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Research Article

Evaluation of miR-141-3p over-expression in ovarian cancer

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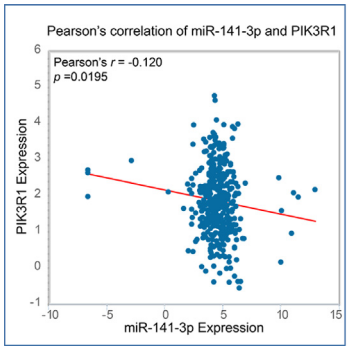
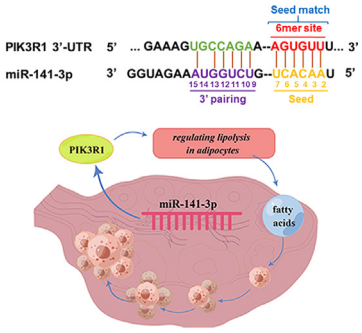
GRAPHICAL ABSTRACT





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ABSTRACT

Background: The expression of miR-141-3p in many malignant tumors has been verified. Nevertheless, the relationship between ovarian cancer and miR-141-3p remains undetermined. Therefore, further exploration is required.

Results: According to data from 100 samples, the final results of RT-qPCR showed that miR-141-3p was highly expressed in ovarian cancer. Furthermore, miR-141-3p was able to distinguish ovarian cancer cells from ovary tissues. The most significant Kyoto Encyclopedia of Genes and Genomes pathway, was regulation of lipolysis in adipocytes in ovarian cancer. The expression of PIK3R1 was negatively correlated with miR-141- 3p. PIK3R1 has a combing site with miR-141-3p.

Conclusions: This study examined the expression levels and mechanism of miR-141-3p in ovarian cancer for the first time. The results suggested that miR-141-3p may promote the occurrence of ovarian cancer by down-regulating PIK3R1.

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1. Introduction

Ovarian cancer (OV) is one of the most common gynecological malignancies worldwide, and its mortality ranks first among all kinds of gynecological cancer [1]. Globally, about 313,959 new cases of OV are diagnosed each year, and 207,252 patients die of OV [2]. Moreover, the incidence and mortality of OV have increased each year [2,3]. The overall survival (OS) rate of OV is low, around 40% [4], and the incidence rate of OV is younger than before [4]. With lacking of peritoneal coverage on the surface of ovaries, OV can metastasize to the abdominal cavity at an early stage, which is also one of the reasons for the poor prognosis of patients with OV [5]. As OV is characterized by gynecological malignant tumors, its occurrence not only affects the patient's quality of life and health but also the patient's future fertility [6,7,8,9,10]. OV occurs in a multi-step process that is affected by numerous factors, including DNA repair, oncogene activation, and abnormal cell apoptosis [11,12]. For instance, Wnt/β-catenin pathway involves in tumorigenesis of OV by promoting the self-renewal of cancer stem cells [11]. Some researchers believe that changes in the tumor microenvironment, such as changes in the biological signal pathway and extracellular matrix, are also key factors affecting the occurrence and progression of OV [13,14,15,16]. A variety of genetic and epigenetic abnormalities also exist in different OV tissues [17]. Furthermore, some studies reported that some transcription factors participated in the tumorigenesis of OV [18].

MicroRNA (miRNA), a class of short non-coding RNA molecules, participate in the post-transcriptional regulation of gene expression [19]. Currently, the role of miRNAs in cancers has received increasing attention [20,21,22,23]. For instance, miRNA-489 was demonstrated to involve in the regulation of proliferation and apoptosis of tumor cells by serving as a tumor suppressor, and can affect the sensitivity of chemotherapy [24]. Up-regulation of miR-23a-5p promoted renal cell carcinoma cell proliferation, migration and invasion and inhibited apoptosis [25]. Similarly, miRNA-194 contributed to promotion of OV cell growth, migration and invasion [26]. Obviously, in-depth exploration of the role of miRNAs in cancer is of great significance for exploring the mechanism of cancer occurrence and development. Among numerous miRNAs, the effect of the miR-200 family (including miR-200a, miR-200b, miR-200c, miR-429 and miR-141) in multiple cancers aroused much attention [27]. It was reported that the miR-200 family regulates epithelial-mesenchymal transition (EMT) and can reverse EMT-related drug resistance [28]. The study by Bin Wen et al. [29] also indicated that miR-200 members were expressed differently in various cancers and had an impact on the EMT process [29,30]. MiR-141-3p, a member of the miR-200 family, is a mature miRNA processed from the 3′-end arm of miR-141 precursor [31]. Numerous studies have shown that the deviant expression of miR-141-3p is closely related to the occurrence, development, and drug-resistance of cancer [32,33,34]. In different cancers, miR-141-3p can participate in tumorigenesis by controlling the expression level of target genes. The promoting role of miR-141 has been reported in the occurrence of non-small cell lung cancer [35], small cell lung carcinoma [36], and prostate carcinoma [37]. Both *in vivo* and *in vitro* experiments have found that miR-141 can interact with human umbilical vein endothelial cells through the exosomes of packaged small cell lung cancer cells. After human umbilical vein endothelial cells internalize miR-141, miR-141 starts the miR-141/klf12 pathway. This pathway targets and reduces the expression of klf12, promoting the proliferation, invasion, and migration of human umbilical vein endothelial cells and accelerating the growth of small cell lung carcinoma [38]. Since miR-141 is remarkably up-regulated in prostate cancer, the combination of miR-141, miR-21, and miR-375 is often used as a potential prognostic tool for prostate cancer [38]. Moreover, miR-141 can reduce the survival time of patients with bladder cancer and promote the invasion and recurrence of cancer cells by regulating hormones and inducing the growth of LNCaP cells [39]. However, miR-141 can also inhibit tumorigenesis. For example, it can inhibit the expression of BMI 1 in nasopharyngeal carcinoma cells, especially in metastatic tumor cells, thereby restraining the growth and metastasis of nasopharyngeal carcinoma [40]. In pancreatic cancer, miR-141, as one of the candidate miRNAs, has the strongest negative regulatory effect on NRP-1. It can bind to the 3′-untranslated region (3′ UTR) of NRP-1 and inhibit its formation, thus counteracting the activation effect of the TGF-β pathway and continuously inhibiting the epithelial mesenchymal transition of pancreatic cancer cells [41].

