators for MAPK signaling, TGF-β signaling pathways, and others [50]. Zou et al. utilized web-available microarray datasets from GEO for A2780/A2780 DDP and identified nine dysregulated miRNAs in A2780 DDP. Only

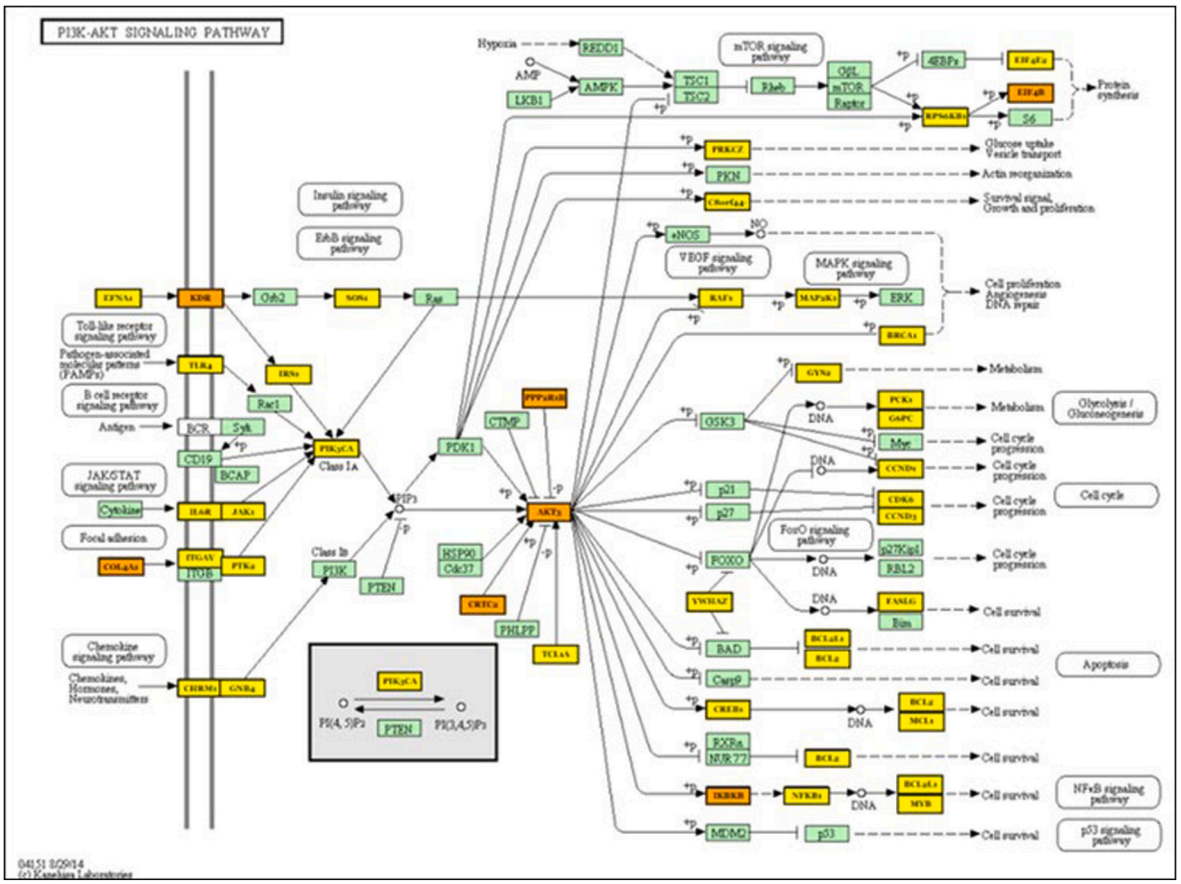


Fig. 4. Effect of differentially expressed miRNAs related to cisplatin resistance on PI3K-Akt signaling pathway. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis was used to identify nine differentially expressed miRNAs' putative targets (highlighted by different colors). The yellow color indicates the target genes that are targeted by one of the miRNAs, the orange color indicates the target genes that are targeted by more than one miRNA, and the green color indicates the rest of the pathway genes that are not targeted by the studied miRNAs.

