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ORIGINAL RESEARCH

The lncRNA *TUG1* promotes epithelial ovarian cancer cell proliferation and invasion via the WNT/β-catenin pathway

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Purpose: Epithelial ovarian cancer (EOC) is among the most common malignant tumors of the endocrine system. Numerous studies have shown that genetic factors are important in the development of EOC, and there is evidence that long noncoding RNA molecules (lncRNAs) can regulate gene expression at the transcription, posttranscription, and epigenetic levels to influence cancer proliferation and invasion, cell differentiation, and apoptosis. However, the roles of lncRNAs in the pathogenesis of EOC remain unclear. Here, we investigated the role of the lncRNA, taurine upregulated gene 1 (*TUG1*), in EOC.

Patients and methods: *TUG1* mRNA levels were evaluated in EOC and matched normal tissue samples and in EOC cell lines by quantitative real-time PCR. Lentiviral vectors expressing the lncRNA, *TUG1*, and siRNA targeting *TUG1* were constructed and transfected into EOC cells. MTT and Transwell assays were used to determine the effects of *TUG1* on cell proliferation, migration, and invasion. Western blotting was performed to determine the influence of *TUG1* up- or downregulation on WNT/β-catenin signaling, which is involved in the occurrence and development of cancer.

Results: *TUG1* expression was clearly elevated in EOC compared with control tissue and cells. Moreover, *TUG1* expression was associated with lymphatic metastasis, T stage, and clinical stage in patients with EOC. Downregulation of *TUG1* in EOC inhibited cell proliferation, migration, and invasion. In EOC cells, levels of the WNT/β-catenin pathway factors, β-catenin, cyclin D1, and c-Myc, were significantly up- and downregulated in response to *TUG1* over- and underexpression, respectively.

Conclusion: Our data suggest that knockdown of *TUG1* may represent a novel therapeutic approach for the management of EOC.

Keywords: epithelial ovarian cancer, long noncoding RNA, prognosis, molecular mechanisms

Introduction

Ovarian cancer is one of 3 major gynecological malignant tumors and remains a major cause of death worldwide. There are a wide range of ovarian cancer subtypes, of which 85%–90% are epithelial ovarian cancer (EOC). EOC is thought to originate from undifferentiated cells in the cambium layer of the ovary surface; genetic mutation in these cells increases the likelihood of the development of a malignant tumor.[1] Therefore, improved understanding of the pathogenesis of EOC may assist in the development of novel diagnostic, therapeutic, and preventive strategies for this disease.

Long noncoding RNAs (lncRNAs) are a class of RNA transcripts >200 nucleotides in length that have no evidence of protein coding potential.[2] lncRNAs can regulate gene expression through diverse mechanisms, including epigenetic silencing, mRNA splicing,

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and lncRNA–miRNA interaction.[3,4] Dysregulation of lncRNAs is involved in the pathophysiological processes underlying various human diseases, including cancers. For example, Liu et al[5] demonstrated that upregulation of the lncRNA, *CCAT1*, correlates with tumor progression and poor prognosis in EOC.

Taurine upregulated gene 1 (*TUG1*), a 7.1-kb lncRNA mapping to chromosome 22q12.2, was initially identified as a transcript upregulated in retinal cells treated with taurine.[6] Subsequently, *TUG1* was found to be dysregulated in various tumors and was found to participate in the progression of diverse malignancies, possibly by tumor suppressor or oncogenic activity.[7,8] *TUG1* is aberrantly overexpressed in osteosarcoma tissues and cells and acts as a possible oncogene in osteosarcoma development;[9] however, the relationship between *TUG1* expression and EOC development is unknown.

In the present study, the expression of *TUG1* lncRNA was determined in EOC tissues and cell lines by quantitative real-time PCR (qRT-PCR). Associations between *TUG1* expression and the clinicopathological features of EOC were also investigated. Moreover, we determined the effects of *TUG1* on EOC cell proliferation, migration, and invasion in vitro and evaluated the effect of *TUG1* on the WNT/β-catenin pathway.