Current studies related to miR-141-3p and OV have only reported the phenomenon of high expression of miR-141-3p, which inhibits the cisplatin resistance, invasion, and metastasis of OV [42,43]. The current research has not studied the relationship between expression levels of miR-141-3p and OV, and the latent molecular mechanism of miR-141-3p in OV is still unclear. To explore this relationship and mechanism, this study examined the expression of miR-141-3p in OV using RT-qPCR and public databases. Furthermore, the potential target genes of miR-141-3p were predicted, and the mechanism of miR-141-3p in the tumorigenesis of OV was revealed for the first time.

2. Materials and methods

2.1. Total RNA extraction and detection of miR-141-3p expression levels by RT-qPCR

The OV tissues and non-cancer tissues were selected by two pathologists. All samples were collected from the Second Affiliated Hospital of Guangxi Medical University. The experiment has been approved by the medical ethics committee of the Second Affiliated Hospital of Guangxi Medical University with the approval number of 2019-KY(0104). Informed consent was obtained from all participants. According to the manufacturer's instructions, an RNA kit was used to extract the total RNA of the sample tissues. Then, a micro nucleic acid detector, which was calibrated through diethylprocarbonate (DEPC)-treated water, was used to determine the quality and concentration of the total extracted RNA.

The reverse transcription of the qualified total RNA (A260/A280 ratio range of 1.8∼2.1) was executed using the Mir-X™ miRNA First-Strand Synthesis Kit (TAKARA, USA). The expression levels of miR-141-3p in the sample tissues were determined using RT-qPCR and calculated with the 2-ΔΔCq method. The specific primer sequence of miR-141-3p was GCACACTGTCTGGTAAAGATGGAA, and the general primer sequence was provided by the kit. The reaction system is shown in Table 1.

2.2. Data mining of miR-141-3p expression levels in the GEO database

As of December 10, 2019, all expression profiles of miR-141-3p were obtained from the Gene Expression Omnibus (GEO, https://

Table 1
RT-qPCR reaction system for detecting miR-141-3 expression in various tissues.

Reaction System Components	**Volume (μl)**
ddH2O	9
TB Green Advantage Premix (2X)	12.5
ROX Dye (50X)	0.5
miR-141-3p or U6 forward primer (10 μM)	0.5
mRQ 3′ or U6 reverse primer (10 μM)	0.5
cDNA	2.0
Total Volume	25

Table 2
Microarray of OV gene in geo database.

Category	Accession	Year	Author	Country	Platforms	Cancer	Normal
OV-miRNA	GSE119056	2019	Dong S	China	GPL21572	6	3
	GSE83693	2017	Nam EJ	South Korea	GPL22079	16	4
	GSE53829	2014	Ruo-Ying T	China	GPL18138	45	14
	GSE14985	2009	Navon R	Israel	GPL8227	3	3

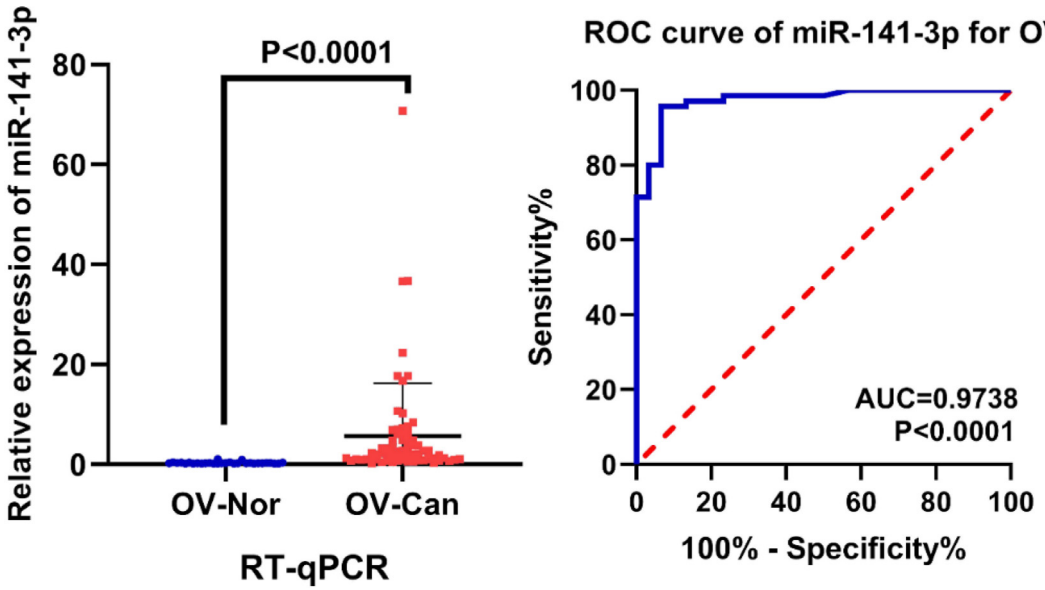

Fig. 1. RT-qPCR was used to examine the expression of miR-141-3p in normal ovarian and ovarian cancer tissues.

