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RESEARCH PAPER

lncRNA TUG1 promotes the development of oral squamous cell carcinoma by regulating the MAPK signaling pathway by sponging miR-593-3p

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ABSTRACT

Dysregulation of non-coding RNAs (ncRNAs) has been proved to play important roles in oral squamous cell carcinoma (OSCC). This study aimed to determine the combined role of lncRNA TUG1, miR-593-3p, and MAPK signaling in oral squamous cell carcinoma (OSCC) development. Here, we found that TUG1 was up-regulated in OSCC tissues and cell lines. Silencing TUG1 suppressed proliferation migration, invasion and promoted apoptosis of OSCC cells. We also validated that knockdown of TUG1 suppressed MAPK signaling pathway and inhibited EMT process in OSCC cells. Then, a novel LncRNA TUG1/ miR-593-3p/MAPK axis was verified to rescue cell viability in OSCC cells. Mechanistically, miR-593-3p bound to lncRNA TUG1, and lncRNA TUG1 positively regulated MAPK related proteins through acting as RNA sponger for miR-593-3p. Further gain- and loss-of-function experiments evidenced that the protective effects of lncRNA TUG1 knock-down on OSCC cells were abrogated by silencing miRNA-593-3p. The OSCC nude mice model experiments demonstrated that depletion of TUG1 further inhibited tumor growth. In conclusion, appropriate diagnostic biomarkers and therapies for OSCC can be identified by targeting the TUG1/miR-593-3p/MAPK axis.

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Introduction

Oral cancer is a subtype of head and neck cancer, and oral squamous cell carcinoma (OSCC) comprises approximately 90% of all oral cancer cases [1,2]. Globally, approximately 350000 patients are diagnosed with OSCC each year, resulting in over 17000 deaths [3]. Despite improvements and innovations in treatments, such as chemotherapy, radiation, and surgery, the overall 5-year survival rate remains below 50% [4]. Consequently, there is a growing need to develop novel therapeutic strategies against OSCC by exploring the underlying molecular mechanisms.

LncRNAs are a class of RNA molecules that lack protein-coding capabilities [5]. LncRNAs modulate gene transcription and post-transcriptional regulation and participate in various pathological processes [6,7]. Multiple studies have demonstrated that dysregulated lncRNAs are correlated with specific clinical phenotypes and clinicopathological parameters of cancer [8,9]. For example, the sequestration of miR-216a induced by the lncRNA DANCR promotes lung cancer [10]. lncRNA CDC6 promotes the progression of breast cancer and targets CDC6 as a ceRNA via microRNA-215 sponging [11]. Located in chromosome 22q12.2, Taurine up-regulated 1 (TUG1) was initially identified as a taurine regulated transcript. Previously, lncRNA TUG1 was reported to have connections with many cancers. For example, TUG1 ncRNA aided the proliferation and migration of the papillary thyroid cancer cells via targeting miR-145 [12]. TUG1 is also involved in the development of small cell lung cancer by regulating LIMK2b [13]. In addition, colorectal cancer development is promoted by the lncRNA TUG1 through the miR-138-5p/ZEB2 axis [14]. However, despite these numerous studies, the role of TUG1 in OSCC remains unclear.

MicroRNAs (miRNAs) are small and single strand RNA consisting of 22 nucleotides that regulate mRNA translation [15]. miRNAs play an important role in cell survival, development, and apoptosis. Accumulating evidence has indicated

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that abnormally expressed miRNAs are involved in tumorigenesis. miR-593-3p, a tumor-related miRNA, has been found to be involved in the development of gastric, breast, and lung cancers [16–18]. LncRNAs primarily operate through a mechanism that involves competitive endogenous RNA (ceRNA), which enables lncRNAs to interact with miRNAs such that miRNAs do not interfere with downstream genes [19,20]. However, the relationship between miR-593-3p and OSCC, TUG1, and miR-593-3p has not yet been investigated.

