Long non-coding RNA taurine-upregulated gene 1 predicts unfavorable prognosis, promotes cells proliferation, and inhibits cells apoptosis in epithelial ovarian cancer

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Abstract
The aim of this study was to evaluate the correlation of long non-coding RNAs (lncRNAs) taurine-upregulated gene 1 (TUG1) with clinicopathological characteristics as well as overall survival (OS) in epithelial ovarian cancer (EOC) patients, and investigate its function in EOC cells proliferation and apoptosis in vitro.

LncRNA TUG1 expressions were detected in tumor tissues and paired adjacent tissues obtained from 96 EOC patients. Blank mimic, lncRNA TUG1 mimic, blank inhibitor, and lncRNA TUG1 inhibitor plasmids were transfected into SKOV3 cells. CCK-8, annexin V-FITC–propidium iodide, qPCR and western blot assays were performed to detect cells proliferation, cells apoptosis, RNA expression, and protein expression, respectively.

LncRNA TUG1 expression was higher in tumor tissue compared to paired adjacent tissue (P < .001), and it was positively correlated with pathological grade (P = .022), tumor size (P = .011) and FIGO stage (P < .001). Kaplan-Meier curve showed that LncRNA TUG1 high expression was associated with worse OS (P = .003). Multivariate Cox analysis indicated that lncRNA TUG1 high expression (vs. low expression) (P = .035) was independently predictive factor for shorter OS. In vitro, cells proliferation was promoted after treatment with lncRNA TUG1 mimic and was suppressed after treatment with lncRNA TUG1 inhibitor. In addition, cells apoptosis rate was decreased in lncRNA TUG1 mimic group compared to NC1 mimic, and increased in lncRNA TUG1 inhibitor group compared to NC2 inhibitor.

In conclusion, lncRNA TUG1 is positively correlated with advanced disease and poor prognosis, and it promotes cells proliferation and inhibits cells apoptosis in EOC cells.

Abbreviations: BCA = bicinchoninic acid, CA125 = carbohydrate antigen 125, CCAT2 = colon cancer associated transcript 2, EOC = epithelial ovarian cancer, FIGO = International Federation of Gynecology and Obstetrics, lncRNAs = long non-coding RNAs, OS = overall survival, qPCR = quantitative polymerase chain reaction, RPMI = Roswell Park Memorial Institute, TUG1 = taurine-upregulated gene 1, ZEB2 = zinc finger E-box-binding homeobox 2.

Keywords: cells apoptosis, cells proliferation, epithelial ovarian cancer, LncRNA TUG1, prognosis

1. Introduction
Epithelial ovarian cancer (EOC) is the seventh common diagnosed cancer and the fourth leading cause of cancer-related mortality in women, accounting for nearly 5% of all cancer and 4.2% of all cancer deaths among female all over the world.\cite{1-3} According to 2015 global cancer statistics, EOC affects estimated 239,000 populations and leads to 151,900 deaths during 2012.\cite{4}

In China, there are approximately 52,100 new cases and 22,500 deaths causing by EOC during 2015.\cite{5} In addition, an increasing trend in mortality owing to EOC is observed in the last 2 decades because of several factors, including late diagnosis, chemoresistance, and complexed pathological process via dysregulation of tumor-related genes.\cite{6-8} Hence, further understanding of molecular mechanisms underlying EOC progression may help improve the diagnosis and develop novel therapeutic targets.

Long non-coding RNAs (lncRNAs), a heterogeneous class of endogenous RNA molecules composed of >200 nucleotides, is characterized by the limiting or no protein-coding capacity.\cite{9, 10} Accumulating evidences have proven that lncRNAs play critical roles in biological processes, such as cells proliferation, cells apoptosis, cells invasion as well as cells differentiation, and their aberrant expressions involve into the process of tumorigenesis and cancer progression via mediating oncogenic or tumor-suppressing pathways.\cite{11, 12}

LncRNA taurine-upregulated gene 1 (TUG1), a novel lncRNA with 6.7-kb nucleotides, has been promulgated as an oncogene contributing to the development and prognosis of several carcinomas, including bladder cancer, osteosarcoma, and colorectal cancer.\cite{13-16} However, the role of lncRNA TUG1 in EOC and its function in EOC cells are still unclear. Therefore, the...
purpose of this study was to evaluate the correlation of lncRNA TUG1 with clinicopathological characteristics as well as overall survival (OS) in EOC patients, and investigate function on EOC cells in vitro.