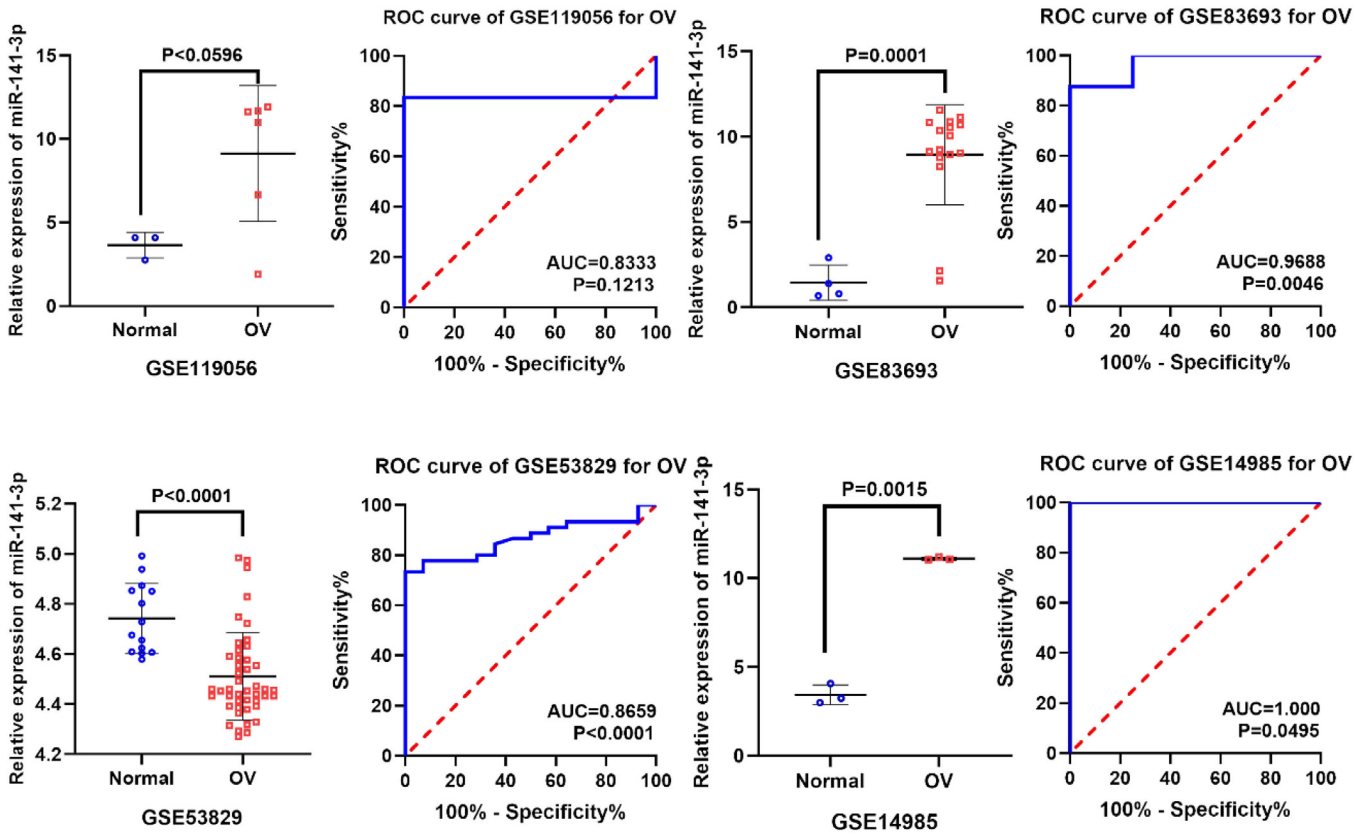

Fig. 2. Expression of miR-141-3p in OV miRNA microarrays.

www.ncbi.nlm.nih.gov/gds/) database. To explore the expression of miR-141-3p in OV samples, the following retrieval method was used to obtain miRNA transcriptome and microarray data for OV: (ovarian OR ovary) AND (cancer OR carcinoma) AND (miRNA OR microRNA). The screening flow chart is shown in Fig. S1.

According to the inclusion and exclusion criteria, the dataset was selected, and the data of the human transcriptional group were tested by chip, microarray, or RT-qPCR. The dataset included three or more cancer groups and normal control groups without any treatment. Finally, four OV chips conforming to the inclusion criteria were obtained (Table 2). After downloading the chips, the gene expression profiles of each chip were combined, and the data were normalized for further analysis using log2.

2.3. Comprehensive evaluation of miR-141-3p expression in OV

To enhance the reliability of the results, the data obtained by RT-qPCR were combined with the datasets obtained from the GEO database for integrated analysis. The receiver operating characteristic (ROC) curves were drawn using GraphPad Prism (v8.3.0). Stata (v15.1) software was used for comprehensive analysis of the dataset, as follows:

1. An standardized mean difference (SMD) forest map was exhibited to estimate the expression levels of miR-141-3p comprehensively.
2. Egger's funnel map was drawn to verify whether the obtained data had publication bias.
3. The summary ROC (sROC) curve, sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic score, and OR value were shown in forest maps to judge the identification value of miR-141-3p in OV.

If the heterogeneity test found that heterogeneity was low (I^2 < 50%, p > 0.05), the fixed effect model was chosen. Otherwise, the random effect model was utilized.

In addition, we collected 70 OV patients' clinicopathological parameters, and used Student's t-test method to determine the relationship between the miR-141-3p and clinicopathological parameters.

2.4. Recognition of candidate miR-141-3p target genes

The target genes of miR-141-3p were screened using 11 online tools, including mirdb, miRanda, DIANA, microT-CDS, miRmap, miRwalk, miRNAmap, PITA, RNA22, PicTar, TargetScan v7.2, and TargetMiner. The genes that overlapped at least three times were selected as the miR-141-3p target genes. The microarray of the OV expression profile was downloaded from the GEO database. The affy package in R software was used for robust multi-array average (RMA) processing and background correction.

The gene chips from the same platform were combined, and the batch effect was removed using the Combat function of the sva package. At the same time, the RNA-sequencing data from the Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) were combined, and the batch effect was removed using the Combat function of the sva package. Then, the SMD of each gene expression was calculated, and the low expression genes were screened according to SMD < 0 and 95% CI, excluding 0. Finally, the low expression genes of OV were obtained. Then, the low expression genes were overlapped with the target genes using Funrich (v3.1.3) [44], and the candidate miR-141-3p target genes were obtained.