seven genes were validated in lab using SKOV3 cell line versus its cisplatin resistant variant cells (SKOV3/DDP) and A2780 cell line versus its cisplatin variant resistant cells (A2780/DDP) cells using real-time quantitative PCR. The results showed that miR-199a-5p, miR-199a-3p, miR-199b-3p, miR-645, miR-335, miR-18b, and miR-141 were consistently dysregulated in both SKOV3/DDP and A2780/DDP cells, corroborating the findings with the web-available microarray data. This study also provided a comprehensive overview of potential pathways involved in drug resistance [51]. Another study performed miRNA expression profiling using miRNA arrays on A2780, A2780CIS and A2780CP20 cells, identifying over 6000 differentially abundant miRNAs. They validated 12 miRNAs using qPCR and identified miR-18a-5p as a tumor suppressor using functional assays in vitro and in vivo. This miRNA was suggested as a therapeutic target for cisplatin-resistant ovarian cancer [52]. Other profiling study on A2780/DDP and A2780 cells identified 32 differentially expressed miRNAs. Four miRNAs (miR-146a, miR-130a, miR-374a, and miR-182) were selected for further study. Their involvement in cisplatin resistance was explored through regulation of MDR1 and PTEN gene expression [53]. Other microarray analysis for A2780 and A2780CP20 identified 320 genes differentially expressed in A2780CP20 (cisplatin resistant) vs. A2780 (cisplatin sensitive) cells, they verified that miR-21 levels are upregulated in A2780CP20 using RT-PCR. They also overexpressed miR-21 and noticed the impact on cisplatin sensitivity and the JNK-1/c-Jun [54]. These previous studies provide a detailed miRNAs profiling and further validated the expression changes for selected group in cisplatin resistant variant compared to the parental cell line.

Our study explores changes in miRNA expression patterns in vitro models, specifically A2780 and its cisplatin-resistant derivative A2780cis. We then extended our investigation to another ovarian cancer cisplatin-resistant model, SK-OV-3, to identify miRNAs with a common pattern of dysregulation. This approach ensures that the identified miRNAs are associated with the cisplatin resistance phenomenon rather than cell-specific changes. Our research aligns with literature that focuses primarily on miRNA expression profiling and correlative analyses to provides a valuable background to nominate miRNAs as chemoresistance related and prognostic biomarkers markers in ovarian and other types of cancers [14,32,55–58]. Moreover, we conducted gene ontology and pathway analyses to uncover the biological functions of these differentially expressed miRNAs and the target genes and pathways that could regulate cellular tolerance to cisplatin. Additionally, we performed survival analysis to validate the potential clinical applicability of these miRNAs using data from ovarian cancer patients. While our approach builds on existing methodologies, the integration of cross-model validation, survival data and comprehensive pathway analysis enhances the depth and clinical applicability of our findings.

MiRNA expression profiling in the cisplatin-sensitive A2780 cell line and cisplatin-resistant cells lines A2780cis and SK-OV-3 reveled that hsa-miR-133b, hsa-miR-203a-3p, hsa-miR-512-5p, hsa-miR-21-5p, hsa-miR-708-5p, hsa-miR-451a, hsa-miR-15b-5p, hsa-miR-200b-3p and hsa-miR-625-5p were overexpressed in A2780cis and SK-OV-3 cells compared to the sensitive cells A2780. Gene Ontology (GO) analysis was carried out to determine the characteristics and probable functions of the 9 differentially expressed miRNAs in the ovarian cancer cells acquired cisplatin resistance. Interestingly, the most meaningful finding was that these miRNAs were involved in major biological processes and

