Original Article
miRNA-612 suppresses ovarian cancer cell tumorigenicity by downregulating NOB1

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Abstract: MicroRNAs (miRNAs) play crucial roles in cancer progression. Our previous study demonstrated that NIN1/RPN12 binding protein 1 homolog (NOB1) was a functional regulator in the progression of ovarian cancer (OC). However, the role of miRNA-612 (miR-612) in OC has not been elucidated. In this study, we aimed to investigate the regulatory mechanism of NOB1 targeting miRNA, miR-612, in OC tumorigenicity. The miR-612 expression was downregulated in OC patient tissues and four OC cell lines (Caov3, A2780, SKOV3 and OVCAR3). The miR-612 level was negatively correlated with NOB1 expression, and dual-luciferase reporter assay indicated that miR-612 suppressed NOB1 expression by targeting the 3’UTR of NOB1 transcript. Up-regulation of miR-612 mediated by lentiviral transduction suppressed cell proliferation, colony formation, migration, invasion, and induced apoptosis in OC cell lines. In addition, miR-612 overexpression inhibited tumor growth of OC in vivo by sequestering NOB1 expression. In conclusion, our results suggested that miR-612 directly targeted NOB1 to suppress OC progression. Therefore, the miR-612-NOB1 axis could serve as therapeutic targets for OC.

Keywords: Ovarian cancer, miR-612, NOB1, tumorigenicity

Introduction

Ovarian cancer (OC) is one of the most common gynecologic cancers causing death [1-3]. Despite the initial chemosensitivity of OC, the recurrence is frequent and the median overall survival is less than 5 years [4, 5]. OC is a global health problem, often diagnosed at an advanced stage, and there are no effective screening strategies [6, 7]. The pathogenesis of OC is not yet fully understood. Therefore, elucidating the abnormally altered proteins or miRNAs in OC is crucial for the regulation of cancer progression, identification of OC detection markers and development of potential antitumor drugs.

The NIN1/RPN12 binding protein 1 homolog (NOB1) gene encodes the NOB1 protein containing a PilT amino terminus (PIN) domain and a C terminal zinc ribbon domain [8]. The human NOB1 gene is composed of nine exons and eight introns and is localized on human chromosome 16q22.1 [9]. Nob1 is involved in prerRNA processing. In a late cytoplasmic processing step, Nob1 cleaves a 20S rRNA intermediate at cleavage site D to produce the mature 18S rRNA [10]. Since NOB1 is involved in ribosome biogenesis and 26S proteasome function in the nucleus, it may have the potential to regulate cell proliferation. The dysfunction of NOB1 was associated with hearing loss [11] and Diamond-Blackfan anemia [12]. Our previous study indicated that NOB1 was highly expressed in OC samples, and downregulation of NOB1 suppressed OC cell proliferation by inducing cell apoptosis [13], indicating that NOB1 could be developed as a potential therapeutic target for OC.

MicroRNAs (miRNAs) are the small noncoding RNAs (around 20 nucleotides) that regulate nearly all biological pathways in multicellular organisms [14, 15]. The miRNA expression in human cancers is dysregulated by various mechanisms, including amplification or deletion of miRNA genes, aberrant transcriptional control of miRNAs, dysregulated epigenetic changes and defects in miRNA biogenesis mechanisms [16]. miRNAs can also function as
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Oncogenes or tumor suppressors. Dysregulated miRNAs have been shown to affect hallmarks of cancer, including maintenance of proliferative signaling, evasion of growth suppressors, resistance to cell death, activation of invasion and metastasis, and induction of angiogenesis [17]. Previous studies have indicated that miRNAs could be used as potential biomarkers for human cancer diagnosis, prognosis and therapy [18]. MicroRNA-612 (miR-612) is located on human chromosome 11 and has been implicated to be a tumor suppressor in various cancers, such as hepatocellular carcinoma (HCC) [19], colorectal cancer (CRC) [20] and esophageal squamous cell carcinoma (ESCC) [21].