2.5. MiR-141-3p target genes and enrichment analysis

Enrichment of the candidate miR-141-3p target genes with Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) was analyzed using KOBAS 2.0 (https://kobas.cbi.pku.edu.cn/kobas3/?t=1) [45]. GO annotation analysis histogram and KEGG enrichment analysis bar plots were drawn using the online drawing tool Hiplot. In addition, the Human Protein Atlas (THPA, https://www.proteinatlas.org/) was used to verify the protein expression level of the genes enriched in the KEGG pathway with the highest score in OV. In order to further explore the expression of miR-141-3p target gene in OV tissues, we verified the expression level of related target genes in OV. Pearson correlation analysis was applied to verify the correlation between miR-141-3p

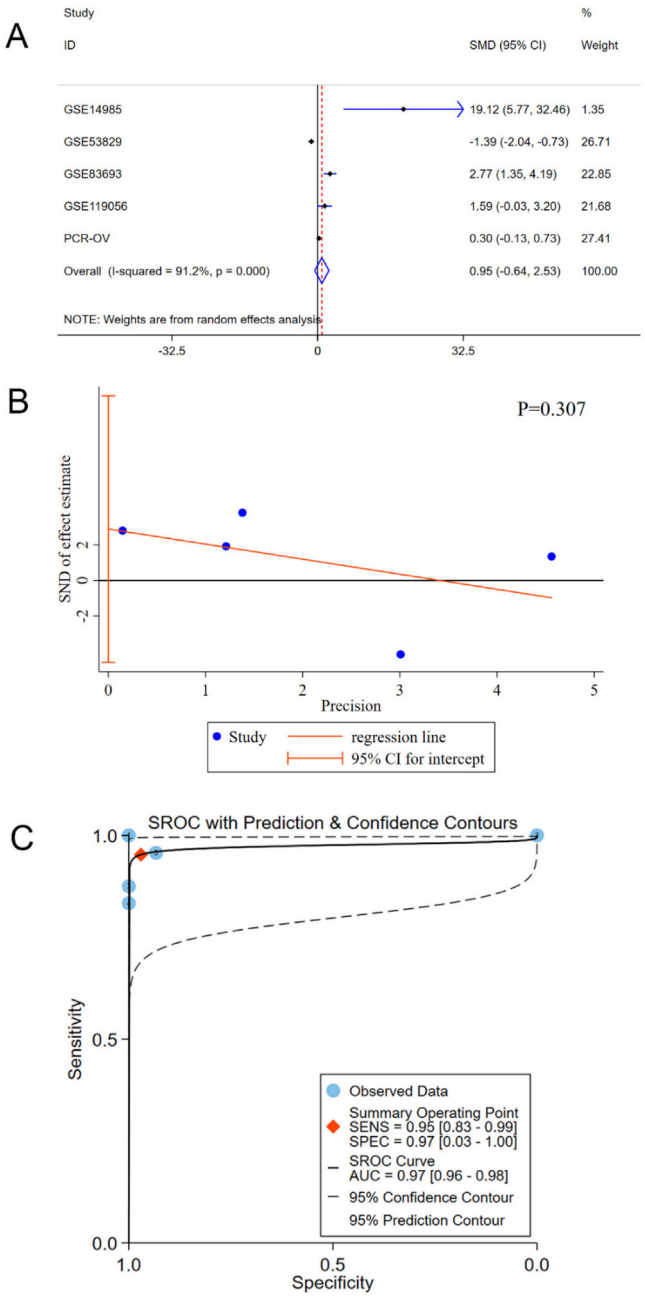

Fig. 3. (A) Forest map of miR-141-3p expression in ovarian cancer patients by integrated analysis. (B) Publication bias. (C) Evaluation of miR-141-3p in the diagnosis of OV by SROC curve.

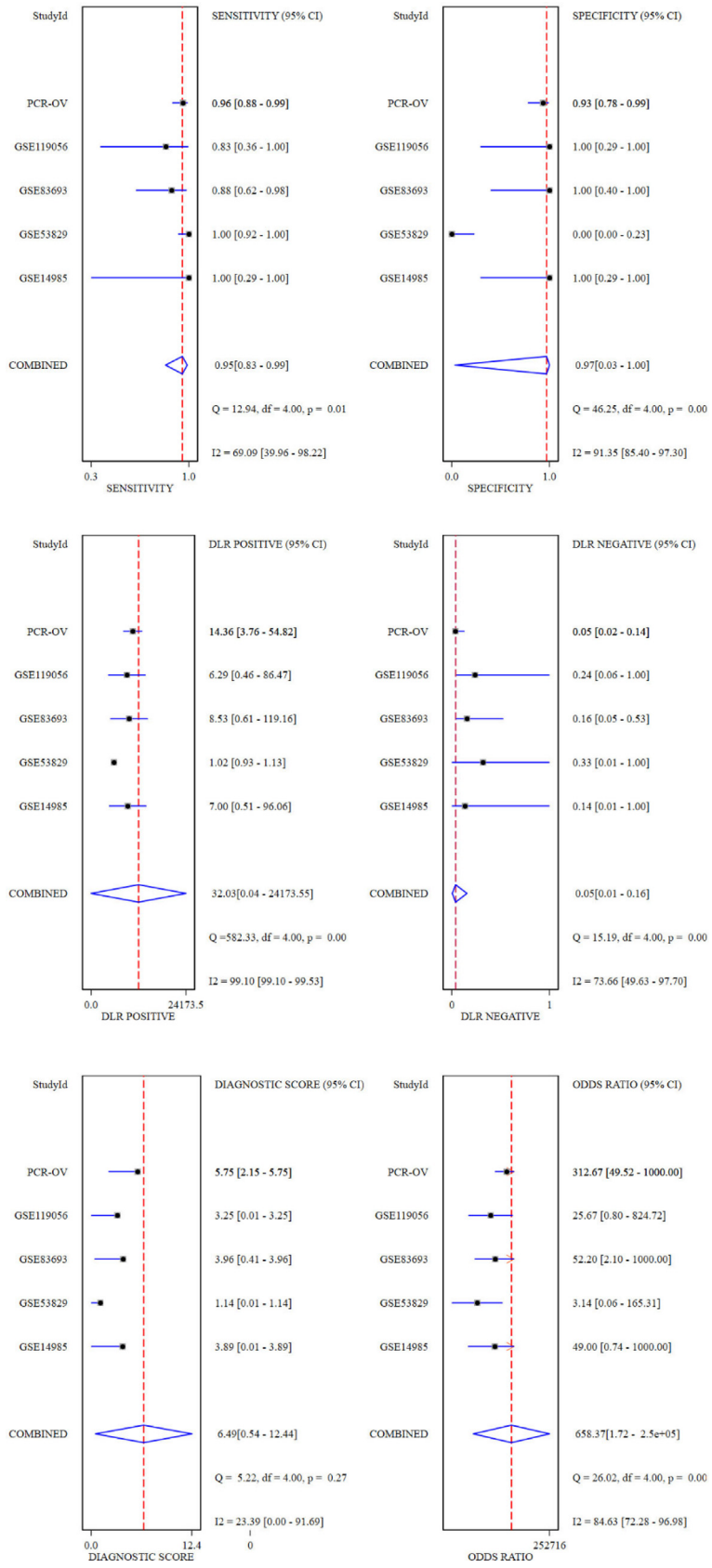

Fig. 4. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic score, odds ratio.

