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LINC00707 promotes multidrug resistance of ovarian cancer cells by targeting the miR-382-5p/*LRRK2* axis

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Multidrug resistance severely limits the efficacy of ovarian cancer (OC) treatment. Recent studies have revealed the carcinogenic role of *LINC00707* RNA. However, the role of *LINC00707* in the development of multidrug resistance in OC has not been clarified. Therefore, the aim of this study was to investigate the relationship between *LINC00707* and multidrug resistance in OC, which can facilitate the development of new therapeutic agents for effectively addressing this issue. The RNA expression of *LINC00707*, *miR-382-5p* and leucine-rich repeat kinase 2 (*LRRK2*) in SKOV3 (a human OC cell line) cells was detected by qRT-PCR. The effects of *LINC00707* on the proliferation and viability of SKOV3 cells were determined by MTT assay and colony formation assay. The interaction of *LINC00707*, *miR-382-5p*, and *LRRK2* was bioinformatically predicted and verified with dual-luciferase reporter assay. In addition, the effect of *LINC00707* on drug resistance in SKOV3 cells through targeting the *miR-382-5p/LRRK2* axis was explored. The expression of *LINC00707* and *LRRK2* was significantly increased in SKOV3 cells, while *miR-382-5p* expression was significantly decreased. The results of bioinformatic prediction and colony formation assay demonstrated that *LINC00707* could regulate *LRRK2* expression in SKOV3 cells by targeting *miR-382-5p*. Additionally, knockdown of *LINC00707* markedly increased expression of miR-382-5p and decreased that of *LRRK2*, increased cell proliferation and viability, as well as sensitivity to chemotherapeutic agents in SKOV3 cells. Notably, these manifestations were more obvious with simultaneous knockdown of *LINC00707* and *miR-382-5p* compared with knockdown of *LINC00707* alone. *LINC00707* is overexpressed in SKOV3 cells and promotes SKOV3 cell proliferation and resistance to chemotherapeutic drugs via targeting the *miR-382-5p/LRRK2* axis.

Keywords: ovarian cancer; *LINC00707*; *miR-382-5p*; *LRRK2*; multidrug resistance

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Abbreviations: ATCC, American Type Culture Collection; FBS, fetal bovine serum; IgG, immunoglobulin G; LRRK2, leucine-rich repeat kinase 2; miRNAs, MicroRNAs; OC, ovarian cancer; PVDF, polyvinylidene fluoride; qRT-PCR, Quantitative real-time PCR; S,D., standard deviation

INTRODUCTION

Ovarian cancer (OC) is one of the deadliest malignancies in women. Global cancer statistics in 2020 reported more than 310,000 new cases and nearly 210,000 deaths of OC, with increasing morbidity and mortality rates each year (Kuroki & Guntupalli, 2020; Sung *et al.*, 2021). Although more than a third of OC patients can be diagnosed at an early stage (Sadeghi *et al.*, 2011), distant metastases usually occur in about 60% of these patients, which results in a five-year survival rate of only 30% (Siegel *et al.*, 2020). In addition, surgical resection of the tumor and cisplatin-based chemotherapy are the two major standard treatments for newly diagnosed OC patients in clinical settings. Unfortunately, clinical data have shown that with prolonged treatment, OC loses sensitivity to cisplatin and can even completely acquire resistance to it, resulting in treatment failure (Luo *et al.*, 2020). Consequently, resistance, particularly multidrug resistance, continues to be the primary challenge when employing chemotherapeutic drugs for OC. Therefore, it is important to explore the mechanism of drug resistance in OC cells.

To date, multiple studies have shown that the acquisition of drug resistance in OC is affected by multiple factors, of which genetic and epigenetic factors are the most significant (Bast *et al.*, 2009). Particularly, long noncoding RNAs (lncRNAs), a class of RNA transcripts with more than 200 nucleotides but no capacity for protein coding, play a key role in the development of multidrug resistance. By interacting with chromatin, RNA, and proteins, lncRNAs affect numerous processes in a cancer cell such as cell proliferation, anti-apoptosis, and migration (Raveh *et al.*, 2015). Moreover, lncRNAs have also been reported to be associated with acquired resistance in cancer cells. When paclitaxel-resistant cells were subjected to lncRNA sequencing, Xu and others speculated that five upregulated lncRNAs and 21 downregulated lncRNAs were linked to multidrug resistance (Xu *et al.*, 2018). Wang *et al.* suggested that lncRNA *EPIC1* could promote AKT-mTORC1 signaling and resistance to rapamycin in breast cancer and OC by binding to the transcription factor Myc (Wang *et al.*, 2020). Shi *et al.* discovered a significant increase in the expression of *LINC01118* in paclitaxel-resistant OC tissues, which promoted cell migration and invasion while inhibiting apoptosis (Shi & Wang, 2018). All these data indicate the significance of lncRNAs in the multidrug resistance of OC. Notably, *LINC00707* has been shown to behave as a cancer-promoting factor in both colorectal and cervical malignancies (Guo *et al.*, 2021). A recent study on cisplatin-resistant non-small cell lung cancer (NSCLC) cells showed that knocking down *LINC00707* expression significantly restored the sensitivity of the resistant cells to cisplatin (Zhang *et al.*, 2019). In summary, *LINC00707* not only promotes cancer development, but

also increases the susceptibility of cancer cells to medication resistance.