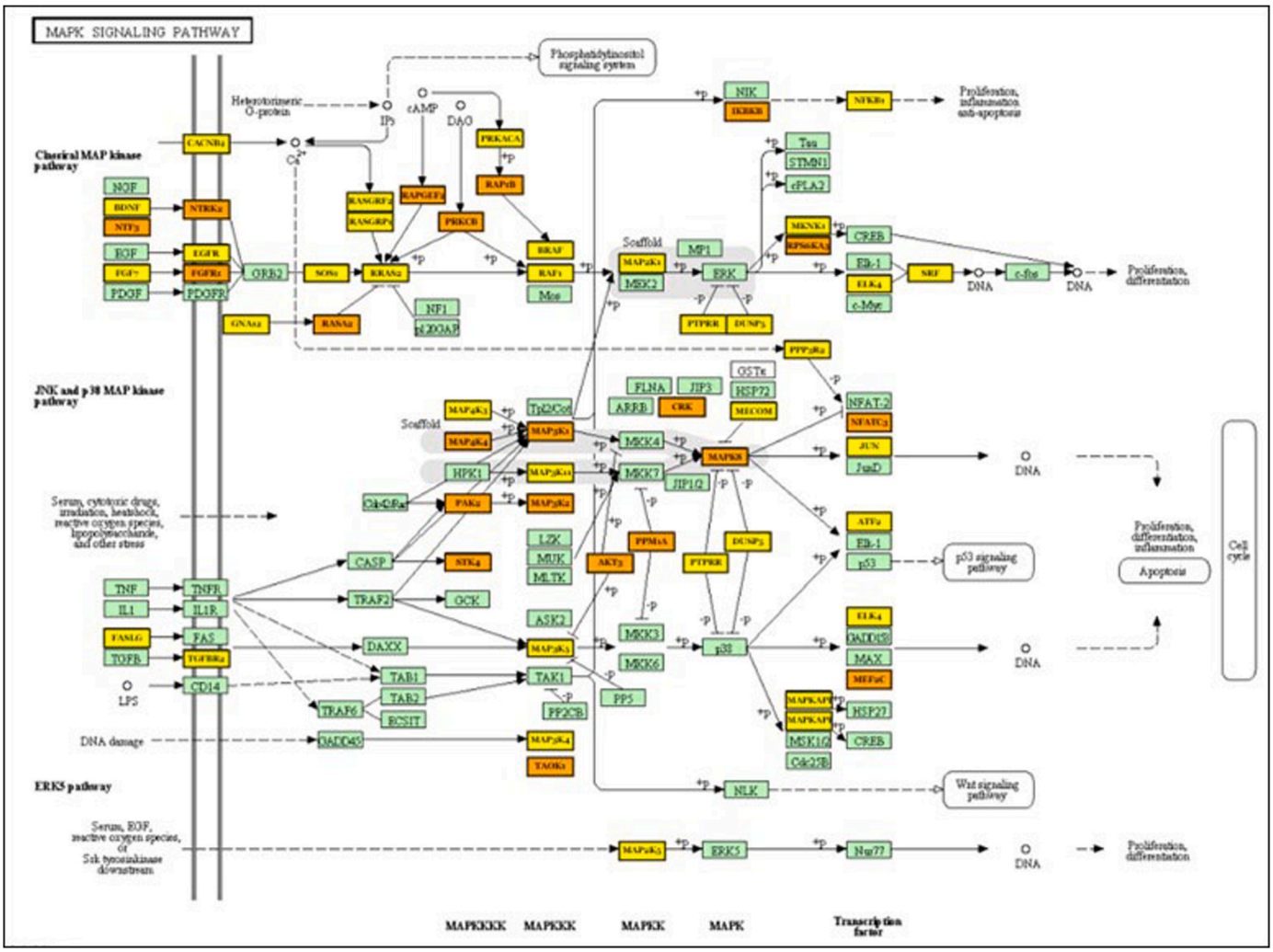