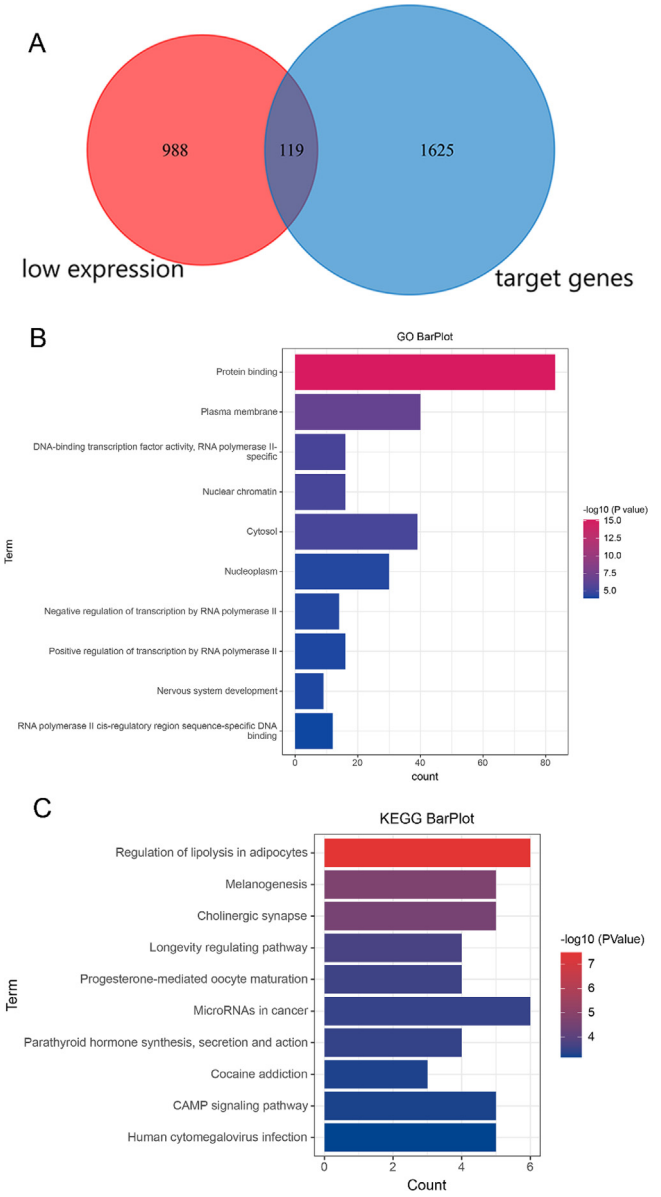

Fig. 5. (A) Venn diagram: intersection of miR-141-3p potential target gene and low expression gene in ovarian cancer mRNA microarray. (B) GO enrichment analysis of miR-141-3p target gene. (C) KEGG analysis of miR-141-3p target gene.

and target gene, and the online tool microT-CDS was utilized to find the combining site of miR-141-3p of the target gene. Schematic diagram was drawn to display the molecular mechanism of miR-141-3p.

3. Results

3.1. Expression status of miR-141-3p in OV samples by RT-qPCR

The expression of miR-141-3p in 70 OV groups and 30 normal control groups was examined using RT-qPCR. The scatter plots showed that the expression levels of miR-141-3p in OV were significantly higher than those in the group of normal ovarian samples ($p < 0.0001$). The ROC curve of miR-141-3p in OV indicated a favorable discriminatory ability (AUC = 0.974, $p < 0.001$, Fig. 1).

3.2. Integrated study

Four microarrays from the GEO database were screened, namely GSE119056, GSE83693, GSE53829, and GSE14985. Among them, the expression of miR-141-3p in OV samples from GSE119056, GSE83693, and GSE14985 was higher than that in normal tissues. The difference in miR-141-3p expression between the OV samples and the normal ovarian samples from GSE83693 and GSE14985 was statistically significant ($p < 0.05$). However, GSE53829 showed the opposite outcome ($p < 0.0001$, Fig. 2). Because $I^2 = 0.919$, a random effect model was applied to analyze the outcomes of GEO chips integrally. The forest plot showed that miR-141-3p was expressed at a high level in OV (SMD: 0.95; 95% CI: −0.64–2.53, Fig. 3A), and the Egger's test exhibited no publication bias ($p = 0.307$, Fig. 3B). The AUC of sROC in each group was 0.97 (95% CI = 0.96–0.98, Fig. 3C). The values for sensitivity, specificity, diagnostic score, negative likelihood ratio (NLR), positive likelihood ratio (PLR) and odds ratio (OR) were 0.95 (95% CI: 0.89–0.99, $p < 0.05$), 0.97 (95% CI: 0.03–1.00, $p < 0.001$), 6.49 (95% CI: 0.54–12.44, $p = 0.27$), 0.05 (95% CI:0.01–0.16, $p < 0.001$), 32.03 (95% CI: 0.04–24173.55, $p < 0.001$), and 658.37 (95% CI: 1.72–250000, $p < 0.001$), respectively (Fig. 4). All these values implied that miR-141-3p could distinguish OV cells from non-cancer cells.

3.3. Correlations between miR-141-3p expression and clinicopathological features

We analyzed the relationship between the expression level of miR-141-3p and clinicopathological features of 70 patients, including grade and clinical stage. The results indicated that there was no significant difference between the expression level of miR-141-3p and clinical stages or grades ($p > 0.05$, Fig. S2).

3.4. The candidate miR-141-3p target genes

In total, 1,625 potential target genes were obtained after screening. To obtain the target genes of miR-141-3p correctly, the 1,625 genes were crossed with 988 low-expressed genes obtained from the analysis of an OV mRNA chip (Fig. 5A). A total of 119 overlapping genes were selected as candidate target genes of miR-141-3p for further exploration.