2. Materials and methods

2.1. Patients

A total of 96 EOC patients who received surgery, from July 2013 to June 2016 in People’s Hospital of Lishui City were retrospectively included in this study. The inclusion criteria were: diagnosis as EOC confirmed by pathological and clinical examinations; age >18 years; completed clinical and pathological data; tumor tissue and paired adjacent tissue were accessible to be obtained from sample storehouse of the Hospital and were available for quantitative polymerase chain reaction (qPCR) assay. Patients with secondary ovarian cancer, history of other tumors, or previous ovarian surgery were excluded. This study was performed according to the Declaration of Helsinki. Institutional Review Board of People’s Hospital of Lishui City approved this study, and written informed consents or oral agreements by telephone (with recording) were obtained from all patients or their guardians.

2.2. Data collection

Clinicopathological data were collected from Electronic Medical Record System or Medical Records Room, which include age, histological subtype, pathological grade, peritoneal cytology, tumor size, volume of ascites, International Federation of Gynecology and Obstetrics (FIGO) stage, carbohydrate antigen 125 (CA125), and survival information. Patients were followed up according to the disease conditions and patients’ willing; the median followed up duration was 23.5 (range 1.0–46.0 months) months, and the last follow-up date was July 1, 2017. OS was calculated from the time of surgery to the date of death from any cause.

2.3. Samples and lncRNA TUG1 determination

Tumor tissue and adjacent tissue were obtained during the surgery and stored in the liquid nitrogen in sample storehouse. LncRNA TUG1 expressions in both tumor tissue sample and adjacent non-tumor tissue sample were measured by quantitative polymerase chain reaction (qPCR) assay.

2.4. Cells culture

Human EOC cells (SKOV3 cells) were purchased from Cell Bank of the Chinese Academy of Sciences (Shanghai, China). After resuscitation, cells were cultured in Roswell Park Memorial Institute (RPMI) 1640 (Sigma-Aldrich) medium supplemented with 10% fetal bovine serum (Gibco), 100 U/mL penicillin, and 100 mg/mL streptomycin in a humidified incubator at 37°C with 5% CO2.

2.5. Cells transfection

After washing with PBS and replacing RPMI 1640 (Sigma-Aldrich) medium supplement, SKOV3 cells were transfected with blank mimic, lncRNA TUG1 mimic, blank inhibitor and lncRNA TUG1 inhibitor plasmids, which were divided into 4 groups, including NC1 mimic, lncRNA TUG1 mimic, NC2 inhibitor, and lncRNA TUG1 inhibitor groups. Transfection efficiency was estimated by qPCR assay. The following TUG1 siRNA sequences were designed: siRNA-TUG1 (SenseSeq: 5’-CCUCAGAUCAUCUAUAAAUTT-3’; AntiSeq: 5’-AUUUGAUUGAGUCUGAGGTT-3’) and negative control siRNA (SenseSeq: 5’-UCUCGGACCGUCACUTT-3’; AntiSeq: 5’-ACGUAGACGUUGCGG AGAATT-3’).

2.6. qPCR

qPCR was determined to assess lncRNA and mRNA expression. Total RNA was extracted by the TRIzol reagent (Invitrogen) according to the manufacturer’s instructions, and then RNA was quantitated by OD 260 (Takara, Japan). After that, RNA from each group was used for cDNA synthesis, and cDNA was then subjected to qPCR with SYBR Green kit (Takara, Japan). The PCR amplification was carried out as follows: 95°C for 5 minutes, followed by 40 cycles of 95°C for 5 seconds, 61°C for 30 seconds. The qPCR results were calculated by using the 2-ΔΔct method and U6 was served as the internal reference. The following primer sequences were as follows: TUG1, forward 5’-TAGGAGTGGATTGTTCG-CAGCA-3’; reverse 5’-TGGTCGGAGATAGGTGTCAATGA-3’; U6, forward-5’-ACGCGTTCGCCAGCACA-3’, reverse 5’-CTCGGTTCGCCAGCACA-3’.