MicroRNAs (miRNAs), small non-coding RNAs of about 20 nucleotides in size, regulate the expression level of genes by binding to the 3' UTR region of target genes, thereby affecting the regular activities of cells (Sun *et al*., 2019). MiRNAs may play a direct or indirect role in the progression of cancer and the emergence of drug resistance to chemotherapeutics. A study showed that downregulated *miR-130a* was associated with multidrug resistance in various cancers, and *miR-130a* targeted *MET* and enhanced TRAIL sensitivity in NSCLC cells (Acunzo *et al*., 2012). According to the results of previous studies, *miR-382-5p* may be a tumor suppressor gene, and reduction of its expression can promote cancer progression (Xie & Pan, 2021). Furthermore, increased *miR-382-5p* expression levels led to significant reduction in iron levels in OC cells (Sun *et al*., 2021). However, no studies have yet been conducted on the role of *miR-382-5p* in acquisition of multidrug resistance in OC cells. Interestingly, an interaction between *LINC00707* and *miR-382-5p* has been revealed, which is shown to affect cancer progression (Guo *et al*., 2021), but the role of this relationship in OC remains unclear. We proposed the multidrug resistance mechanism of OC as follows: *LINC00707* acted as a molecular sponge for *miR-382-5p* and increased OC progression and resistance to chemotherapeutic agents by targeting *miR-382-5p*. This hypothesis was further supported by *in vitro* cell experiments.

MATERIALS AND METHODS

Cell culture and treatment

Human normal ovarian surface epithelial cell line (IOSE80) and human OC cell line (SKOV3) were obtained from the American Type Culture Collection (ATCC, VA, USA). The cells were cultured in DMEM/F12 medium supplemented with 100 U/mL penicillin, 0.1 mg/mL streptomycin sulfate, and 10% fetal bovine serum (FBS), then the medium was incubated at 37°C and 5% CO_2

According to the manufacturer's instructions, the following plasmids or fragments were transfected into the cells using Lipofectamine™ 2000 transfection reagent: control shRNA, LINC00707 shRNA, control pcDNA3.1 vector, pcDNA3.1-LINC00707, control mimics, miR-382-5p mimics, control inhibitor, and miR-382-5p inhibitor. Next, LINC00707 shRNA and miR-382-5p inhibitor were transfected into SKOV3 cells together, upon which the following groups were obtained: sh-NC, sh-LINC00707, control vector, LINC00707, miR-NC, miR-382-5p, Anti-NC, Anti-miR-382-5p, and sh-LINC00707 + Anti-miR-382-5p. The medium was replaced with fresh medium six hours after transfection for two days of culture. Finally, the transfection efficiency was verified using qRT-PCR.

Quantitative real-time PCR (qRT-PCR)

The TRIzol™ Plus RNA Purification Kit was used to extract total RNA from SKOV3 cells following the manufacturer's instructions. The concentration and purity of RNA were subsequently measured by NanoDrop One ultramicrospectrophotometer. With the help of PrimeScript RT Master Mix, cDNA was obtained by reverse transcription. qRT-PCR was performed to detect the expression levels of *LINC00707*, *miR-382-5p*, and leucine-rich repeat kinase 2 (*LRRK2*) according to the instructions of the SYBR Premix Ex Taq II kit. *GAPDH* or *U6* served as an internal control, and six replicates were set up for the experiment. The experimental data obtained by qRT-PCR were used to calculate the relative expression of the target gene with the help of the $2^{-\Delta\Delta Ct}$ method. The primer sequences used are shown in Table 1.

Table 1. Primer Sequences for qRT-PCR

RNA	Sequences (5′ to 3′)
LINC00707	F: 5′- CCAACAGGGTATCAGAATTCTC
	R: 5′- TGCTGACAATAGCCATTAGG
miR-382-5p	F: 5′- CTCGCTTCGGCAGCACA
	R: 5′- TATGGTTGTAGAGGACTCCTTGAC
LRRK2	F: 5′- AGCAAGGGACAGGCTGAAGTTG
	R: 5′- GCAGGCTTTGCGTTGCTTCTCA
U6	F: 5′- AACGCTTCACGAATTTGCGT
	R: 5′- CTCGCTTCGGCAGCACA
GAPDH	F: 5′- GCACCGTCAAGGCTGAGAAC
	R: 5′- ACCACCCTGTTGCTGTAGCCAA