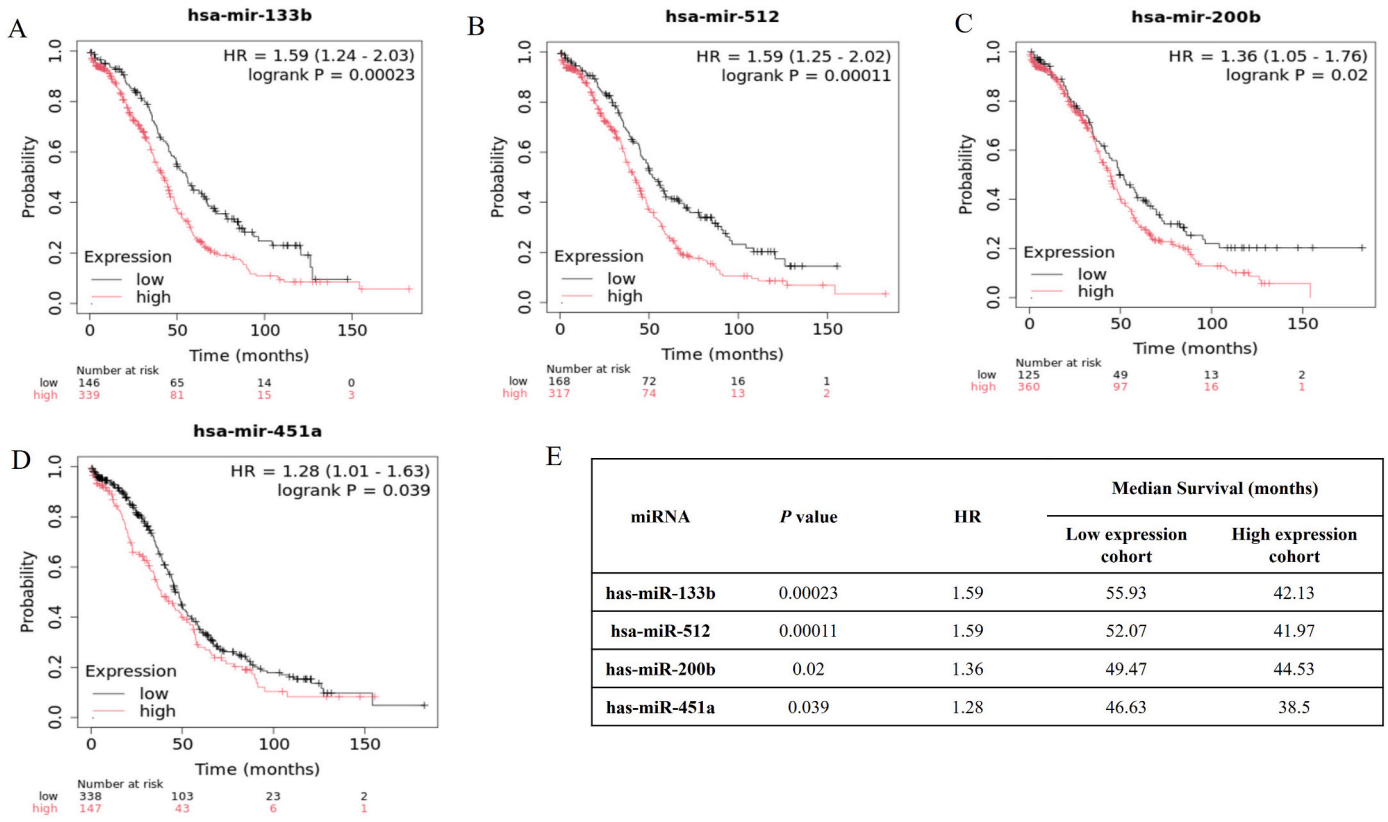