3.5. Potential mechanism of miR-141-3p in OV

To explore the potential mechanisms of miR-141-3p and its target genes, KOBAS 2.0 was used to analyze 119 candidate target genes. These genes were input into KOBAS 2.0 to obtain GO and KEGG enrichment analysis results. Using $p < 0.05$ as the screening condition, the top 10 items were selected to draw the histogram (Fig. 5B). The results of GO annotation illustrated that the top three processes that the targeted miR-141-3p genes were involved in were protein binding, plasma membrane, and DNA-binding transcription factor activity (RNA polymerase II-specific).

In terms of KEGG analysis, the target genes were enriched in the regulation of lipolysis in adipocytes pathway (Fig. 5C). According to the THPA database, the expression levels of PIK3R1 (Fig. 6), IRS1 (Fig. S3), and PRAKCB (Fig. S4) kept a low expression status in OV compared to ovarian tissues. This trend was not found for PTGS2 or GNAI1. Furthermore, no protein expression data for NPY1R in OV tissues were found in the THPA database. These results suggested that miR-141-3p may down-regulate IRS1, PIK3R1, and PRAKCB, which may lead to the abnormality of the regulation of lipolysis in adipocytes pathway, thus inducing the occurrence and development of OV.

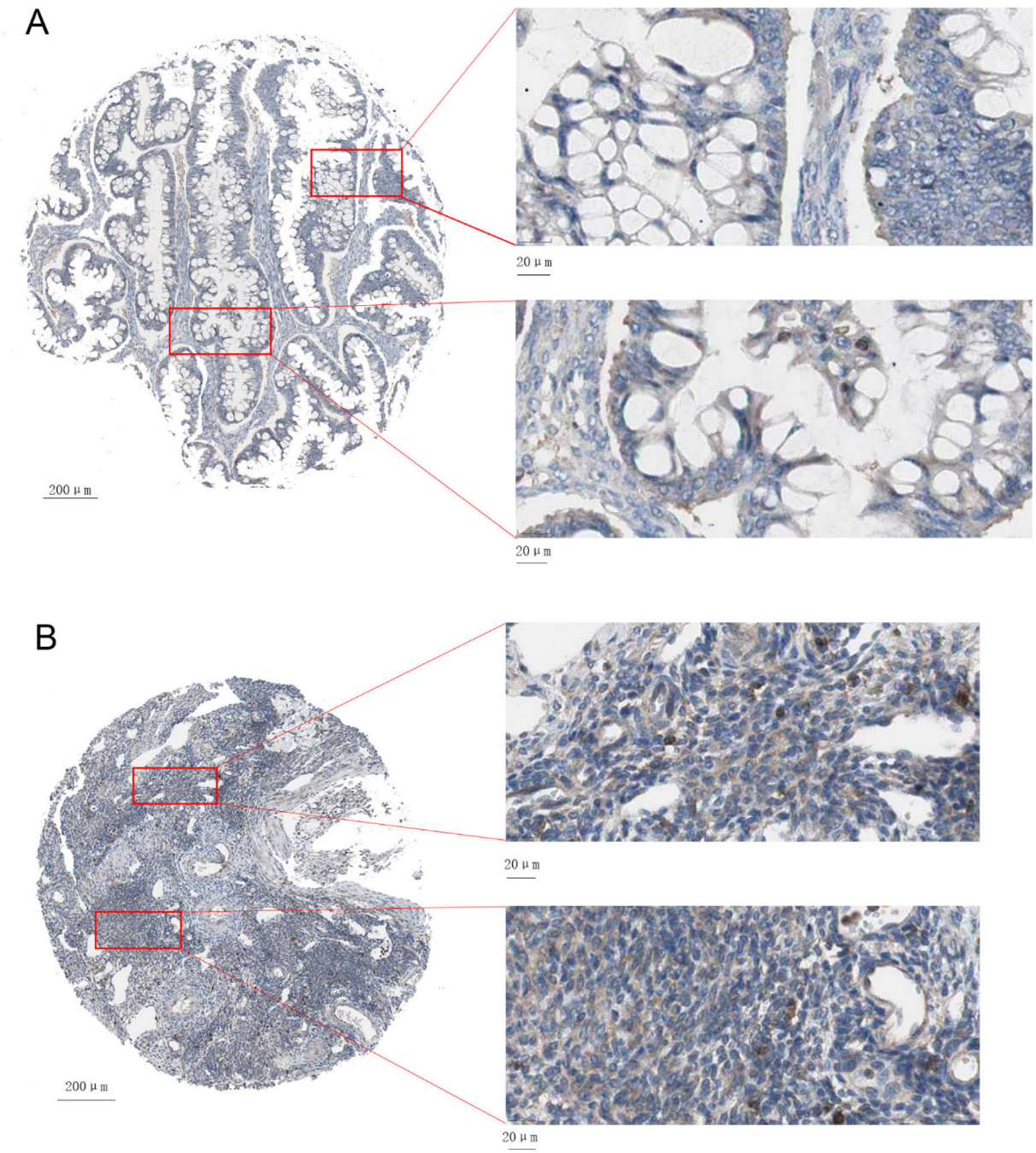

Fig. 6. (A) Expression of PIK3R1 protein in ovary cystadenocarcinoma (Female, aged 73, patient ID: 1844, antibody CAB004268, low staining). (B) Expression of PIK3R1 protein in normal ovary (Female, aged 33, patient ID: 2159, antibody CAB004268, medium staining).

3.6. Validation of PIK3R1 expression in OV

Compared to the non-OV ovarian tissues, the expression level of PIK3R1 in OV tissues was observably lower (SMD = −1.45, 95% CI: −2.63 – −0.26, Fig. 7A). The funnel plot showed no obvious publication bias (P = 0.448, Fig. 7B). The AUC value of sROC was 0.94, which indicated that PIK3R1 had a favourable discriminatory ability between OV and non-OV tissues (95% CI = 0.92–0.96, Fig. 7C). Through Pearson correlation analysis, we found that PIK3R1 was negatively correlated with miR-141- 3p with the Pearson's r = −0.120 (P < 0.05, Fig. 8A). Moreover we identified that a 6mer combining site exited between the 3′-UTR of PIK3R1 and miR-141-3p, which was an exact match to positions 2 to 7 of the mature miRNA (Fig. 8B). The hypothesis diagram of the latent mechanisms of miR-141-3p in OV is displayed in Fig. 8C. The above results demonstrated that miR-141-3p may participate in the occurrence of OV by down-regulating PIK3R1.