MTT assay

The transfected SKOV3 cells were seeded in a 96-well plate at a density of 5×10^3 cells/well, and to each well, 20 μL MTT solution (5 mg/mL) was added. After 4 h of incubation at 37°C, the supernatant was aspirated and 200 μL DMSO was then added into each well. Later, the absorbance values at a wavelength of 490 nm were measured by a microplate reader, and the cell viability was evaluated. In order to observe the drug resistance of cells, the transfected SKOV3 cells were incubated with different concentrations of paclitaxel (PTX, 2, 4, 8, 16, 32 μmol/L), doxorubicin (Dox, 0.5, 1, 2, 4, 8 μmol/L), methotrexate (MTX, 2, 4, 8, 16, 32 μmol/L), and cisplatin (DDP, 0.25, 0.5, 1, 2, 4 μmol/L) for 48 h. Subsequent to the addition of 20 μL MTT solution to each well, the supernatant was aspirated after 4 h of incubation at 37°C. Again, 200 μL DMSO was added to each well, and the absorbance at 590 nm was detected by a microplate reader. Half-maximal inhibitory concentration (IC50) was calculated with the use of GraphPad Prism 7 software.

Colony formation assay

The transfected SKOV3 cells were inoculated into 6-well culture plates at 1×10^6 cells/well and cultured in DMEM/F12 medium containing 10% FBS for two weeks, with the medium replaced every three days. Afterwards, SKOV3 cells were fixed with 4% paraformaldehyde and stained with 0.1% crystal violet.

Dual-luciferase reporter assay

In order to verify the interaction among *LINC00707*, *miR-382-5p*, and *LRRK2*, wild type *LINC00707* and *LRRK2*, or *LINC00707* and *LRRK2* fragments with

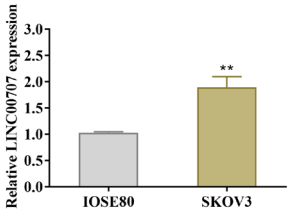

Figure 1. *LINC00707* is upregulated in ovarian cancer (OC) cells. The expression levels of *LINC00707* RNA in human normal ovarian surface epithelial cells (IOSE80) and human OC cells (SKOV3) detected by qRT-PCR. ***p*<0.01, *vs* IOSE80 group.

mutated nucleic acid sequences were constructed and then inserted into the luciferase reporter gene of pMIR-REPORT (pGL3) plasmid (H306, Obio Technology, Shanghai, China) based on the predicted binding sites of *LINC00707* and *LRRK2* with *miR-382-5p*. The cells were accordingly divided into four groups: wild type pGL3-LINC00707 (*LINC00707*-WT) and pGL3-LRRK2 (*LRRK2*-WT) or mutant pGL3-LINC00707 (*LINC00707*-MUT) and pGL3-LRRK2 (*LRRK2*-MUT) vectors. Next, miR-382-5p mimics and pGL3 plasmids were transfected together into SKOV3 cells using Lipofectamine™ 2000. Subsequently, luciferase activity was assessed using the Dual-Luciferase Reporter System Kit (E1910, Promega, USA).

Western blot

The cells were lysed in lysis buffer (RIPA) supplemented with a protease inhibitor (PMSF). Equal amounts of protein (20 μg) were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride (PVDF) membranes. After that, the membranes were blocked with 5% milk in Tris-buffered saline containing 0.1% Tween-20 for 1 h at ambient temperature. The membranes were subsequently incubated overnight at 4°C with primary LRRK2 antibody (1:1000, ab133474, Abcam, Cambridge, UK), followed by 1 h of incubation at 37°C with peroxidase conjugated goat anti-rabbit immunoglobulin G (IgG) antibody (1:3000; ab97051). Next, immunoreactive bands were visualized using enhanced chemiluminescence reagents (Thermo Fisher Scientific, Waltham, USA) and imaged using a Luminescent Image Analyzer ChemiDoc XRS Plus (Bio-Rad). Optical densitometric quantification of band intensities from four independent experiments was performed using Image-Pro Plus 6.0 software, and relative expression levels of target proteins were normalized to band intensities of GAPDH.

Data analysis

Measurement data were presented as mean ± standard deviation (S.D.). The *t*-test was adopted when comparing only two groups, and one-way analysis of variance with Tukey' test was employed when comparing more than two groups. Pearson correlation was applied to analyze the expression correlation. All statistical analyses were performed using SPSS 26.0 software (IBM, Armonk, NY, USA), with two-tailed $p<0.05$ as the level of statistical significance. All experiments were performed in triplicate, with at least three independent experiments.

RESULTS

LINC00707 is upregulated in SKOV3 cells

QRT-PCR was used to determine *LINC00707* expression in OC cells in this study. We found that *LINC00707* was expressed at significantly higher levels in SKOV3 than in IOSE80 cells (Fig. 1), which suggests that *LINC00707* may be involved in OC development.