Materials and methods

Tissue samples

Paired human EOC and adjacent normal tissues from patients with EOC were obtained at the Qilu Hospital of Shandong University from 2014 to 2017. All diagnosis of EOC were confirmed by histology. Patients were excluded from the study if they received chemotherapy or radiotherapy prior to surgery. All patients provided written informed consent prior to surgery. The study protocol was approved by the Ethics Committee of Qilu Hospital of Shandong University and complied with the Declaration of the Helsinki. Samples were immediately snap-frozen and stored in liquid nitrogen until use.

Cell culture and transfection

The human EOC cell lines, HO8910, SKOV3, and CAOV3, and human normal ovarian surface epithelium cells (IOSE80) were obtained from American Type Culture Collection and cultured in humidified air at 37°C with 5% CO_2 in DMEM culture media supplemented with 10% fetal bovine serum, penicillin (100 U/mL), and streptomycin (100 U/mL).

Human EOC cell lines were transfected with 50 nM *TUG1* Lentiviral Vector (ABM Inc., Richmond, BC, Canada), *TUG1* siRNA (si-TUG1) (5′-GTACGTGTCTTGGAAAGTCT-3′), and negative control siRNA (Scrambled control shRNA: 5′-CCGGTTTCTCCGAACGTGTC-3′) using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Forty-eight hours after transfection, cells were harvested for total RNA extraction and qRT-PCR analysis.

Cell proliferation assay

Proliferation of EOC cells was measured using an MTT kit (Sigma, St Louis, MO, USA). Briefly, EOC cells in the logarithmic growth phase were detached from culture dishes by trypsinization, seeded in 96-well plates at a density of 2×10^4 cells/well, and transfected with 50 nM si-TUG1 or si-NC. Cell proliferation was assessed daily for 4 days after transfection. Absorbance at 492 nm was measured after incubation with 20 µL of MTT (Thermo Fisher Scientific, Waltham, MA, USA) for 4 h. A cell proliferation curve was then drawn and proliferation efficiency determined. Experiments were repeated 3 times, independently.

Cell migration and invasion assay

The migration and invasion potentials of cells were measured using Transwell chambers. For migration assays, 5×10^4 cells were seeded into the upper chambers of Transwell plates (BD Bioscience, San Jose, CA, USA). For invasion assays, 1×10^5 cells were added into the upper chambers precoated with Matrigel (BD Bioscience). In both assays, cells were maintained in DMEM medium without serum in the upper chamber, and DMEM medium containing 10% fetal bovine serum was added to the lower chamber as a chemoattractant. After incubation for 24 h, nonmigrated or noninvading cells that remained on the upper surface were removed using cotton swabs. Then, membranes were fixed with 4% paraformaldehyde for 30 min, permeabilized with 0.2% Triton X-100 at room temperature for 15 min, and stained with 0.1% crystal violet for 5 min. Three random fields were counted per chamber using an inverted microscope (Olympus, Tokyo, Japan). Experiments were repeated 3 times independently.

RNA extraction and qRT-PCR

Total RNA was extracted from cells using TRIzol® reagent (Invitrogen) or from tissues samples with a RecoverAll™ Total Nucleic Acid Isolation kit (Ambion, Foster City, CA, USA), according to the manufacturer's instructions. For qRT-PCR, RNA was reverse transcribed into cDNA using a Reverse Transcription Kit (Takara, Dalian, People's Republic of China). qRT-PCR analyses were performed using SYBR Premix Ex Taq (Takara). Results were normalized to the expression of *GAPDH*. The primers for *TUG1* were as follows: forward, 5′-TAGCAGTTCCCCAATCCTTG-3′ and reverse, 5′-CACAAATTCCCATCATTCCC-3′. The primers for *GAPDH* were: forward, 5′-GTCAACGGA TTTGGTCTGTATT-3′ and reverse, 5′-AGTCTTCTGG

GTGGCAGTGAT-3′. Data were analyzed using the $2^{-\Delta\Delta Ct}$ method, and each experiment was performed in triplicate.