Fig. 5. Effect of differentially expressed miRNAs related to cisplatin resistance on MAPK signaling pathway. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis was used to identify nine differentially expressed miRNAs' putative targets (highlighted by different colors). The yellow color indicates the target genes that are targeted by one of the miRNAs, the orange color indicates the target genes that are targeted by more than one miRNA, and the green color indicates the rest of the pathway genes that are not targeted by the studied miRNAs.

functional categories related to the cellular response to cytotoxic therapy and cell death/survival signaling, such as stress activated signaling, apoptosis regulation, DNA damage response signaling, kinase binding, and purine ribonucleotide binding. The dysregulation of these processes and functions was found to be important characteristic for ovarian cancer development and chemoresistance [59,60].

We next analyzed the involvement of the upregulated miRNAs in biological pathways with a specific focus on pathways involved in cancer development and chemoresistance. Specifically, pathway analysis revealed the involvement of these miRNAs several important cellular pathways, including TGF-beta signaling pathway, Proteoglycans in cancer, PI3K-Akt signaling pathway, AMPK signaling pathway, FoxO signaling pathway, MAPK signaling pathway, Pathways in cancer, ErbB signaling pathway, and Focal adhesion. Notably, several studies have shown an enrichment of miRNAs regulating the PI3K-Akt signaling pathway in the development of cell resistance to cisplatin and other therapies in ovarian cancer [16,61–63]. Moreover, this enrichment has also been observed in other chemotherapy-resistant cancers [64]. This pathway regulates many cellular processes, such as metabolism, protein synthesis and proliferation [64,65]. In fact, the PI3K-Akt pathway is fundamentally involved in developing cancers, including ovarian cancer [63,66]. Furthermore, impaired gene expression in this pathway has been linked to poor prognosis [67]. Clearly, *PIK3* and *AKT* are key members of this pathway that directly or indirectly regulate cell cycle progression, cellular growth, and apoptosis [68]. Our results indicated that resistance-related miRNAs in ovarian cancer cell lines might directly or indirectly regulate genes essential in this pathway, such as *PI3K* and *AKT3* the core of the PI3K-Akt pathway. In addition, resistance-related miRNAs target genes involved in protein synthesis in the mTOR pathway, and proteins that regulate cell cycle such as CCND1/3. They can also target apoptosis-regulating proteins like MCL1 and BAD, and other pathways such as the p53 pathway and NFκB pathway that are important in determining cell fate. Results of the pathway analysis indicated that the MAPK signaling pathway may be regulated by miRNAs associated with cisplatin resistance in ovarian cancer. The MAPK signaling pathway acts as a critical pathway involved in cancer cell proliferation, differentiation, apoptosis, and drug resistance [69,70]. Previous studies have shown that the MAPK signaling pathway is activated in diverse types of tumors, including ovarian cancer [71,72]. MAPK signaling pathway consists of four sub-pathways: ERK, JNK, BMK, and p38 [70]. Alteration in MAPK pathway has been linked with cisplatin resistance in different cancer cells, including ovarian cancer cells [73–75]. MAPKs can either activate or inhibit apoptosis, depending on the type of cell and stimuli. Previous studies identified cisplatin as an activator of MAPK pathway in many cancer cells, but this stimulation either prevents or interferes with the induction