Knockdown of LINC00707 suppresses the proliferation of SKOV3 cells

In order to investigate the effect of *LINC00707* on OC, *LINC00707* was knocked down or overexpressed using plasmids, and the transfection efficiency was detected by qRT-PCR. The qRT-PCR results demonstrated that the expression level of *LINC00707* was significantly decreased in cells in the sh-LINC00707 group compared with that in the sh-NC group and was notably increased

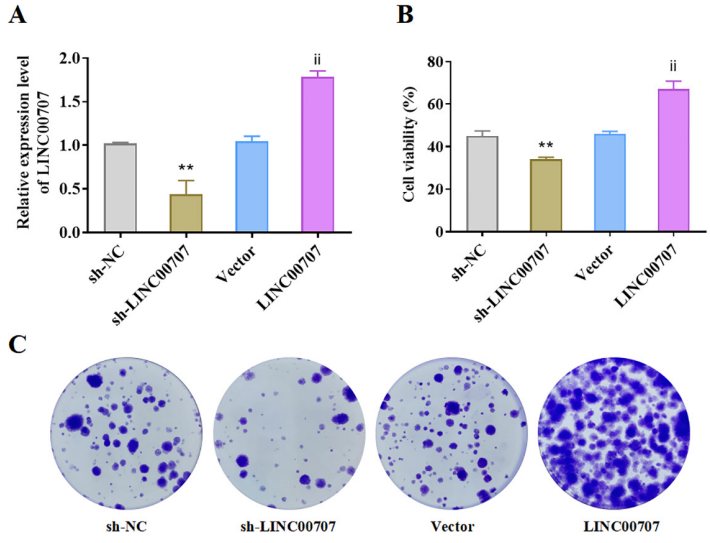

Figure 2. Knockdown of *LINC00707* suppresses the proliferation of ovarian cancer (OC) cells. (**A**) Expression level of *LINC00707* in SKOV3 cells after transfection measured with qRT-PCR. (**B**) The effect of *LINC00707* knockdown or overexpression on SKOV3 cell viability assessed with MTT assay (**C**) Cell colony formation assay results of the effect of *LINC00707* knockdown or overexpression on SKOV3 cell proliferation. ***p*<0.01, *vs* sh-NC; $^{ii}p<0.01$, *vs* Vector. sh, short hairpin; NC, negative control.

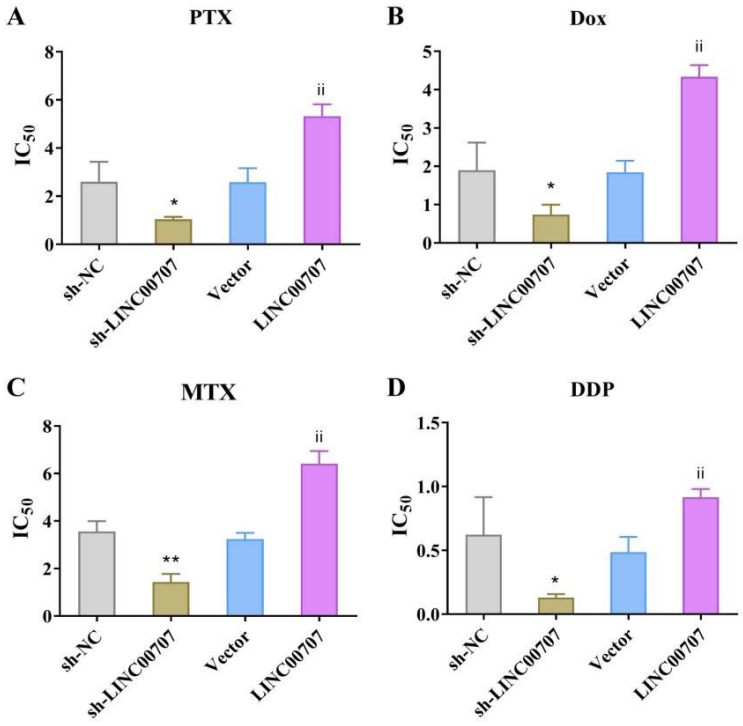

Figure 3. Knockdown of *LINC00707* decreases multidrug resistance in ovarian cancer (OC) cells.
(**A–D**) MTT assay results of the effect of PTX (**A**), Dox (**B**), MTX (**C**) and DDP (**D**) on drug resistance in SKOV3 cells with knocked down or overexpressed *LINC00707*. ***p*<0.01, *vs* sh-NC; ⁱⁱ*p*<0.01, *vs* Vector. sh, short hairpin; NC, negative control; PTX, paclitaxel; Dox, doxorubicin; MTX, methotrexate; DDP, cisplatin.