Western blot analysis

Cell proteins were extracted using a General Protein Kit (Beyotime, Haimen, People's Republic of China). All protein samples were adjusted to equal concentrations, followed by addition of bromophenol blue. After removal of bubbles from the wells of acrylamide gels, equal amounts of proteins were loaded, along with 6 μL of GAPDH protein marker. Protein samples were separated using a predetermined voltage (150 V). Next, proteins were transferred to nitrocellulose membranes and blotted with rabbit polycolonal anti-E-cadherin, anti-Vimentin, anti-β-catenin, anti-Cyclin D1, anti-c-Myc, anti-GAPDH primary antibodies (Cell Signaling Technology, Danvers, MA, USA) at a dilution of 1:1000, followed by horse-radish peroxidase-conjugated secondary antibodies (Cell Signaling Technology). Detection was performed using a LI-COR Odyssey Scanning Infrared Fluorescence Imaging System (LI-COR, Lincoln, NE, USA).

Statistical analysis

All statistical analyses were performed using SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA). All data are presented as means ± SD. Differences between groups were evaluated using the Student's *t*-test, χ^2 test, or Mann–Whitney analysis. *P*-values <0.05 were considered significant.

Results

TUG1 is upregulated in EOC tissues and cell lines

We first evaluated lncRNA *TUG1* expression in the EOC cell lines HO8910, SKOV3, and CAOV3 and the normal human ovarian surface epithelium cell line, IOSE80, by qRT-PCR. Compared with that in IOSE80, lncRNA *TUG1* was upregulated in the HO8910, SKOV3, and CAOV3 cell lines (Figure 1A). We also examined the expression of *TUG1* in 80 paired EOC and adjacent nontumor tissue samples. *TUG1* was significantly upregulated in EOC compared with healthy tissue (Figure 1B). For the clinicopathological correlation analysis, 80 EOC patients were divided into two groups: high TUG1 group and low TUG1 group by adopting the median of TUG1 expression in EOC tissues as a cut-off value. Elevated *TUG1* expression was associated with various clinicopathological characteristics, including lymphatic metastasis, T stage, and clinical stage (Table 1). These results indicate that *TUG1* lncRNA may have a role in the progression of EOC.

Downregulation of TUG1 lncRNA inhibits EOC cell proliferation

We transfected HO8910 and SKOV3 cells with *TUG1* siRNA to explore the effect of *TUG1* on cell proliferation. The proliferation rate of EOC cells transfected with si-TUG1 was significantly decreased compared with negative controls (Figure 2).

Downregulation of TUG1 lncRNA suppresses EOC cell migration and invasion in vitro

We next investigated the effect of *TUG1* lncRNA on EOC cell migration and invasion. Transwell migration assays demonstrated that downregulation of *TUG1* dramatically suppressed HO8910 and SKOV3 cell migration and invasion relative to negative controls (Figure 3A and B). Furthermore, expression of E-cadherin was upregulated and that of Vimentin downregulated in HO8910 cells (Figure 3C). These findings indicate that *TUG1* lncRNA can induce the migration and invasion of EOC cells.

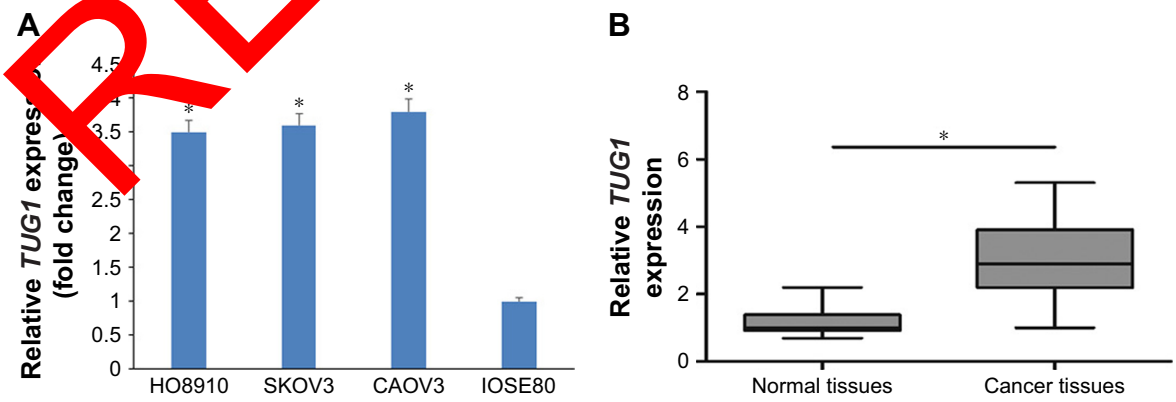

Figure 1 *TUG1* mRNA levels in EOC.