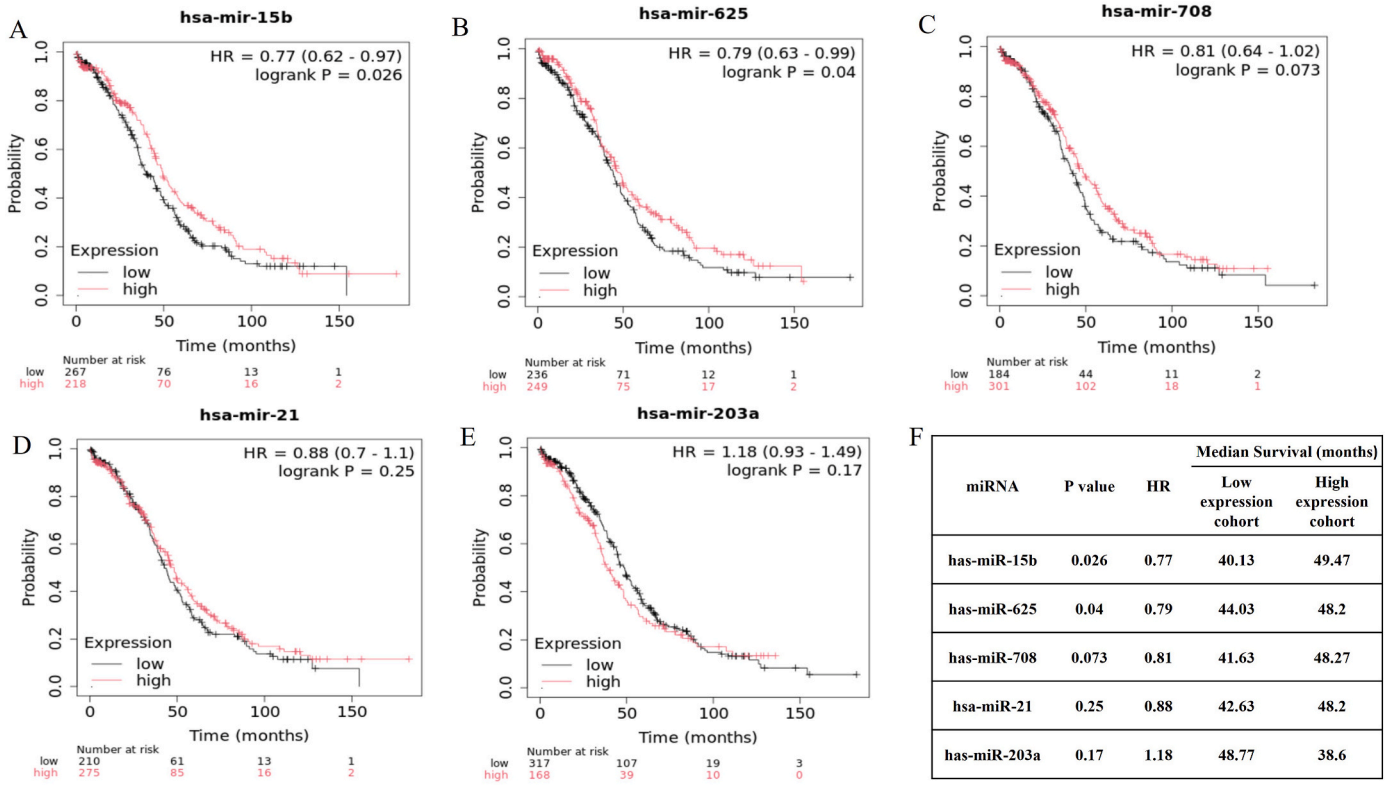
E

miRNA	*P* value	HR	Median Survival (months)	
			Low expression cohort	High expression cohort
has-miR-133b	0.00023	1.59	55.93	42.13
hsa-miR-512	0.00011	1.59	52.07	41.97
has-miR-200b	0.02	1.36	49.47	44.53
has-miR-451a	0.039	1.28	46.63	38.5

Fig. 6. Kaplan–Meier (KM) overall survival analysis for ovarian cancer patients based on the expression of hsa-miR-133b, hsa-miR-512, hsa-miR-200b, and hsa-miR-451a. Median survival for 486 ovarian cancer patients was analyzed after categorizing samples into high (red) or low (black) expression groups for each miRNA (A–D). Median survival in months, hazard ratios (HR), confidence intervals (CI), and log-rank p-values are represented in the Kaplan-Meier survival curves and summarized in table E.

of cisplatin-induced apoptosis [202,207,208], which makes the role of this pathway needs further studies. Cisplatin stimulates ERK, causing activation of the p53 gene that directly regulates target genes that control sensitivity to apoptosis, such as PUMA [75]. Indeed, activation of p53 also causes upregulation of p21, GADD45 and Mdm2, which may lead to cell cycle arrest and thus support cisplatin-induced DNA damage repair [76]. JNKs and p38 can also induce apoptosis and regulate cell proliferation, and sustained activation of this pathway by cisplatin treatment in ovarian cancer cells causes apoptosis [77]. Consistent with our results, studies reported an enrichment of miRNAs regulating the MAPK pathway in cisplatin and taxane-resistant ovarian cancer cells [16,50,78,79]. Pathways in cancer were the pathways in which the miRNAs were predicted to have the most significant impact, with the largest number of genes targeted by these miRNAs belonging to this pathway. Moreover, the pathways in cancer may be one of the most important pathways that may determine cellular resistance to cisplatin because it contains many known pathways, including the cell cycle, p53 signaling pathway, MAPK signaling pathway, TGF-β signaling pathway, and the PI3K-Akt signaling pathway. These pathways regulate important cellular functions such as apoptosis, proliferation, differentiation, migration and metastasis formation, which makes this pathway a major influence on chemoresistance development. Notably, enrichment in microRNAs and the genes regulating this pathway have been observed in several chemoresistant cancer cells such as ovarian cancer [14–17], and other cancers [80–85]. These findings make resistance-associated miRNAs a promising target for reversing resistance and increasing treatment efficiency in ovarian cancer cells.