In this study, we examined the role of TUG1 in OSCC and its associated mechanism, as well as its interaction with miR-593–3p. We also validated the critical roles of the MAPK/EMT signaling pathway during this process. Thus, we revealed the oncogenic importance of TUG1 in OSCC with a possible therapeutic objective.

Materials and methods

Human tissue samples

Clinical OSCC and paired normal tissue samples were obtained from Zhongnan Hospital of Wuhan University. All patients signed an informed consent form. This study was approved by the ethics committee of Zhongnan Hospital of Wuhan University.

Cell culture

HOMEC cells, OSCC Tca8113 cells, OSCC SCC25 and CAL27 cells. Cell lines, sourcing from Chinese Academy of Sciences (Shanghai, China), were cultivated with DMEM/F12 medium (Thermo, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (Thermo, Carlsbad, CA, USA) and penicillin–streptomycin (1%).

Vector construction and transfection

Synthesis of miR-593-3p mimics/inhibitors and negative control (NC) was carried out by Genepharma Inc. (China). Transfection of cells with TUG1 targeting siRNA (si-TUG1) and si-NC was measured using Lipofectamine 3000 (Invitrogen). Cells were collected 48 h after transfection.

Luciferase reporter assay

Cells were transfected in a 24-well plate together with TUG1 mutant (MUT) or wild-type (WT) TUG1, and miRNAs (miR-593-3p mimic or mi-NC) using Lipofectamine® 3000 (Invitrogen). 24 h post-transfection, the luciferase activity was measured using fluoresce in reporter kit (NEB Cor.).

Transwell assay

In this experiment to assess cell invasiveness, the upper chamber surface of the bottom Transwell membrane was coated with diluted Matrigel. SCC25 and CAL27 cells were transferred to the upper compartment containing serum-free media supplemented with bovine serum albumin. Then, 500 µL of complete medium supplemented with 10% FBS was added to the lower compartment. Invasive cells were fixed for 30 min following 48 h of incubation with 90% ethanol (v/v). Next, the cells were stained with 0.1% crystal violet solution (4°C, 10 min) and photographed using a light microscope.

Cell apoptosis assay

SCC25 and CAL27 cells were firstly transfected with si-NC or si-TUG1, then staining was performed with propidium iodide/ Annexin V-FITC (PI; BD Biosciences, San Jose,CA, USA) following 48 hours of transfection. A flow-cytometer (BD Biosciences) was used to adopted to qualify apoptotic cells.

Cell proliferation assay

Cell proliferation was determined using cell counting kit-8 (CCK-8; Beyotime). Cells (2×10^4) were cultivated for 24–72 h at a 12-hour interval in five 96-well plates treated with 10 µl of CCK-8 solution. Absorbance at 450 nm was measured using a microtiter plate reader.

RT-qPCR assay

OSCC tissue or RNAisO Plus(Takara, Japan)-treated cells were extracted of total RNA. PrimeScript RT reagent Kit with gDNA Eraser

(Takara, Japan) was adopted for synthesis of cDNA. Quantitative real-time PCR was performed using a 2× SYBR Premix Ex TaqTMII. Relative expression was quantified using the $2^{-\Delta\Delta Ct}$ method, with the levels normalized to those of GAPDH. All PCR primers used in this study are listed below. Each experiment was performed in triplicate.

miR-593-3p-F: 5′- AGAATCTGTC AGGCACC AGCC-3′;

miR-593-3p-R: 5′- ACAAACCCAGCA CC ACTCCT-3′.

TUG1-F: 5′- TAGCAGTTCCCCAATCCTT G-3′;

TUG1-R: 5′- CACAAATTCCCATCATTCC-3′.

GAPDH-F: 5′- TCAAGATCA TCAGCAATGC C-3′;

GAPDH-R: 5′- CGATACCAAAGT TGTCATG GA-3′.

Western blotting

Cells were lysed for 30 min with a phosphatase inhibitor and phenylmethylsulfonyl fluoride. The supernatant was harvested by centrifugation (14000 × g, 15 min). Protein concentrations were determined using a BCA Protein Assay Reagent Kit (Beyotime, China). Next, the protein samples (30 μg) were subjected to 10% SDS-PAGE and transferred onto a PVDF membrane (0.45-micrometer, Millipore, MA, USA), followed by blocking in 5% skim milk and incubation. Protein expression levels were subsequently compared.