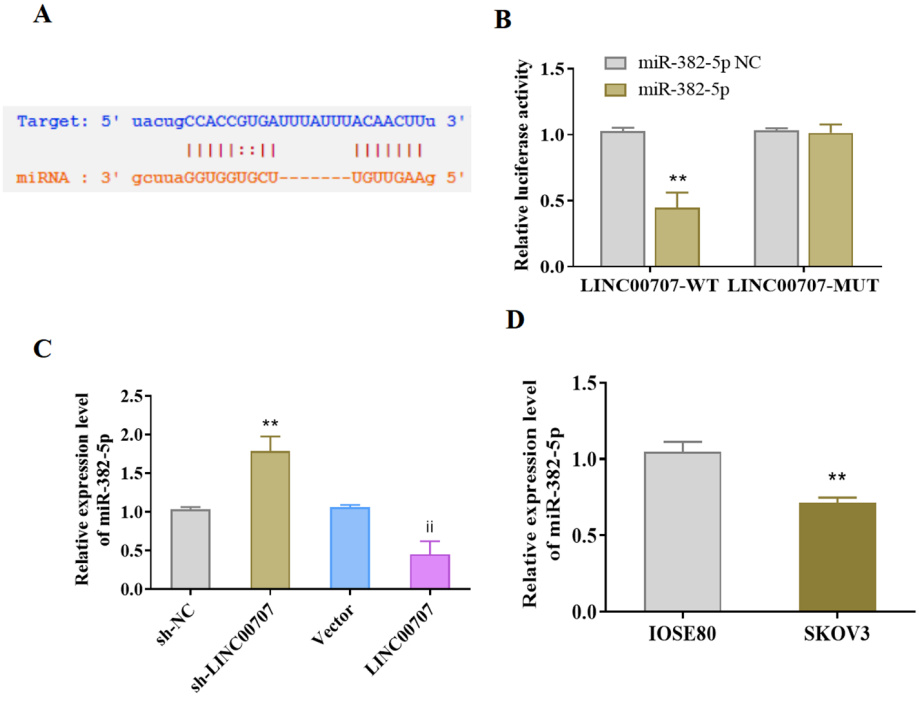

Figure 4. *LINC00707* targets miR-382-5p and negatively interacts with *miR-382-5p* in ovarian cancer (OC) cells.
(**A**) The binding sites between *LINC00707* and *miR-382-5p* predicted by lncBASE software. (**B**) Dual-luciferase reporter assay results of relative fluorescein activity in SKOV3 cells transfected with LINC00707 WT + miR-382-5p mimics and LINC00707 MUT + miR-382-5p mimics. (**C**) qRT-PCR results of the expression level of *miR-382-5p* in SKOV3 cells transfected with LINC00707. (**D**) qRT-PCR results of the expression levels of *miR-382-5p* in IOSE80 cells and SKOV3 cells. ***p*<0.01, *vs*. sh-NC (or miR-382-5p NC); ⁱⁱ*p*<0.01, *vs* Vector. WT, wild type; MUT, mutant; sh, short hairpin; NC, negative control.

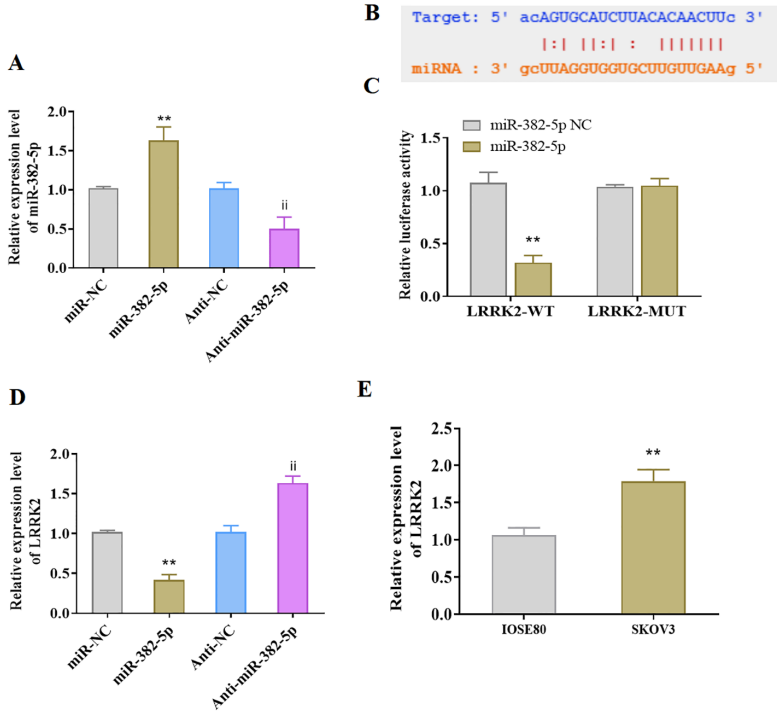

Figure 5. MiR-382-5 targets *LRRK2* mRNA and negatively interacts with *LRRK2* expression in ovarian cancer (OC).
(**A**) qRT-PCR results of the expression of *miR-382-5p* in SKOV3 cells after transfection. (**B**) The targeting relationship of *miR-382-5p* to *LRRK2* mRNA predicted by starbase2.0 (https://starbase.sysu.edu.cn/starbase2/index.php), and the predicted miR-382-5p binding site in *LRRK2* mRNA. (**C**) Dual-luciferase reporter assay results validating the association between *miR-382-5p* and *LRRK2*. (**D**) qRT-PCR results of the expression level of *LRRK2* mRNA in SKOV3 cells transfected with *miR-382-5p*. (**E**) qRT-PCR results of the expression level of *LRRK2* mRNA in IOSE80 cells and SKOV3 cells. $^{**}p<0.01$ *vs* sh-NC (or miR-382-5p NC); WT, wild type; MUT, mutant.

in the LINC00707-oe group compared with the control vector group (Fig. 2A). Later, we examined cell proliferation and viability through MTT and colony formation assays. Combining the results of both assays, we observed that the proliferation and viability of cells in the sh-LINC00707 group were much lower than those in the sh-NC group, and the proliferation and viability of cells in the LINC00707-oe group were much higher than those in the control vector group (Fig. 2B, 2C). Thus, knockdown of *LINC00707* can significantly inhibit SKOV3 cell proliferation.