2.7. Cells proliferation assay

After adding 10 μL of CCK8 (Dojindo, Japan) and 90 μL RPMI 1640 medium into each plate of cells, the sections were incubated at 37°C under 5% CO2, and microplate reader (Biotek) was subsequently used to measure OD value. The proliferative-detection was performed at 0, 24, and 48 hours after transfection.

2.8. Annexin V-FITC–propidium iodide assay

For the analysis of cells apoptosis, cells were digested by pancreatic and washed three times with PBS, then suspended in 100 μL blinding buffer. After adding 5 μL Annexin V-FITC (AV) (Invitrogen), incubation was performed at room temperature for 15 minutes in the dark, and then 5 μL propidium iodide (PI) (Invitrogen) was added to the cell suspension and incubated at room temperature for 15 minutes in the dark. The cells stained with AV and PI were detected with flow cytometry.

2.9. Western blot assay and antibody

At 48 hours after transfection, total protein was extracted from lysing cells in 1 mL of RIPA buffer (Thermo Fisher Scientific). A bicinchoninic acid kit (Pierce Biotechnology) was used to measure the protein concentration, which was subsequently adjudged based on the standard curve. After that, 20-μg protein sample was fractionated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to polyvinylidene fluoride membranes (Millipore). Five percent skim milk was then used to block the protein for 2 hours. The primary antibody (Table 1) was added for incubation of membranes at 4°C overnight. Subsequently, secondary antibody (Table 1) was added for incubation for 1 hour at room temperature. Blots were exposed to x-ray films for chemiluminescence following treatment using an enhanced chemiluminescence kit (Millipore).

2.10. Statistics

Statistics was carried out using 2010 of Statistics (GraphPad). Data were presented in
mean ± standard deviation, median (25th–75th) or count (%). Comparison was determined by Wilcoxon rank sum test, Kaplan-Meier (K-M) curves and log-rank test were used to compare OS between different groups. Univariate Cox proportional hazard regression was used to assess all factors affecting OS, whereas all factors with P value no more than .1 were further detected by multivariate Cox proportional hazard regression. P < .05 was considered significant.

### 3. Results

#### 3.1. Baseline characteristics

Mean age of 96 EOC patients was 53.44 ± 11.95 years (Table 2). The number of patients with pathological grade 1 (G1), G2, and G3 were 9 (9.4%), 30 (31.2%), and 57 (59.4%), respectively. Sixty (62.5%) patients were with ascites ≥ 100 mL, whereas others (N = 36 [37.5%]) were with ascites < 100 mL. As to FIGO stage, the numbers of patients in stage I, II, III, and IV were 14 (14.6%), 21 (21.9%), 57 (59.4%), and 4 (4.1%), respectively. There were 35 (36.5%) patients with CA125 (≥ 1000 U/mL) and 61 (63.5%) patients with CA125 (< 1000 U/mL). Other baseline characteristics were presented in Table 2.

#### 3.2. Comparison of lncRNA TUG1 expression in tumor tissue and paired adjacent tissue

Wilcoxon rank sum test was performed to compare lncRNA TUG1 expression in tumor tissue and paired adjacent tissue (Fig. 1). The expression of lncRNA TUG1 was higher in tumor tissue compared to paired adjacent tissue (P < .001). The median value of lncRNA TUG1 expression in tumor tissue and paired adjacent tissue was 2.344 (1.394–3.403) and 1.182 (0.738–1.849), respectively.

#### 3.3. Correlation between tumor lncRNA TUG1 expression and clinicopathological characteristics

Analyses of tumor lncRNA TUG1 expression in subgroups classified by clinicopathological features were performed (Fig. 2). Higher expression of lncRNA TUG1 was correlated with pathological grade G3 (vs. G1/2) (P = .022, Fig. C), tumor size ≥ 10 cm (P = .011, Fig. 2E) and FIGO stage III-IV (vs. stage I-II) (P < .001, Fig. 2G), whereas no difference of tumor lncRNA TUG1 expression in other subgroups was observed (all P > .05), including age (≥ 50 vs. < 50 years) (Fig. 2A), histological subtype (serous vs. others) (Fig. 2B), peritoneal cytology (positive vs. negative) (Fig. 2D), the volume of ascites (≥ 100 mL vs. < 100 mL) (Fig. 2F), and CA125 (≥ 1000 U/mL vs. < 1000 U/mL) (Fig. 2H).