The current study aimed to investigate the relationship and function of NOB1 and miR-612 in regulating OC. Our results indicated that the level of miR-612 and NOB1 was down-regulated and up-regulated, respectively, in OC tissues and cells. The expressions of miR-612 and NOB1 were negatively correlated. Functional analysis indicated that miR-612 overexpression inhibited OC cell proliferation, colony formation, migration and invasion, but induced cell apoptosis by impairing NOB1 expression. miR-612 also regulated OC metastasis in vivo. Our data suggested that miR-612 is critical in regulating OC growth and could be developed as a novel therapeutic target for OC therapy.

Methods and materials

Clinical specimens

Sixty-two paired OC and adjacent normal tissues were collected from patients hospitalized at the Second Hospital of Jilin University between March 2018 and January 2020. The patients did not receive any chemotherapy, radiotherapy or immune therapy, and the histological sections were checked by two pathologists to confirm the diagnosis. All specimens were stored at -80°C freezer until use. This study was approved by the Ethics Committee of the First Affiliated Hospital Jilin University (20180011), and all patients have signed informed consents.

Cell culture

All reagents used for cell culture were obtained from Gibco (ThermoFisher, USA). The human ovarian surface epithelial cells (OSE) and human OC cell lines (Caov3, A2780, SKOV3 and OVCAR3) were obtained from Procell (Wuhan, China). Above cells were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 100 U/mL penicillin/streptomycin at 37°C in a 5% CO₂ humidified incubator.

Generation of stable cell line by lentivirus

The second-generation lentiviral plasmids psPAX2 and pMD2.G were obtained from Addgene. The transfer plasmids containing miRNA-612 and miRNA-NC were customized and ordered from Comate Bioscience (Jilin, China). HEK293T cells were transfected with psPAX2, pMD2.G and transfer plasmid expressing miRNA-612 or miRNA-NC using Lipofectamine 3000 (Invitrogen, USA). The viral supernatants were harvested at 48 h and 72 h post-transfection and filtered by a 0.45 μm filter (Millipore). To generate miRNA-612 overexpression cell lines, Caov3 and SKOV3 cells were transduced with filtered lentiviral supernatants supplemented with 10 μg/ml polybrene (Millipore). Stable cell lines were screened by 6 μg/ml puromycin treatment for 2 weeks.

Cell viability assays

The cell viabilities were determined by Cell Counting Kit-8 (CCK-8, Dojindo, Kumamoto, Japan). Briefly, 5 × 10³ cells were seeded into each well in 96-well plates. Cells were incubated for indicated time (0, 24, 48, 72 h) in a humidified incubator. Subsequently, 10 μl of CCK-8 solution was added into wells and incubated for 4 h at 37°C. The absorbance was determined at 450 nm by a microplate reader (Potenov Technology, Beijing, China).

Western blot

Proteins in cell and tissue samples were isolated by RIPA buffer (Beyotime, China) and T-PER tissue protein extraction reagent (ThermoFisher, USA), respectively. The proteins were subjected to sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto the PVDF membranes. After blocking with 5% non-fat milk in TBST, the membranes were incubated with the primary antibodies and followed by incubation with secondary antibodies. Subsequently, the membranes were visualized by sensitive enhanced chemilu-
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**Table 1.** The primers used in this study for RT-PCR

<table>
<thead>
<tr>
<th>Primer name</th>
<th>Primer sequences (5'-3')</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOB1-F</td>
<td>CCGGGAGGTGGTGCACTGAGA</td>
</tr>
<tr>
<td>NOB1-R</td>
<td>GATGTCGGTGCCAGAGGCG</td>
</tr>
<tr>
<td>miR-612-F</td>
<td>CCTGCTGGGCAAGGCTTCTG</td>
</tr>
<tr>
<td>miR-612-R</td>
<td>TGGCTGCGGCAAGGAGGGG</td>
</tr>
<tr>
<td>GAPDH-F</td>
<td>GATGTCATCATACTGCGAGGTTT</td>
</tr>
<tr>
<td>GAPDH-R</td>
<td>CTCGCCTTGGCGACACA</td>
</tr>
<tr>
<td>U6-F</td>
<td>ACGCTTCAGAAATTGCCT</td>
</tr>
<tr>
<td>U6-R</td>
<td>ACGCTTCAGAAATTGCCT</td>
</tr>
</tbody>
</table>

minescence (ECL) detection kit (ProteinTech, China). The antibodies used in this study were as follows: NOB1 polyclonal antibody (1:500, 14456-1-AP, ProteinTech), GAPDH monoclonal antibody (1:1000, AF0006, Beyotime), HRP-conjugated Affinipure Goat Anti-Mouse IgG (H+L) (1:5000, SA00001-1, ProteinTech) and HRP-conjugated Affinipure Goat Anti-Rabbit IgG (H+L) (1:3000, SA00001-2, ProteinTech).