Notes: (**A**) *TUG1* mRNA levels in 3 EOC cell lines and 1 normal human ovarian surface epithelium cell line. Expression of *TUG1* mRNA was evaluated by qRT-PCR in the indicated cell lines. The constitutively expressed *GAPDH* gene was used as an internal control. (**B**) qRT-PCR analysis of *TUG1* expression in EOC and adjacent normal tissue samples ($P<0.05$). Relative levels of *TUG1* mRNA in EOC tissues were normalized to those of *GAPDH* and compared with levels in adjacent normal tissues. *$P<0.05$.

Abbreviations: EOC, epithelial ovarian cancer; qRT-PCR, quantitative real-time PCR; *TUG1*, aurine upregulated gene 1.

Table 1 Correlation between TUG1 expression and clinicopathologic characteristics of EOC patients

Characteristics	TUG1		Fisher's exact test (*P*-value)
	High	Low	
Age (years)			0.16
≥60	26	21	
<60	16	17	
Gender			0.24
Male	20	15	
Female	25	20	
Clinical stage			<0.001
I–II	13	15	
III–IV	36	16	
T classification			<0.001
T1–T2	15	13	
T3–T4	40	12	
Lymphatic metastasis			<0.001
Yes	25	7	
No	23	25	
M classification			0.09
M0	16	18	
M1	21	25	

Abbreviations: EOC, epithelial ovarian cancer; *TUG1*, taurine upregulated gene 1.

TUG1 lncRNA induces EOC cell proliferation, migration, and invasion via the WNT/β-catenin pathway

To determine the possible mechanism underlying TUG1 lncRNA regulation of the progression of EOC cells, Western blot analysis was used to explore the effects of TUG1 overexpression (TUG1-WT) or knockdown (si-TUG1) on the WNT/β-catenin pathway, which is often aberrantly activated in human cancers and contributes to enhanced cell proliferation, migration, and invasion. TUG1 overexpression significantly increased the levels of β-catenin, cyclin D1, and c-Myc in EOC cells, while TUG1 inhibition led to significant decreases in expression of the same proteins (Figure 4; $P<0.05$). These data suggest that the WNT/β-catenin pathway may participate in TUG1-induced proliferation, migration, and invasion of EOC cells.

Discussion

EOC is the most aggressive subtype of ovarian cancer, with significantly higher recurrence and mortality rates