To verify the clinical significance of the resistance-associated miRNAs, Kaplan–Meier survival analysis was conducted. Overall, four upregulated miRNAs were associated with worse survival in patients diagnosed with ovarian cancer. In contrast, two of the upregulated miRNAs were associated with better survival. However, the rest of the identified miRNAs were not significantly associated with overall survival in patients with ovarian cancer. Remarkably, higher expression levels of hsa-miR-133b, hsa-miR-512, hsa-miR-200b, and hsa-miR451a were associated with poor overall survival of ovarian cancer patients. Our results correlate high expression levels of hsa-miR-133b, hsa-miR-512-5p, hsa-miR-200b-3p, and hsa-miR-451a with chemoresistance acquisition, consistent with several studies on different cancer cell lines and patients. These studies focused on molecular drivers of chemoresistance and aimed to suggest miRNAs with prognostic potential. For example, miRNA's expression profiling in the SGC -7901 line resistant to 5-fluorouracil revealed that hsa-miR-133b upregulation occurring upon resistance acquisition. Thus, the researchers suggested hsa-miR-133b as a potential marker of resistance [86]. Furthermore, a study focused on osteosarcoma showed that hsa-miR-133b promotes resistance to cisplatin, giving cancer cells the ability to migrate and evade cell death [87]. Interestingly, Opławski et al. evaluated the clinical and molecular characteristics of 48 diagnosed ovarian cancer patients. The study showed that overexpression of hsa-miR-133b significantly correlated with drug resistance to chemotherapy [88]. Moreover, expression profiling studies in patients with prostate and bladder cancer revealed that upregulation of hsa-miR-133b is linked to poor outcomes and may serve as prognostic marker [89,90]. Regarding hsa-miR-200b-3p, literature extensively studied the role of the hsa-miR-200b family in various cancers. However, depending on the type of tumor, hsa-miR-200b-3p can perform various functions. It has a tumor-suppressive effects and was downregulated in the majority of cases of colorectal cancer [91], hepatocellular carcinoma [92], pancreatic cancer [93], breast cancer [94], glioma [95], and prostate cancer [96]. On the other hand, hsa-miR-200b-3p can also be oncogenic in a variety of cancers, including prostate cancer [97], lung cancer [98], breast cancer [99], and



F

miRNA	P value	HR	Median Survival (months)	
			Low expression cohort	High expression cohort
has-miR-15b	0.026	0.77	40.13	49.47
has-miR-625	0.04	0.79	44.03	48.2
has-miR-708	0.073	0.81	41.63	48.27
hsa-miR-21	0.25	0.88	42.63	48.2
has-miR-203a	0.17	1.18	48.77	38.6

Fig. 7. Kaplan–Meier (KM) overall survival analysis for ovarian cancer patients based on the expression of hsa-miR-15b, hsa-miR-625, hsa-miR-708, hsa-miR-21 and hsa-miR-203a. Median survival for 486 ovarian cancer patients was analyzed after categorizing samples into high (red) or low (black) expression groups for each miRNA (A–E). Median survival in months, hazard ratios (HR), confidence intervals (CI), and log-rank p-values are represented in the Kaplan-Meier survival curves and summarized in table F.

colorectal cancer [100]. This dual function of hsa-miR-200b is influenced by the cellular environment, the presence of other regulatory molecules, and the specific genetic and epigenetic landscape of each cancer type [12,101]. However, without functional validation and mechanistic studies such as gene knockdown, overexpression studies, and in vivo models, it is challenging to definitively determine whether these miRNAs function as oncogenes or tumor suppressors in ovarian cancer. Yet, it was mentioned that higher expression of hsa-miR-200b was significantly correlated with a poor prognosis in patients with serous ovarian carcinoma treated with platinum-based chemotherapy [102]. Besides, elevated expression of hsa-miR-200b was linked to increased cancer aggressiveness and decreased overall survival in epithelial ovarian cancer patients [103]. Bagnoli et al. correlated low expression of hsa-miR-200b-3p with a good prognosis in patients with epithelial ovarian cancer [104]. This literature may suggest the oncogenic role of hsa-miR-200b-3p in ovarian cancer, but this requires validation using functional studies. In this study, hsa-miR-451a was identified as an upregulated miRNA in the cisplatin-resistant lines. Our results are consistent with a study on doxorubicin-resistant A2780DX5 ovarian cancer cell line and KB-V1 cervical cancer cell line, which showed increased expression of hsa-miR-451 upon acquisition of resistance. This upregulation induced the expression of the *MDR1* gene, which is associated with resistance to several chemotherapies [105]. Similarly, the role of hsa-miR-451a in stimulating cellular growth and migration capacity has also been demonstrated in glioma, renal, and colon cancer cells, and inhibiting the expression of hsa-miR-451 promoted cell death and inhibited tumor cell growth and migration [106–108]. Our study also showed upregulation of hsa-miR-512-5p in ovarian cancer cell lines resistant to cisplatin compared to the sensitive cell line A2780. When examining the literature, the lack of research was noted on hsa-miR-512-5p and its role in cancer cells and cellular resistance to treatment. However, a research on triple negative breast cancer patients indicated that lower hsa-miR-512-5p expression levels were associated with a better pathologic response to chemotherapy [109]. Accordingly, our findings suggest that one of the molecular changes that occurred in the studied cisplatin resistant ovarian cancer cells is the dysregulation of several miRNAs' expression: upregulation of hsa-miR-133b, hsa-miR-512-5p, hsa-miR-200b-3p, and hsa-miR-451a. These miRNAs have molecular function and regulated pathways related to treatment response and may be considered as prognostic markers for ovarian cancer patients.