**RT-qPCR**

The total RNAs in cell and tissue samples were isolated by FastPure Cell/Tissue Total RNA Isolation Kit (Vazyme, China). The first-strand cDNA was synthesized by TransScript® First-Strand cDNA Synthesis SuperMix (Transgen, China). Real-time PCR was performed on the ABI 7500 Realtime System (ABI, USA) with TransStart® Green qPCR SuperMix (Transgen, China). The amplification reaction contained an initial denaturation at 94°C for 30 s, followed by 45 cycles of denaturation at 94°C for 5 s and extension at 60°C for 30 s. The RNA relative levels were determined using 2^−ΔΔCt method with GAPDH and U6 as endogenous controls for NOB1 and miRNAs, respectively. The primers used for RT-qPCR were presented in Table 1.

**Luciferase assay**

The pmirGLO-NOB1-WT, pmirGLO-NOB1-DEL and pmirGLO-NOB1-MUT dual-luciferase expression plasmid was co-transfected with miR-612 mimics or miR-NC (Comate Bioscience, China) into Caov3 and SKOV3 cells using Lipofectamine 3000 (Invitrogen, USA) according to the manufacturer’s protocols. After 24 h, the firefly and Renilla luciferase activities were measured by a Dual-Luciferase Reporter Assay System (Promega, USA).

**Colony formation assay**

Approximately 250 cells in each well were plated into 24-well plates. The cells were maintained for 2 weeks and then fixed with pre-chilled 4% paraformaldehyde (Beyotime, China) for 20 min at 4°C. After washing with PBS, cells were stained with 0.1% crystal violet (Biosharp, China) for 15 min. After extensive washing with PBS, the colonies were imaged using a digital camera.

**Flow cytometry**

Apoptosis was determined by TransDetect Annexin V-FITC/PI cell apoptosis detection kit (Transgene, China). Briefly, cells were detached and harvested, and then washed with PBS. The pelleted cells were incubated with pre-chilled Annexin V binding buffer containing Annexin V-FITC and PI, and maintained in the dark for 15 min. The stained cells were analyzed by the BD Accuri™ C6 Cytometer (BD, USA). The data were analyzed using Flowjo software (BD, USA). For each sample, at least 10,000 events were acquired.

**Transwell migration and invasion assays**

Transwell assay was performed in the 8 µm transwell chambers in a 24-well plate. Initially, 100 µl/well diluted Matrigel (1:20 dilution, BD, USA) was coated in the upper chamber and incubated at 37°C for 4 h. Subsequently, 5 × 10^4 cells/well with serum-free medium were added into the upper chamber and 750 µl media containing 10% FBS per well was added into lower chambers. After 24 h incubation, cells in upper chamber were washed and fixed, and then stained with 0.1% (w/v) crystal violet. Each sample was conducted in triplicate.

**Mice xenograft**

The procedures related to the animal experiments were approved by Committee of Animal Care and Use of the First Affiliated Hospital of Jilin University with the approval number KT-202003006. Ten 6 weeks old female BALB/c nude mice were obtained from the Experimental Animal Center of Jilin Province (Changchun, China) and maintained under Specific Pathogen Free (SPF) conditions. Stable SKOV3 cells (2 × 10^6 cells for each mouse) expressing miR-612/miR-NC were injected subcutaneous-
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For tumorigenesis assay (n = 5 for each group). Tumor growth was determined every 5 days using a vernier caliper by measuring tumor length (L) and width (W). Tumor volumes were calculated as \( (L \times W^2)/2 \). After 30 days, mice were sacrificed, and the tumors were dissected and weighed.

**Statistical analysis**

The statistical analyses were performed using GraphPad PRISM version 9.0 (GraphPad Software, San Diego, CA, USA). Data were presented as the mean ± SD. Differences were determined by the two-sample t test for two groups and one-way ANOVA followed by Bonferroni post hoc test for multiple groups. The expression relationship between miR-612 and NOB1 was explored by Pearson’s correlation analysis. A \( p \) value less than 0.05 indicated statistical significance.