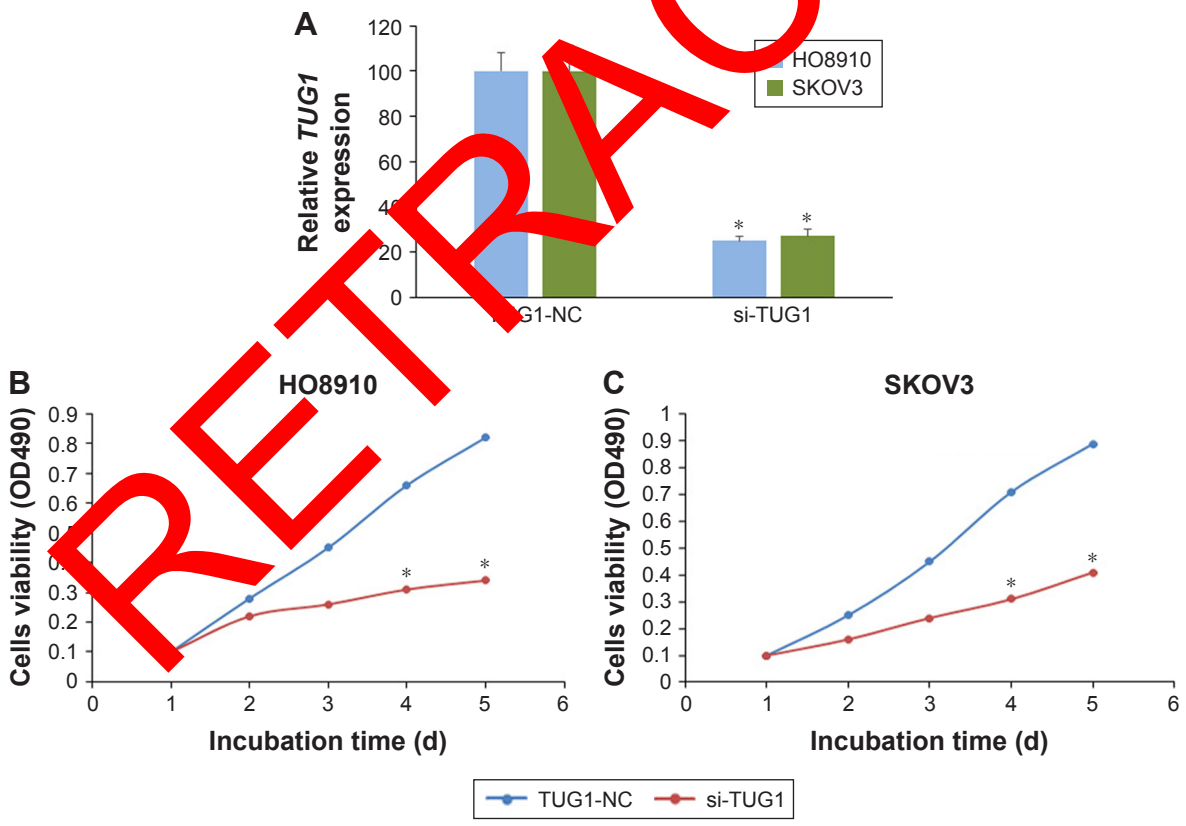

Figure 2 Effect of *TUG1* downregulation on EOC cell proliferation.
Notes: (**A**) qRT-PCR analysis of the efficiency of *TUG1* downregulation by treatment of HO8910 and SKOV3 EOC cells transfected with si-TUG1. MTT analysis 5 days after transfection in negative control-transfected and TUG1 shRNA-transfected HO8910 (**B**) and SKOV3 (**C**) cell lines (*$P<0.01$).
Abbreviations: EOC, epithelial ovarian cancer; qRT-PCR, quantitative real-time PCR; *TUG1*, taurine upregulated gene 1.