While our findings provide insights into the molecular changes in cisplatin resistant ovarian cells, several limitations should be addressed in the future studies. First, chemoresistance is a multifactorial process involving numerous pathways and interactions so we cannot rule out the possibility that other factors may influence the outcomes besides miRNA dysregulation. Second, this study is exploratory and primarily based on in vitro models and correlative analyses. Functional assays, such as miRNA knockdown or overexpression studies, are essential to establish causal relationships between miRNAs and chemoresistance. Conducting comprehensive functional studies will also address the ambiguity and the context-dependent functions of miRNAs in ovarian cancer cells. This includes examining their effects on cell proliferation, apoptosis, migration, and invasion, as well as their interactions with key signaling pathways involved in chemoresistance. Third, the use of only two cisplatin-resistant cell lines limits the generalizability of the results. Future studies should include a broader range of cell lines and patient-derived tumor samples. Additionally, in vivo validation is necessary to explore the systemic effects of these miRNAs and their interactions within the tumor microenvironment. Investigating how the tumor microenvironment influences the context-dependent functions of these miRNAs will be crucial. However, the context-dependent roles of miRNAs can complicate their universal application. Off-target effects remain a critical concern since miRNAs regulate multiple pathways, and

alterations in their expression may have unintended systemic consequences [110]. Moreover, successfully integrating miRNA with existing therapies, such as chemotherapeutics for restoring dysregulated miRNA levels might aid in enhancing treatment efficacy [111]. However, this integration requires studying of potential interactions between miRNAs and existing therapies. It also needs advanced delivery systems capable of delivering the miRNA therapeutics to the targeted tissue or cells and minimize off-target effects [112]. Extensive preclinical and large-scale clinical validation is necessary to confirm their efficacy and safety [113]. Standardization of detection methods is also critical to ensure reproducibility across studies to identify biomarkers [114]. Despite these hurdles, combining miRNA-targeting strategies with conventional therapies offers potential to overcome resistance, enhance treatment efficacy, and personalize cancer treatment.

5. Conclusion

This study explores miRNA expression dysregulation in cisplatin resistant ovarian cancer cells. We compared the miRNA expression levels in two cisplatin-resistant ovarian cell lines and analyzed the GO enrichment, and KEGG pathways. Moreover, the clinical significance of the dysregulated miRNAs was also determined using survival analysis for ovarian cancer patients' data in KM database. We discovered nine dysregulated miRNAs; hsa-miR-133b, hsa-miR-203a-3p, hsa-miR-512-5p, hsa-miR-21-5p, hsa-miR-708-5p, hsa-miR-451a, hsa-miR-15b-5p, hsa-miR-200b-3p and hsa-miR-625-5p, whose expression was increased in cisplatin-resistant ovarian cancer cells. These miRNAs could influence many biological processes and pathways related to apoptosis, cell survival, and treatment response. Out of nine only hsa-miR-133b, hsa-miR-512-5p, hsa-miR-200b-3p, and hsa-miR-451a higher expression is related to poor survival in patients with ovarian cancer. These findings provide insights into the molecular changes related to cisplatin resistance in ovarian cancer cells. However, the study is exploratory and comes with limitations, including reliance on in vitro models and correlative analyses. Future research should focus on functional validation, in vivo experiments and patient-derived samples. By addressing these limitations, the causal roles of these miRNAs in chemoresistance could be established paving the way for their clinical application in overcoming cisplatin resistance.

CRediT authorship contribution statement

Yaman Alghamian: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chadi Soukkarieh:** Writing – review & editing, Supervision. **Abdulmunim Aljapawe:** Formal analysis. **Hossam Murad:** Writing – review & editing, Validation, Supervision, Conceptualization, Project administration.

Data statement/availability of data and material

All the data are contained in the main text and in the supplementary material.

Financial disclosure

The authors have no funding to disclose.

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.

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Abbreviations

miRNA: microRNA; cis: cisplatin; GO: Gene Ontology; OS: overall survival.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2024.101906.

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