**Results**

**miR-612 levels negatively correlate with NOB1 expression in OC patients and cell lines**

To investigate the regulatory mechanism of NOB on OC proliferation, bioinformatics analysis was performed to identify NOB interacting miRNAs by TargetScan (http://www.targetscan.org). Multiple miRNAs were shown to bind to NOB. Since miR-612 was reported to regulate cancer cell proliferation, it was selected to analyze its regulatory function on NOB1. To investigate the correlation of miR-612 levels with NOB1 expression, we collected 62 paired OC and normal tissue samples from patients before surgery or chemotherapy. Among clinical specimens, downregulated expression of miR-612 was observed in tumor samples compared to the adjacent normal samples (Figure 1A). However, the mRNA levels of NOB1 were elevat-
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Pearson’s correlation analysis indicated that miR-612 was negatively correlated with NOB1 expression (r = -0.511, P < 0.0001, Figure 1C). To further verify this correlation, we assessed the miRNA-612 and NOB1 expressions in four OC cell lines (Caov3, A2780, SKOV3 and OVCAR3) and one normal ovarian epithelial cell line (OSE). The results indicated that the miR-612 levels in OC cells were significantly lower than those in OSE (Figure 1D), and the opposite trends were observed in both mRNA (Figure 1E) and protein (Figure 1F) levels of NOB1, indicating that the miR-612 was negatively correlated with NOB1 in both OC specimens and cell lines. Since miRNA-612 was slightly lower while NOB1 was slightly higher in Caov3 and SKOV3 compared to A2780 and OVCAR3, Caov3 and SKOV3 cell lines were selected for further analysis.

**Figure 2.** NOB1 is a direct target gene of miR-612. (A) Schematic diagram of the dual-luciferase reporter assay. The binding sites between WT NOB1 3'-UTR and miR-612 were highlighted in blue color. The MUT and DEL NOB1 3'-UTR were constructed with mutation and deletion of binding sites (highlighted in red color), respectively. The luciferase activities in SKOV3 (B) and Caov3 (C) were determined 48 h post transfection. Data are mean ± SD of three independent experiments.

To verify if NOB1 is the direct target of miR-612, a series of luciferase reporter plasmids were generated. NOB1 was predicted to contain a putative miR-612 target site in the 3'-UTR (position 388-395). Therefore, wild type (WT), mutated (MUT) and deleted (DEL) NOB1 3'-UTRs (Figure 2A) were cloned into pmirGLO vector and co-transfected with miR-612 mimic. Our results revealed that miR-612 rather than non-functional control miR-NC significantly decreased the luciferase activity of WT NOB1 in both SKOV3 and Caov3 cells (Figure 2B and 2C). However, miR-612 mimic had no effects on alternations of luciferase activities of MUT or DEL NOB1 (Figure 2B and 2C), indicating that NOB1 was a direct target gene of miR-612.

**miRNA-612 overexpression suppresses tumorigenicity of OC cells in vitro**

To evaluate the miR-612 function on tumorigenicity of OC cells in vitro, the miR-612 stably expressing Caov3 and SKOV3 cell lines mediated by lentiviral transduction were generated. Initially, we compared the gene expressions and growth viability between parental (control, no lentiviruses transduced cells) and miR-NC expressing cells, but no differences were observed between two types of cells (data not shown). The overexpression efficiency of the miR-612 was verified by RT-qPCR (Figure 3A). Both mRNA and protein levels of NOB1 (Figure 3B, 3C) were down-regulated in miR-612 overexpressed cell lines. To further determine the miR-612 function in OC cells, CCK-8 assay was employed to determine the cell viability at 0, 24, 48 and 72 h post-seeding. The results revealed that miR-612 overexpression significantly inhibited OC cell proliferation (Figure 3D). In addition, highly expressed miR-612 also suppressed the colony formation (Figure 3E), migration (Figure 3F) and invasion (Figure 3G) of OC cells. Moreover, upregulation of miR-612 significantly increased the proportion of apoptotic SKOV3 and Caov3 cells (Figure 3H). Taken together, miR-612 overexpression suppressed the OC cell tumorigenicity and induced apoptosis by down-regulating NOB1 expression.
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A. Relative miR-612 level
B. Relative mRNA levels of NOB1
C. Integrated density
D. CCCK-8 (Absorbance at 450 nm)
E. Colony number
F. Cells per field
G. Annexin-V-FITC