#### 3.4. Correlation of lncRNA TUG1 expression with OS

K-M curve and log-rank test were performed to evaluate the correlation of lncRNA TUG1 expression with OS (Fig. 3), high expression of lncRNA TUG1 was associated with worse OS compared to low expression of lncRNA TUG1 (P = .003).

#### 3.5. Factors affecting OS

All factors affecting OS were assessed by univariate Cox proportional hazard regression, which suggested that higher expression of tumor lncRNA TUG1 (P = .004), pathological grade G3 (vs. G1/2) (P = .045), the volume of ascites ≥ 100 mL (P = .024) and FIGO stage III-IV (vs. I-II) (P = .008) were correlated with worse OS in EOC patients (Table 3). In addition, factors with a P value below 0.1 in univariate Cox’s proportional hazard regression were further evaluated in multivariate Cox’s proportional hazard regression, which indicated that high expression of tumor lncRNA TUG1 (P = .035) and the volume of ascites ≥ 100 mL (P = .031) were independently predictive factors for shorter OS in EOC patients.

#### 3.6. LncRNA TUG1 expression after plasmids transfection

We further explored the function of lncRNA TUG1 in EOC cells in vitro. After transfection, PCR assay was performed. We observed that transfection rates were all >90% in NC1 mimic, lncRNA TUG1 mimic, NC2 inhibitor, and lncRNA TUG1 inhibitor groups (Fig. 4A), and lncRNA TUG1 expression was

### Table 1

| Antibody                        | Company/country | Dilution ratio |
|---------------------------------|-----------------|----------------|
| Primary antibody                |                 |                |
| Cleaved caspase-3 rabbit mAb    | CST             | 1:1000         |
| Caspase-3 rabbit mAb            | CST             | 1:1000         |
| Anti-Bcl-2 antibody             | Abcam           | 1:1000         |
| Anti-GAPDH antibody             | Abcam           | 1:1000         |
| Second antibody                 |                 |                |
| Goat anti-rabbit IgG H&L (HRP)  | Abcam           | 1/2000         |

HRP = Horseradish peroxidase.

### Table 2

| Baseline characteristics | EOC patients (N = 96) |
|--------------------------|-----------------------|
| Age, y                   | 53.44 ± 11.95         |
| Histological subtype(*)  |                       |
| Serous (n/%)             | 59 (61.5)             |
| Others (n/%)             | 37 (38.5)             |
| Pathological grade       |                       |
| G1 (n/%)                 | 9 (9.4)               |
| G2 (n/%)                 | 30 (31.2)             |
| G3 (n/%)                 | 57 (59.4)             |
| Peritoneal cytology(*)   |                       |
| Positive (n/%)           | 46 (47.9)             |
| Negative (n/%)           | 34 (35.4)             |
| Tumor size               |                       |
| ≥ 10 cm (n/%)            | 47 (49.0)             |
| < 10 cm (n/%)            | 49 (51.0)             |
| The volume of ascites    |                       |
| ≥ 100 mL (n/%)           | 60 (62.5)             |
| < 100 mL (n/%)           | 36 (37.5)             |
| FIGO stage               |                       |
| I (n/%)                  | 14 (14.6)             |
| II (n/%)                 | 21 (21.9)             |
| III (n/%)                | 57 (59.4)             |
| IV (n/%)                 | 4 (4.1)               |
| CA125                    |                       |
| ≥ 1000 U/mL (n/%)        | 35 (36.5)             |
| < 1000 U/mL (n/%)        | 61 (63.5)             |

Data were presented as mean ± standard deviation or count (%). CA125 = carbohydrate antigen 125, EOC = epithelial ovarian cancer, FIGO = International Federation of Gynecology and Obstetrics.