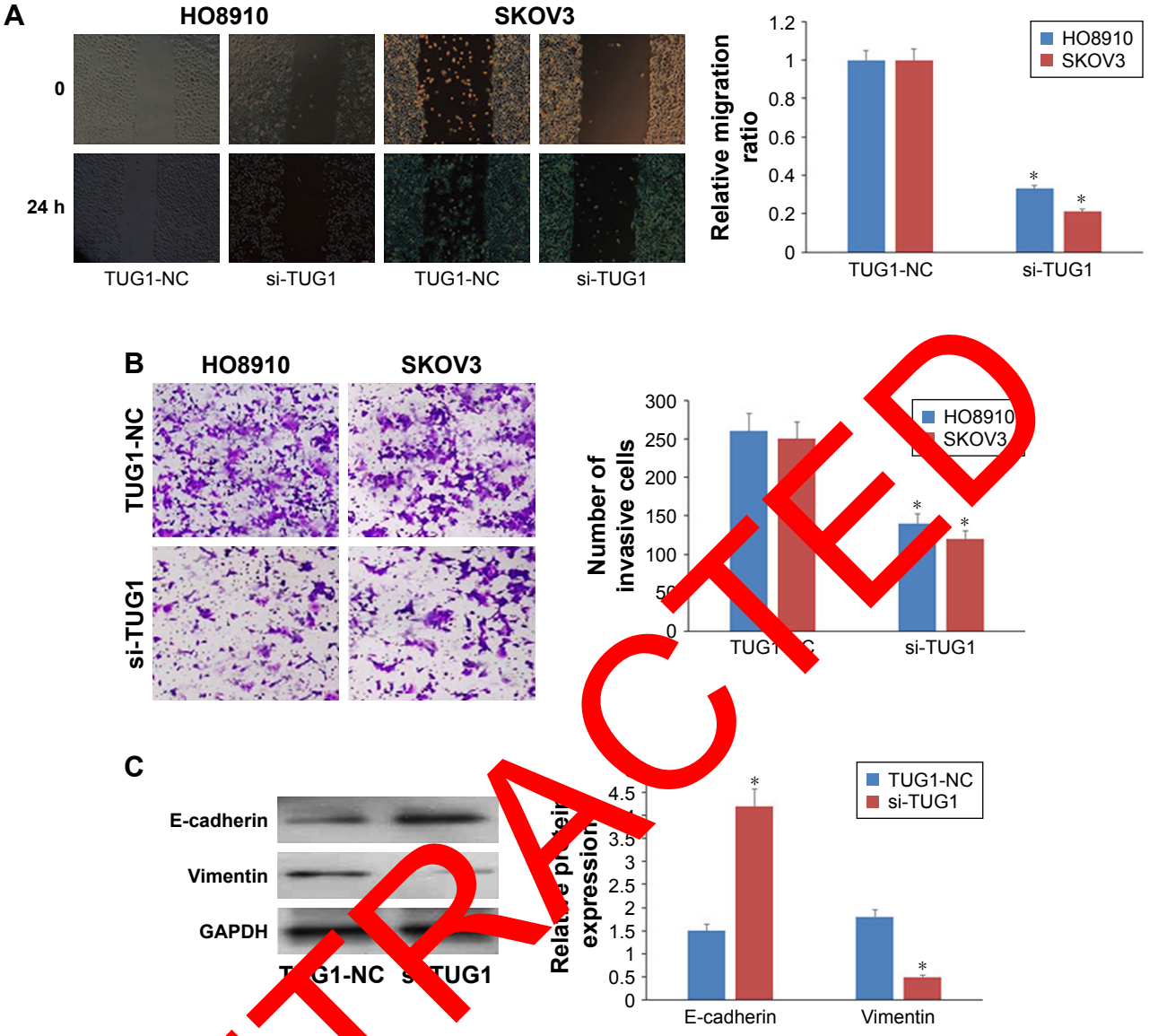

Figure 3 Effect of *TUG1* on EOC cell migration and invasion.
Notes: (**A**) Cell migration and (**B**) cell invasion were significantly inhibited after overexpression of *TUG1* in HO8910 and SKOV3 cells (*$P<0.05$). (**C**) Western blot analysis showed that downregulation of *TUG1* resulted in elevated levels of E-cadherin and inhibition of Vimentin in HO8910 cells. Scale bars, 100 μm.
Abbreviations: EOC, epithelial ovarian cancer; *TUG1*, taurine upregulated gene 1.

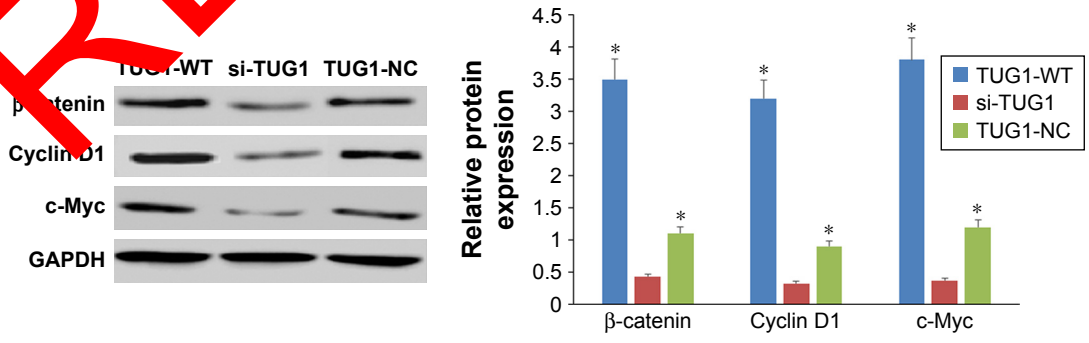

Figure 4 Effect of *TUG1* on WNT/β-catenin signaling in EOC cells.
Notes: Western blot analysis showing that up- or downregulation of *TUG1* resulted in up- or downregulated β-catenin, cyclin D1, and c-Myc in HO8910 cells. *$P<0.05$.
Abbreviations: EOC, epithelial ovarian cancer; *TUG1*, taurine upregulated gene 1.