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To further elucidate the relationship between NOB1 and miR-612 in OC cells, full-length NOB1 coding region was inserted into pCAGGS vector and designed as pCAGGS-NOB1. The pCAGGS-NOB1 plasmid or an empty pCAGGS vector was transiently transfected into SKOV3 cells stably expressing miR-612. Our results indicated that NOB1 expression was increased (Figure 4A). The ectopic expression of NOB1 partially rescued cell proliferation (Figure 4B), migration (Figure 4C) and invasion (Figure 4D) abilities. In addition, the portion of apoptotic cells was also reversed (Figure 4E). These results indicated that recovered NOB1 expression partially rescued the inhibitory effect of miR-612 overexpression on OC cell tumorigenicity.

miR-612 inhibited tumor growth of OC in vivo by altering NOB1 expression

To verify the inhibitory effect of miR-612 on tumor growth of OC in vivo, SKOV3 cells stably overexpressing miR-612 and control (miR-NC) were implanted subcutaneously into nude mice. Tumor sizes were determined every 5 days, and the mice were sacrificed and photographed at 30 days post-implantation. The tumors in miR-612 group were dramatically smaller than those in miR-NC group (Figure 5A). The tumor volume curve (Figure 5B) and tumor weights (Figure 5C) also indicated that overexpression of miR-612 significantly inhibited the tumor growth in vivo. The RT-qPCR results revealed that the miR-612 expression level in the implanted tumor xenografts was significantly up-regulated (Figure 5D). In contrast, the tumor xenografts with miR-612 implantation expressed lower levels of both NOB1 mRNA and protein compared to the control group (Figure 5E, 5F). In addition, SKOV3 cells overexpressing NOB1 were also implanted into nude mice, and miR-612 level was dramatically decreased in NOB1 overexpression group compared to control group (Figure 5G). These results indicated that miR-612 significantly suppressed the tumor growth of OC in vivo by down-regulating NOB1 expression.
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Discussion

OC is one of the three major malignant tumors of the gynecological reproductive system, and the mortality ranks first among gynecological malignant tumors [22]. The mortality/incidence ratio of OC is as high as 0.85 in China, and the mortality is relatively close to the incidence, indicating that OC seriously threatens the health and life of patients [23]. Surgical resection is the treatment of choice for OC. However, due to the lack of effective early diagnosis methods, most cases are already in the advanced stage at the time of diagnosis, and the effect of surgical treatment is poor. In addition, efficacy of chemotherapy drugs are also seriously affected due to their shortcomings such as cumulative toxicity, nephrotoxicity and ototoxicity, and resistance to chemotherapy [24]. Therefore, it is urgent to seek new treatments in order to improve the curative effect. Surgical techniques and the effectiveness of chemotherapy have made great strides in recent years, but the 5-year survival rate for patients with OC is still only 30-40% [25]. Therefore, targeted therapy of OC has become a current research hotspot, but there is still a lack of effective therapeutic targets. The treatment of OC faces the following two challenges. First, there is no effective clinical method for early diagnosis. Most patients have already developed OC metastasis when they are diagnosed, and the effect of surgical treatment is poor. Second, radiotherapy and chemotherapy have a series of problems such as high cytotoxicity [26]. Therefore, there is an urgent need to develop new therapeutic methods that can reduce the metastasis, recurrence, and drug toxicity during/after OC treatments. With the
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development of targeted drugs, people have begun to pay attention to their important value in the treatment of OC. Therefore, looking for intervention targets that can be used for OC treatment has become one of the potential ways to overcome the above challenges.