Knockdown of LINC00707 decreases multidrug resistance in SKOV3 cells

Subsequently, in order to observe the effect of *LINC00707* on chemoresistance of SKOV3 cells, the resistance of LINC00707-knock-down and LINC00707 overexpressing SKOV3 cells to PTX, Dox, MTX, and DDP was studied using MTT assay. The MTT results showed that the IC50 of SKOV3 cells treated with PTX, Dox, MTX, and DDP was markedly decreased in the sh-LINC00707 group compared with the sh-NC group, while being considerably increased in the LINC00707-oe group relative to the control vector group (Fig. 3A–D). In brief, knockdown of *LINC00707* can reduce the resistance of SKOV3 cells to chemotherapeutic agents.

LINC00707 targets miR-382-5p

LINC00707 was predicted to target *miR-382-5p* using lncBASE software (Fig. 4A). According to the findings of dual-luciferase reporter assay, co-transfection of WT-LINC00707 3'-UTR with miR-382-5p mimics in the miR-382-5p group greatly reduced the luciferase activity compared with the miR-NC group (Fig. 4B). qRT-PCR results indicated that SKOV3 cells in which *LINC00707* was knocked down showed significant increase in the *miR-382-5p* expression compared with the cells in the sh-NC group, and those with *LINC00707* overexpression showed significant downregulation of *miR-382-5p* expression compared with those in the control vector group (Fig. 4C). In addition, the expression level of *miR-382-5p* was much lower in SKOV3 cells than in IOSE80 cells (Fig. 4D). Overall, *LINC00707* targets *miR-382-5p* and sh-LINC00707 can significantly upregulate the *miR-382-5p* expression in OC.

LRRK2 is a target gene of miR-382-5p

Firstly, we generated SKOV3 cells with *miR-382-5p* knock down or overexpression to determine the relationship between miR-382-5p and *LRRK2*. The expression level of *miR-382-5p* in SKOV3 cells was significantly elevated in the miR-382-5p group compared with the miR-NC group and the expression level of *miR-382-5p* was markedly lowered in the Anti-miR-382-5p group relative to the Anti-NC group (Fig. 5A). Subsequently, with the help of starbase2.0 (https://starbase.sysu.edu.cn/starbase2/index.php), *miR-382-5p* was predicted to target *LRRK2* mRNA (Fig. 5B). The dual-luciferase reporter assay results showed that the *miR-382-5p* group presented a significant decrease in luciferase activity after co-transfection of the WT-LRRK2 3'-UTR with miR-382-5p mimics (Fig. 5C). qRT-PCR results indicated that *miR-382-5p* overexpression could considerably reduce *LRRK2* expression compared with the miR-NC group in SKOV3 cells, while *miR-382-5p* knockdown significantly upregulated *LRRK2* expression compared with the Anti-