(*) Other pathological types included mucinous adenocarcinoma, endometroid adenocarcinoma, and mixed types.

(*) Eighty patients had peritoneal cytology records.
increased after transfection with lncRNA TUG1 mimic, and was decreased after transfection with lncRNA TUG1 inhibitor (Fig. 4B).

3.7. CCK8 Assay after transfection

We subsequently investigated whether lncRNA TUG1 could regulate cells proliferation by CCK8 assay after transfection. Cells proliferation was promoted after treatment with lncRNA TUG1 mimic and was suppressed after treatment with lncRNA TUG1 inhibitor, indicating that lncRNA TUG1 could facilitate proliferation in EOC cells (Fig. 5).

3.8. Cells apoptosis after transfection

Cells apoptosis after transfection was also performed, which revealed that cells apoptosis rate was decreased after treatment with lncRNA TUG1 mimic compared to NC1 mimic, and was increased after treatment with lncRNA TUG1 inhibitor compared to NC2 inhibitor (Fig. 6A and B). We also detected cells apoptosis related protein. As shown in Figure 6C, lncRNA TUG1 mimic decreased the expression of C-Caspase 3, and lncRNA TUG1 inhibitor increased the expression of C-Caspase 3. As to Bcl-2 expression, lncRNA TUG1 mimic increased Bcl-2 expression and lncRNA TUG1 inhibitor decreased Bcl-2 expression. These finding suggested that lncRNA TUG1 could repress apoptosis in EOC cells.

4. Discussion

In the present study, we observed that: LncRNA TUG1 expression was higher in tumor tissue compared to paired adjacent tissue. The expression of lncRNA TUG1 was higher in tumor tissue compared to paired adjacent tissue. Comparison between groups was performed by Wilcoxon rank sum test. \( P < .05 \) was considered significant. lncRNAs = long non-coding RNAs, TUG1 = taurine-upregulated gene 1.
adjacent tissue; LncRNA TUG1 expression was positively correlated with advanced disease, multivariate Cox analysis indicated that tumor lncRNA TUG1 higher expression could independently predict for shorter OS in EOC patients; ncRNA TUG1 promoted cells proliferation and inhibited cells apoptosis in EOC cells.

LncRNAs are considered as new modulators in the process of tumorigenesis and progression in cancer by regulating several genes and pathways.\[13–15\] Accumulating evidences have proven that lncRNAs involve in many types of gene regulation through multiple mechanisms, including chromatin remodeling; mediating transcription factors and co-activators (cis-acting) recruitment; alternatively splicing pre-mRNAs; inhibiting RNA polymerase II activity; sequestrating microRNAs; mediating mRNA stability, to sequentially accumulate the development of various carcinomas, such as EOC, breast cancer, and colorectal cancer.\[15–22\] To EOC that is the most deadly gynecological malignancy, several lncRNAs, including HOX transcript antisense RNA (HOTAIR), colon cancer-associated transcript 2 (CCAT2), and nuclear paraspeckle assembly transcript 1, have been reported to dedicate to the prognosis in EOC patients.\[23–25\]

An interesting study indicates that lncRNA CCAT2 is positively associated with FIGO stage, tumor grade as well as distant metastasis, and its high expression was correlated with worse OS and disease-free survival, which constitutes a potential biomarker for poor prognosis in EOC patients.\[24\] Another study determines that high expression of lncRNA protein sprouty homolog 4 (SPRY4)-intron 1 may be an independent predictive biomarker for shorter prognosis-free survival and OS in EOC patients.\[22\] These data suggest that lncRNAs involve in the progress of EOC and could be developed as prognostic biomarkers in EOC patients.