The NOB1 is an RNA-binding protein that is ubiquitously expressed in normal tissues such as lung, liver and spleen [27]. Its core function is to maintain RNA metabolism and stability, and to regulate protease activity [10, 28]. NOB1 is overexpressed in various cancers, such as pancreatic cancer, non-small cell lung cancer, OC, prostate cancer, osteosarcoma, papillary thyroid cancer, colorectal cancer and glioma [19, 29-31]. NOB1 is also a molecular chaperone that regulates the linkage of 20S to 19S proteasome granules in the nucleus and can promote the 26S protein 5 enzyme maturation [32]. NOB1 is integral to the process of proteolysis dependent on the ubiquitin-proteasome pathway (UPP). The mutation and abnormal expression of NOB1 will lead to the accumulation of polyubiquitin protein in cells, resulting in the abnormality of the ubiquitin-proteasome system, reducing its degradation of oncoprotein and tumor suppressor protein, and blocking the apoptosis of mutant cells, which eventually lead to tumorigenesis [33, 34].

An increasing number of evidence indicated that abnormal expression of NOB1 is associated with cancer growth and poor prognosis [35, 36]. NOB1 has the potential to become an anti-tumor drug target and a biological detection indicator. However, the underlying molecular mechanisms of NOB1 are still not fully understood, and elucidating the regulatory effects of NOB1 on tumors is important for cancer therapy. Our previous study demonstrated that NOB1 expression was up-regulated in OC tissue, and its knockdown decreased cell proliferation, colony formation and induced G1-S cell cycle arrest [13]. This study aimed to identify the NOB1 targeting miRNAs and explore the regulatory roles of miRNA in OC tumorigenicity through NOB1 regulation.

Accumulating studies have shown that miRNAs play a key role in tumorigenesis and tumor progression [15, 16]. Almost all human cancers are accompanied by abnormal expression changes of miRNAs [37-41]. Therefore, miRNAs were considered as effective molecular biomarkers for cancer diagnosis and therapeutic target for tumors. In this study, bioinformatic analysis was performed to identify the NOB1 binding miRNAs. Among the multiple identified miRNAs, we focused on miR-612 as it was served as a tumor suppressor in several cancer types. However, the miR-612 levels differed among different tumors. miR-612 expression was downregulated in CRC and HCC samples and cells [19, 20]. In contrast, miR-612 was highly expressed in ESCC specimens [21]. Our data suggested that miR-612 levels were downregulated and negatively correlated with NOB1 expression in OC specimens and cell lines. Dual-luciferase reporter assay further verified that miR-612 directly targeted the 3’-UTR of NOB1. We further generated SKOV and Caov3 cells stably expressing miR-612 mediated by lentiviral transduction, and miR-612 was significantly increased in both cell lines, thereby downregulating NOB1 expression. miR-612 overexpression dramatically suppressed the OC cell proliferation, colony formation, migration, invasion, and further induced apoptosis. Restoration of NOB1 level by ectopic pCAGGS-NOB1 transfection partially reversed the impaired OC cell growth mediated by miR-612 overexpression. Finally, we determined the function of miR-612 in tumor growth of OC in vivo through a mouse tumor xenograft model. Overexpression of miR-612 significantly inhibited OC progression in vivo by sequestering NOB1 expression. In addition, to further validate the negative correlation between NOB1 and miR-612, we tested the effect of NOB1 overexpression on miR-612 level, and our data indicated that highly expressed NOB1 decreased miR-612 level. These data demonstrated a strong correlation between miR-612 and NOB1, implicating the importance of miR-612-NOB1 in OC tumorigenesis. In addition to NOB1, miR-612 reduces invadopodia formation, possibly through HADHA-mediated changes in cell membrane cholesterol, with concomitant inhibition of Wnt/β-catenin-regulated EMT in HCC [19]. miR-612 impairs CRC cell proliferation and migration by inhibiting AKT2 in vitro and in vivo [20], miR-612 is associated with ESCC development and metastasis by regulating TP53 expression [21]. These studies suggested that miR-612 functioned as a multi-mediator in different cancers and could develop as a potential therapeutic target.
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In conclusion, we have identified a miRNA, miR-612, that is enriched and dysregulated in OC, and found that it sequesters NOB1 through interaction within 3'-UTR to regulate NOB1 expression. Furthermore, miR-612 overexpression suppressed the OC tumorigenicity in vitro and in vivo by downregulating NOB1. Our study revealed the therapeutic potential of targeting miR-612-NOB1 to affect OC progression.

Acknowledgements

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Disclosure of conflict of interest

None.

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