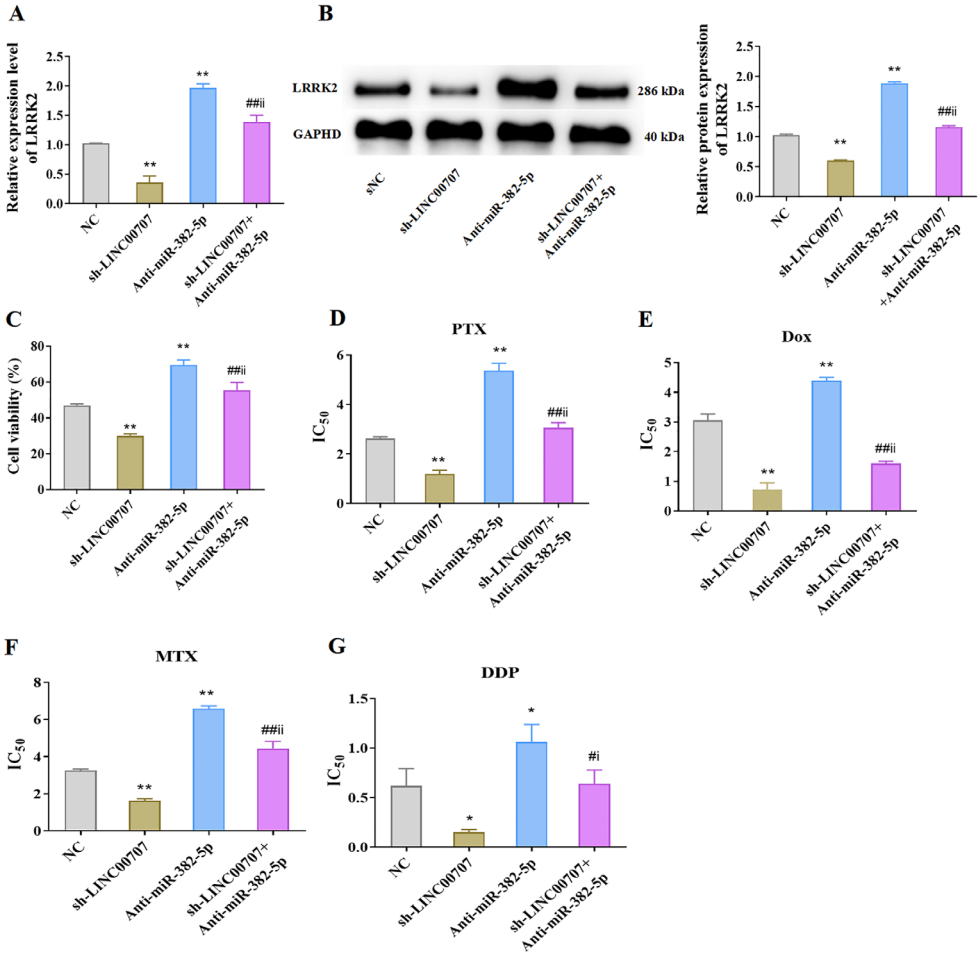

Figure 6. *LINC00707* promotes proliferation and resistance of ovarian cancer (OC) cells to chemotherapeutic agents by targeting the *miR-382-5p/LRRK2* axis.
(**A**) QRT-PCR results of the expression level of *LRRK2* in SKOV3 cells after simultaneous transfection of *LINC00707* shRNA and *miR-382-5p* inhibitor. (**B**) Western blot results of LRRK2 protein levels in SKOV3 cells after transfection. (**C**) MTT results of the viability of SKOV3 cells after transfection. (**D–G**) MTT results of the tolerance of SKOV3 cells to PTX (**D**), Dox (**E**), MTX (**F**), and DDP (**G**) after simultaneous transfection of *LINC00707* shRNA and *miR-382-5p* inhibitor. $^{**}p<0.01$, *vs.* NC; $^{\#}p<0.05$, *vs.* sh-LINC00707; $^{\text{i}}p<0.05$, *vs.* Anti-miR-382-5p. sh, short hairpin; NC, negative control.

NC group (Fig. 5D). Additionally, *LRRK2* was expressed at quite higher levels in SKOV3 cells than in IOSE80 cells (Fig. 5E). Collectively, we found that *miR-382-5p* expression and *LRRK2* expression are upregulated in OC, *miR-382-5p* directly targets *LRRK2*, and knockdown of *miR-382-5p* significantly promotes *LRRK2* expression.

LINC00707 promotes proliferation and multidrug resistance of SKOV3 cells by targeting the *miR-382-5p/LRRK2 axis*

In order to further investigate the effect of *LINC00707* on OC cell viability and drug resistance, the expression level of *LRRK2* was detected by qRT-PCR and Western blot by targeting the *miR-382-5p/LRRK2* axis, after simultaneous knockdown of *LINC00707* and *miR-382-5p* in SKOV3 cells. The results showed that the sh-LINC00707 + Anti-miR-382-5p group displayed a much higher expression level of *LRRK2* than the sh-LINC00707 group; and the expression level of *LRRK2* was significantly decreased in the sh-LINC00707 + Anti-miR-382-5p group compared with the Anti-miR-382-5p group (Fig. 6A, 6B). The MTT assay outcomes indicated that cell viability was considerably increased in the sh-LINC00707 + Anti-miR-382-5p group compared with the sh-LINC00707 group, but significantly reduced in the sh-LINC00707 + Anti-miR-382-5p group compared with the Anti-miR-382-5p group (Fig. 5C). Next, the resistance of SKOV3 cells to chemotherapeutic agents (PTX, Dox, MTX, and DDP) was detected using MTT assay. We discovered that the sh-LINC00707 + Anti-miR-382-5p group had a much higher IC50 than the sh-LINC00707 group, and the sh-LINC00707 + Anti-miR-382-5p group presented a lower IC50 than the Anti-miR-382-5p group (Fig. 6D–G). These results suggest that *LINC00707* promotes proliferation and resistance of SKOV3 cells to chemotherapeutic agents by targeting the *miR-382-5p/LRRK2* axis.

DISCUSSION

OC, one of the gynecological malignancies with the highest mortality rates, poses a severe threat to female health worldwide. Research suggests that chemoresistance of OC cells significantly contributes to the high mortality (Barriga-Rivera *et al.*, 2016). Currently, the combination of Dox and PTX is typically effective at first, but the

condition relapses in the majority of patients, and is then usually incurable, with just an 18-month-survival rate (Yang *et al.*, 2017). Therefore, a thorough understanding of the molecular mechanism of multidrug resistance in OC is crucial for improving the prognosis. Our study's findings showed that *LINC00707*, which was expressed at a considerably higher level in OC, could boost cellular resistance to chemotherapeutic drugs by targeting the *miR-382-5p*/*LRRK2* axis.