4. Discussion

Previously, the few research studies on the relationship between miR-141-3p expression levels and OV examined only the function of miR-141-3p expression level changes in cisplatin resistance [42] and cancer cell metastasis and invasion [43]. These

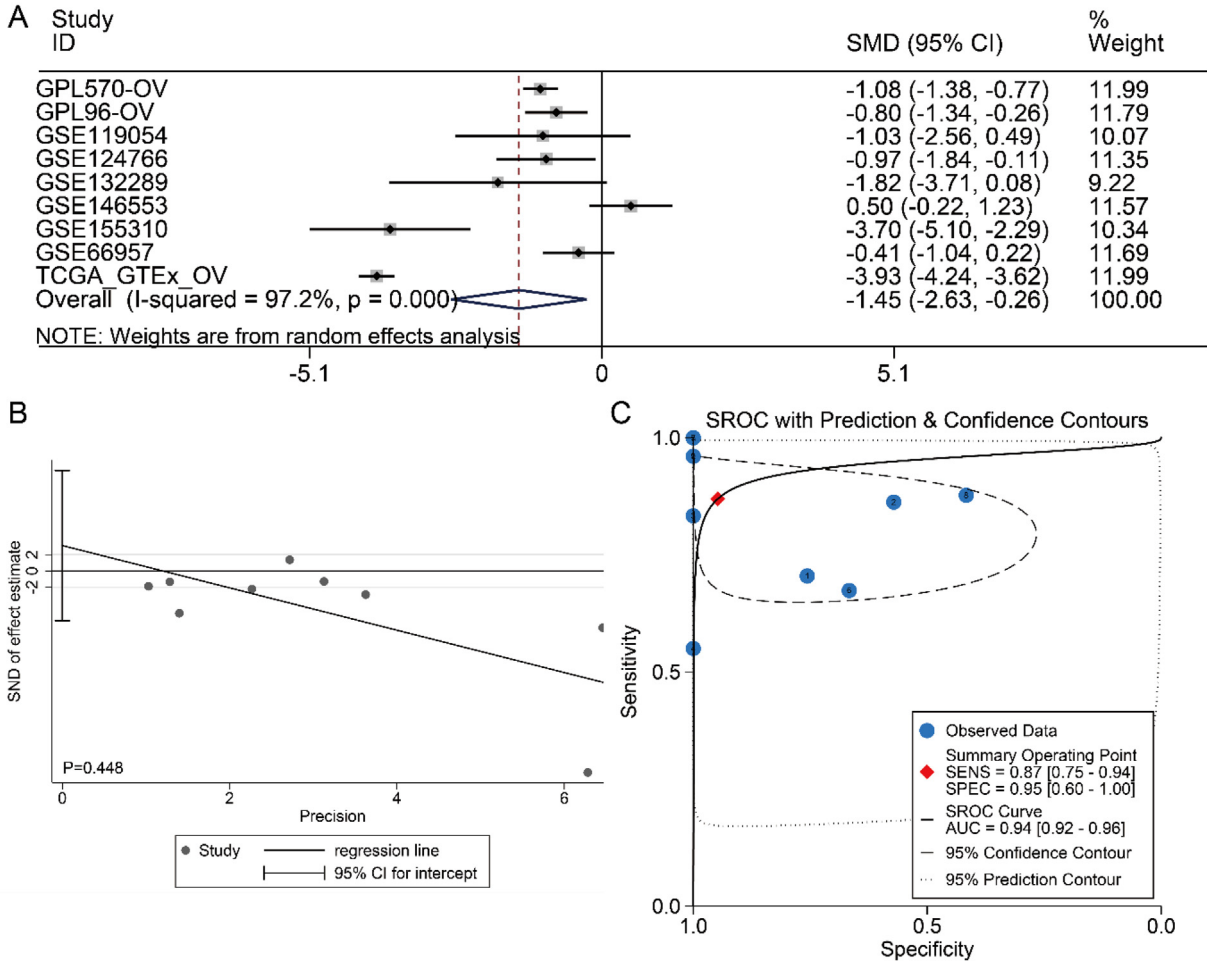

Fig. 7. (A) Forest map of PIK3R1 expression in ovarian cancer patients by integrated analysis. (B) Egger's funnel map. (C) Evaluation of PIK3R1 in the diagnosis of OV by SROC curve.

studies did not report the role of miR-141-3p expression in the occurrence of OV.

Through the comprehensive study of OV (n = 144) and non-OV (n = 54) samples, and by calculating SMD, this study found that miR-141-3p was overexpressed in OV tissues. Additionally, it investigated the ability of miR-141-3p to distinguish OV from non-OV, as well as the prognostic significance of miR-141-3p expression in OV patients. Furthermore, the potential molecular mechanisms of miR-141-3p in OV were also explored for the first time via GO and KEGG signaling pathway analyses.

As a member of the miR-200 family, miR-141-3p plays a key role in the regulation of epithelial mesenchymal transition [46] and angiogenesis [47], and its expression levels vary in different types of tumors. For example, miR-141-3p is up-regulated in prostate cancer [32], esophageal cancer [34], breast cancer [33] and uterine cervical cancer [48]. In contrast, miR-141-3p levels showed a decreasing trend in colorectal cancer [49], non-small cell lung carcinoma [50], papillary thyroid cancer [51], gastric cancer [52] and hepatocellular carcinoma [53]. However, the difference of miR-141-3p expression between OV and non-OV has not been comprehensively reported before.

In this study, RT-qPCR was first applied to identify the mRNA expression levels of miR-141-3p in OV. Using the results of RT-qPCR combined with gene chip data, the study found that miR-141-3p was remarkably overexpressed in OV. This differential expression of miR-141-3p in OV tissues was consistent with the results of previous studies. In terms of the clinical significance of miR-141-3p, the present study also found that the expression levels of miR-141-3p can be used as an indicator to distinguish OV and normal ovarian tissues.