LncRNA TUG1, located on chromosome 22q12, is commonly expressed in human tissues and carcinomas cells, which has been verified as an oncogene to several cancers.\[26–28\] Recent data prove that lncRNA TUG1 is positively correlated with tumor size, distant metastasis as well as TNM stage, and it might act as a diagnostic and prognostic biomarker in patients with breast cancer.\[26\] Also another study illustrates that overexpression of lncRNA TUG1 is associated with worse lymph nodes metastasis and advanced TNM stage in patients with gastric cancer.\[27\] Furthermore, upregulated expressions of lncRNA TUG1 are

**Table 3**

| Factors                      | Univariate Cox proportional hazard regression | Multivariate Cox proportional hazard regression |
|------------------------------|-----------------------------------------------|-----------------------------------------------|
|                              | P     | HR   | 95% CI     | P     | HR   | 95% CI     |
| Tumor lncRNA TUG1 higher expression | .004  | 3.236 | 1.441 7.269 | .035  | 3.021 | 1.084 8.423 |
| Age ≥50 y                    | .975  | 0.987 | 0.443 2.022 | —     | —     | —       |
| Histological subtype serous (vs. others) | .594  | 0.804 | 0.360 1.794 | —     | —     | —       |
| Pathological grade G3 (vs. G1/2) | .045  | 2.331 | 1.018 5.336 | .053  | 2.775 | 0.987 7.803 |
| Peritoneal cytology positive | .098  | 2.095 | 0.872 5.030 | .051  | 2.449 | 0.995 6.025 |
| Tumor size ≥10 cm            | .163  | 1.757 | 0.795 3.879 | —     | —     | —       |
| The volume of ascites ≥100mL | .024  | 2.644 | 1.137 6.150 | .031  | 3.029 | 1.109 8.275 |
| FIG Stage III-IV (vs. I-II)  | .008  | 3.639 | 1.421 10.375 | .114  | 2.618 | 0.780 10.190 |
| CA125 ≥1000U/mL              | .144  | 1.911 | 0.857 4.291 | —     | —     | —       |

Data were presented as P value, HR, 95% CI. Multivariate Cox proportional hazard regression was performed to analyze factors with a P value <.1 in univariate Cox analysis. P < .05 was considered significant.

CA125 = carbohydrate antigen 125, CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio, OS = overall survival, TUG1 = taurine upregulated 1.

**Figure 4.** LncRNA TUG1 expression after plasmids transfection. (A) Transfection rate swere all >90% in 4 groups. (B) LncRNA TUG1 expression was increased in lncRNA TUG1 mimic group and decreased in lncRNA inhibitor group compared to NCs. *P < .05, **P < .01, lncRNAs = long non-coding RNAs, TUG1 = taurine-upregulated gene 1.
correlated with shorter OS in breast cancer, colorectal cancer as well as clear cell renal cell carcinoma, and so on.[26,28,29] These data have proven that lncRNA TUG1 may serve as a convinced unfavorable prognosis factor for some carcinomas, while little is known about the role of lncRNA TUG1 in EOC. Therefore, we investigated the role of IncRNA TUG1 in EOC, and found that lncRNA TUG1 expression was positively associated with pathological grade, tumor size, as well as FIGO stage, and it could be served as an independent risk factor for OS in EOC patients, indicating that lncRNA TUG1 may be a potential biomarker for tumor prognosis in EOC patients. However, the sample size in this study was relatively small with enrollment of 96 EOC patients; thus, the role of lncRNA TUG1 in EOC is needed to be further validated in larger number of patients.

To explore the effects of lncRNA TUG1 in pathological process of cancer and its potential mechanism, several vitro experiments have been performed. For example, lncRNA TUG1 accumulates cells proliferation and represses cells apoptosis by promoting zinc finger E-box-binding homeobox 2 (ZEB2) mediated by miR-142 through the inactivation of Wnt/β-catenin pathway in bladder cancer cells.[30] Also, lncRNA TUG1 promotes oral squamous cell carcinoma cells proliferation and invasion through inhibiting miR-219 or inducing formin-like
Another study identifies that lncRNA TUG1 facilitates cells proliferation and invasion in papillary thyroid cancer cells via regulating miR-145/5p/143 signal pathway. In the present study, the results showed that lncRNA TUG1 induced cells proliferation and inhibited apoptosis in EOC. These might suggest that lncRNA TUG1 contributes to EOC pathology via mediating cells proliferation and cells apoptosis through several genes or pathways.

In conclusion, lncRNA TUG1 is positively correlated with advanced disease and poor prognosis, and it promotes cells proliferation and inhibits cells apoptosis in EOC cells.

Author contributions

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