LncRNAs, described in recent studies, hold promise as potential biomarkers for cancer diagnosis, prognosis, and treatment. Notably, many lncRNAs are dysregulated in OC, which may play crucial roles in the incidence and progression of tumors (Wang *et al.*, 2018). Among them, lncRNA *HOXD-AS1* is an OC-associated lncRNA that is overexpressed in both OC tissues and cells and can indicate poor prognosis in patients (Zhang *et al.*, 2017). Recently, Zahra and coworkers performed high-throughput sequencing and found that *LINC00707* was highly upregulated in OC tissues and has potential as a diagnostic marker (Zahra *et al.*, 2021). Although earlier research indicated that *LINC00707* is a proto-oncogene (Guo *et al.*, 2021), it is not clear how *LINC00707* and OC are related. Therefore, the aim of our study was to investigate the effect of *LINC00707* in OC and its molecular mechanism. In this study, *LINC00707* was overexpressed in SKOV3 cells, and *LINC00707* overexpression markedly increased the proliferation and viability of SKOV3 cells, while *LINC00707* knockdown inhibited the proliferation and viability of cells. Furthermore, studies on several malignancies have shown that lncRNAs have a role in controlling chemosensitivity (Xu *et al.*, 2018). Our findings clearly showed that *LINC00707* overexpression increased resistance to PTX, Dox, MTX, and DDP in SKOV3 cells. These findings are in line with the results of *LINC00707* overexpression in cancer cells in the bladder (Gao & Ji, 2021) and breast (Yuan *et al.*, 2020). Thus, it is clear that *LINC00707* overexpression induces OC resistance to chemotherapeutic agents.

Recent evidence has suggested that the interaction between lncRNAs and microRNAs may have an impact on a number of pathological mechanisms, including the development of cancer and the acquisition of drug resistance. By functioning as a competitive endogenous RNA sponge for miR-17 and altering *STAT3* expression, lncRNA *H19* was discovered by Huang *et al.* to accelerate the development of NSCLC (Huang *et al.*, 2018). Li *et al.* discovered that lncRNA *SNHG1* promoted the resistance of hepatocellular carcinoma cells to sorafenib by increasing *miR-21* expression to activate the Akt pathway (Li *et al.*, 2019). Through bioinformatic predictions and several experiments in our study, we demonstrated that there was a binding site in *LINC00707* for miR-382-5p, and *LINC00707* acted as the molecular sponge of *miR-382-5p*. Interestingly, Guo *et al.* also proved the interaction between *LINC00707* and miR-382-5p (Wang *et al.*, 2020). However, our study is the first to find that *miR-382-5p* expression is significantly downregulated in OC cells and inversely correlated with *LINC00707* expression. Although *miR-382-5p* has only been the subject of a few studies, they have shown that this microRNA suppresses the genes involved in tumor development. For instance, the expression level of *miR-382-5p* is significantly downregulated in colorectal cancer tissues (Xie & Pan, 2021). Likewise, few studies were conducted on the downstream target genes of *miR-382-5p*. In this regard, our study discovered that *miR-382-5p* targeted the *LRRK2*mRNA 3'-UTR region and regulated the expression level of *LRRK2*. Mutations in *LRRK2* were first thought to be critical for inducing familial Parkinson's disease (Deniston *et al.*, 2020). Interestingly, the expression level of *LRRK2* was found to be significantly downregulated in NSCLC tissues (Ma *et al.*, 2019). However, the role of *LRRK2* in cancer has rarely been reported. In our study, the expression level of *LRRK2* was discovered to be significantly upregulated in SKOV3 cells and was clearly inversely regulated by *miR-382-5p*; *LRRK2* expression level in SKOV3 cells was significantly higher when *LINC00707* and *miR-382-5p* were simultaneously knocked down than that when either of them was knocked down alone. Moreover, SKOV3 cells in the sh-LINC00707 + Anti-miR-382-5p group were significantly more resistant to chemotherapeutic agents than those in the Anti-miR-382-5p group, but significantly less resistant than those in the sh-LINC00707 group. Therefore, *LINC00707* induced multidrug resistance of SKOV3 cells by targeting the *miR-382-5p*/*LRRK2* axis.

CONCLUSION

In summary, *LINC00707* is highly expressed in SKOV3 cells. *LINC00707* regulates the expression of *LRRK2* by targeting *miR-382-5p*, thereby enhancing the proliferation and viability of SKOV3 cells and inducing multidrug resistance in them. Therefore, knocking down *LINC00707* expression is key for addressing multidrug resistance in OC cells. However, the role of *LINC00707* is multifaceted, and more research is required to fully elucidate its function.

Declarations

Conflict of Interest. All authors declare no conflict of interest.

Consent for Publication. Not applicable.

Authors' Contributions. Min-Wen Zhao conceived and designed the experiments; Chang-Jie Lin analyzed and interpreted the results of the experiments; YZM performed the experiments; and Jian-Ping Qiu revised the manuscript.

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