than other subtypes.[10] EOC is characterized by late clinical manifestation, subtle symptomatology, and rapid disease progression. As a consequence, up to 75% of patients with EOC have already developed metastases at first diagnosis. Despite the great advances achieved in surgery and chemotherapy over the last few decades, the prognosis of EOC patients remains poor, with a 5-year survival rate of only 30%.[11] In light of these observations, new biomarkers are still needed to overcome the diagnostic and therapeutic obstacles in a subset of patients with EOC.[12]

lncRNAs are involved in cellular processes including apoptosis, cell proliferation, migration, and invasion,[13–15] and there is also evidence that lncRNAs are crucial determinants of gastric cancer metastasis.[16–18] Identification of lncRNAs involved in cancer progression will improve understanding of cancer; these molecules can exert their regulatory functions through a variety of mechanisms, including chromatin remodeling, RNA processing, localization, translation, and modification of mRNA stability, and they can even function as competing endogenous RNA.[19–21] Despite growing evidence that aberrant lncRNA expression is key to carcinogenesis and cancer progression,[22] the biological and molecular mechanisms underlying lncRNA functions in diverse tumors are yet to be fully elucidated.

Emerging evidence indicates that *TUG1* is frequently upregulated and has an oncogenic role in the development and progression of multiple tumors. *TUG1* is upregulated in cervical cancer cells, and its downregulation suppresses cell proliferation and activates apoptosis, partly through regulating the expression of Bcl-2 and caspase-3, and inhibits cell invasion and migration via modulation of epithelial–mesenchymal transition (EMT).[23] *TUG1* is also highly expressed in renal cell carcinoma, and its knockdown suppresses cell migration, invasion, and proliferation, while inducing apoptosis.[24] In esophageal squamous cell carcinoma, *TUG1* was reported to be overexpressed, and its silencing using siRNA inhibited cell proliferation and migration and blocked cell cycle progression;[25] however, to the best of our knowledge, the expression of *TUG1* and its function in EOC progression have not previously been described.

In the present study, we identified *TUG1* lncRNA as apparently having a significant role in the promotion of EOC tumors. Our data demonstrate that *TUG1* is considerably overexpressed in EOC tissue samples compared with matched normal tissue. The expression profile of lncRNA in different tissues has only been reported in a few cases.[28] In cell lines, *TUG1* expression profiles were consistent with those in EOC tissue. Furthermore, downregulation of *TUG1* resulted in various changes which are generally associated with curbing of tumor development, including inhibition of cell proliferation, invasion, and migration, in contrast to the effects of *TUG1* upregulation. Down- or upregulation of *TUG1* led to variation in the expression of numerous cancer-associated mRNA molecules. These results suggest that *TUG1* is necessary for the maintenance of the basal activities of cells and has an oncogenic role in the development and progression of multiple tumors.

WNT/β-catenin signaling is critical in controlling the balance between cell survival and apoptosis. This pathway is usually activated in a wide range of cancers and promotes tumor invasion and metastasis through upregulation of factors regulating EMT.[26] Therefore, inhibition of WNT/β-catenin decreases cell survival and enhances the effects of chemotherapeutic drugs in many types of cancer cell.[27] Recent studies have highlighted the cross-talk between lncRNAs and WNT/β-catenin signaling in various cancers; however, whether lncRNAs participate in processes involving WNT/β-catenin and EMT in EOC has not previously been determined.[29] In the present study, we found that inhibition of *TUG1* significantly decreased the expression levels of β-catenin, cyclin D1, and c-Myc, indicating the WNT/β-catenin pathway might participate in *TUG1*-induced progression of EOC. Our findings expand the known function of WNT/β-catenin signaling in EOC progression.

Conclusion

In conclusion, this study is the first to examine the function of *TUG1* lncRNA in EOC progression. Our data suggest that *TUG1* has potential for use as a diagnostic marker in EOC. *TUG1* lncRNA is involved in various aspects of tumor progression, including cell proliferation, migration, and invasion. Downregulation of *TUG1* by therapeutic agents may be valuable for the prevention of EOC; thus, our findings indicate that knockdown of *TUG1* is a potential novel therapeutic approach for EOC.

Disclosure

The authors report no conflicts of interest in this work.

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