The clinical significance of miR-141-3p was attractive. Thus, there were a large number of studies revealing the clinicopathological value of the aberrant miR-141-3p in multiple malignant tumors. For instance, one study found that the low expression of miR-141-3p was associated with TNM stage and lymph-node metastasis in non-small cell lung cancer patients [50]. Another study discovered that the elevated expression of miR-141-3p was related to the T stage and grade of hepatocellular carcinoma patients [54]. Whereas, the present study showed that the expression of miR-141-3p had no significant correlation with the clinicopathological parameters of OV, which may be due to the small sample size, and it still needs further exploration.

The mechanisms of miR-141-3p in OV remain undetermined. However, KEGG enrichment analysis found that miR-141-3p may promote the occurrence of OV by regulating lipolysis in adipocytes pathway, which was consistent with previous studies [55,56]. Studies have shown that abnormal decomposition of adipocytes provides fatty acids as energy for tumor cells, thus promoting the proliferation of tumor cells [56]. Legion studies have shown that aberrant lipolysis is associated with numerous malignant tumors,

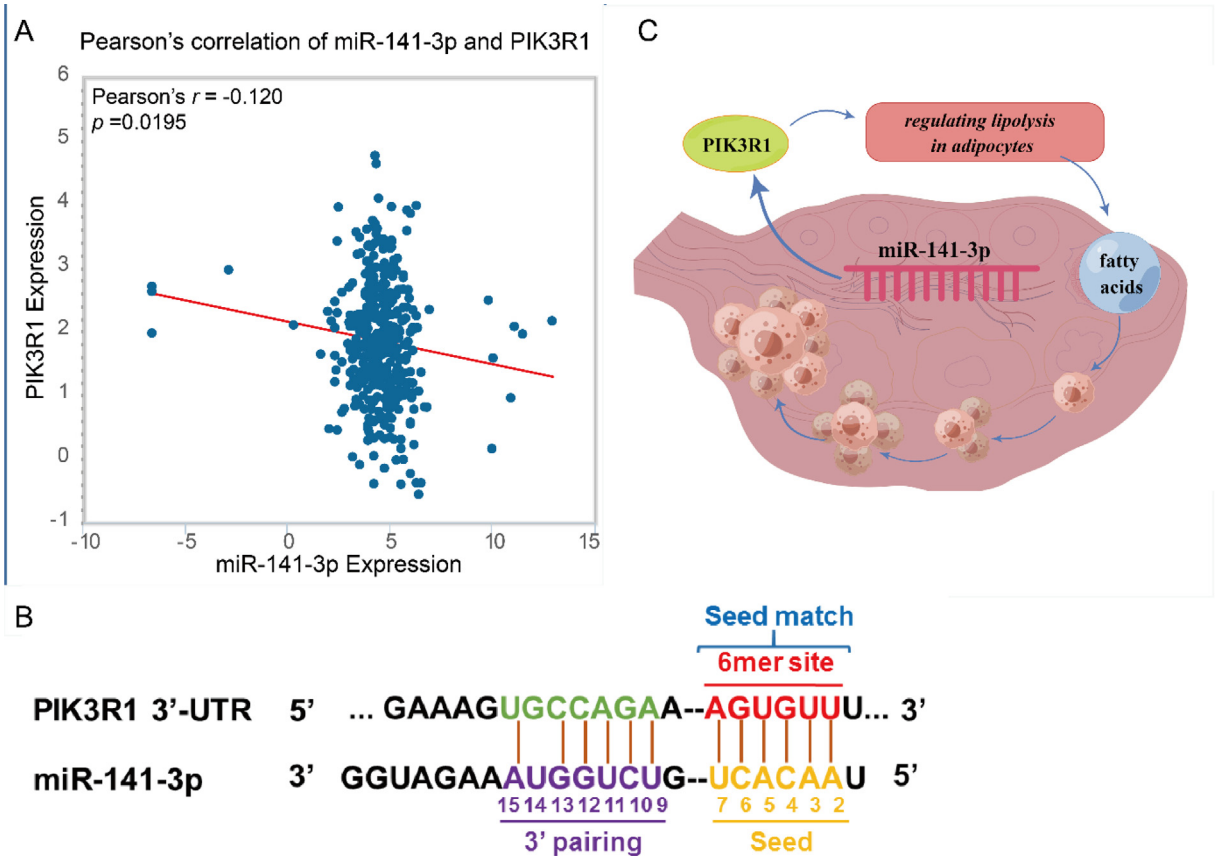

Fig. 8. (A) Pearson correlation analysis between miR-141-3p and PIK3R1. (B) Combining site of PIK3R1 to miR-141-3p. (C) The mechanism of miR-141-3p in OV.

including breast cancer [57,58] and prostate cancer [59]. Among the genes that are involved in the regulation of lipolysis in adipocytes pathway, the protein expression of IRS1, PIK3R1, and PRAKCB in OV was lower than that in normal tissues. PIK3R1 belongs to the PI3K family and encodes three proteins: p85α, p50α, and p55α. A tremendous number of studies have shown that the low expression of PIK3R1 is relevant to the occurrence of multitudinous cancers [60,61,62,63,64]. This is because p85α decreases when PIK3R1 is down-regulated, which leads to the activation of the Akt signaling pathway, which mediates tumorigenesis [65]. Interestingly, our study firstly demonstrated that the expression of miR-141-3p was significantly negatively correlated to PIK3R1 in OV, and that miR-141-3p may down-regulate the expression of PIK3R1 via combining to the 3′-UTR of PIK3R1. Therefore, this study suggested that miR-141-3p may promote the occurrence of OV by means of down-regulating its underlying target gene, PIK3R1.

5. Conclusions

In the present work, the expression and oncogenic role of miR-141-3p in OV were comprehensively analyzed through experiments and high-throughput databases. Although limitations may have existed due to the finite quantity of mRNA chips included in the analysis and the different subtypes of samples analyzed by different research groups, the study preliminarily showed that miR-141-3p is overexpressed in OV tissues. Moreover, the study also illustrated that miR-141-3p may accelerate the tumorigenesis and development of OV by targeting and down-regulating the expression of PIK3R1. This finding provides new insight into the mechanism of miR-141-3p in the tumorigenesis and development of OV, which is worthy of further validation and investigation.

Ethical approval

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University Written informed consent for publication of identifying images or other personal or clinical details was obtained from all participants.

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Conflict of interest

The authors declare there are no competing interests.

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Supplementary material

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