In vivo tumorigenicity assay

Twelve specific pathogen-free (SPF) BALB/c female nude mice (4–6 weeks old, 18 to 22 g) divided into the si-NC group and si-TUG1 group with 6 mice in each group. Then, 0.2 ml of si-NC and si-TUG1 SCC25 cell suspensions with a cell concentration of 5×10^7 cells/ml were injected into the left back of each mouse. The tumor size was observed and recorded every 4 days for 4 weeks. Subsequently, the mice were sacrificed and tumors were resected. During the experiment, the sizes of tumors were measured with caliper at indicated times, and the volume was calculated using $0.5 \times [\text{length}] \times [\text{width}]2$ equation. The tumor weight was recorded using electronic balance on the last day. All animal experimental procedures were approved by the Laboratory Animal Use Management Committee of the Experimental Animal Institute of Wuhan University.

Statistical analysis

Data analysis was performed using SPSS version 23 (IBM, USA). Figures were prepared using GraphPad Prism 7.0 (GraphPad Software, CA, USA). The tests were repeated in triplicate and data were analyzed using Student's t-test and one-way analysis of variance. Statistical significance was set at $P < 0.05$.

Results

TUG1 expression is significantly upregulated in OSCC tissues and cells

First, we analyzed the levels of TUG1 in OSCC tissues collected from 32 OSCC patients using RT-qPCR; adjacent normal tissues were used as controls. The expression of TUG1 was markedly increased in tumor tissues (Figure 1a). Similarly, RT-qPCR assays showed that TUG1 expression in Tca8113, SCC25, and CAL27 cells was remarkably higher than that in HOMEC cells (Figure 1b, $p < 0.05$).

Knockdown of TUG1 inhibited OSCC cell proliferation and promoted apoptosis

Next, we explored the effect of TUG1 on SCC25 and CAL27 OSCC cells. We verified the knockdown efficiency in SCC25 and CAL27 cells and found that TUG1 expression was downregulated (Figure 2a, 2b). CCK-8 assay results indicated that the proliferation of SCC25 and CAL27 cells was markedly decreased after TUG1 knockdown (Figure 2c, 2d). In addition, TUG1 silencing notably promoted apoptosis in SCC25 and

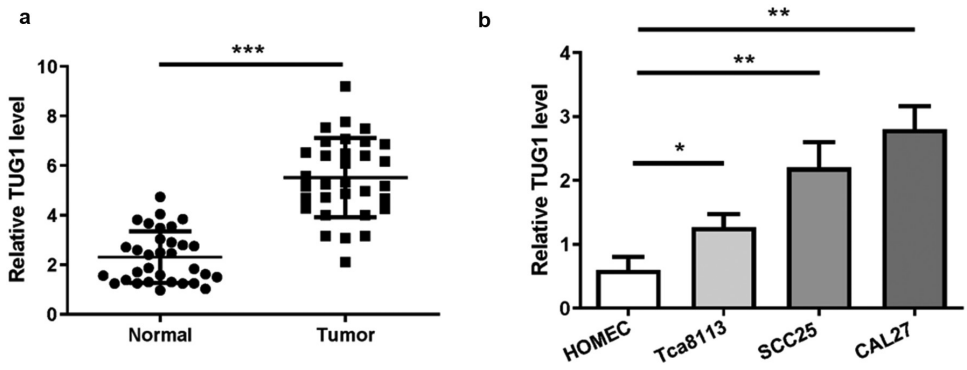

Figure 1. Upregulation of TUG1 expression in OSCC tissues and cells.
A. OSCC and normal tissues were collected, and TUG1 expression was analyzed in them using RT-qPCR. B. OSCC and HOMEC cells were collected, and TUG1 expression was analyzed in them using RT-qPCR (n = 3). *P < 0.05, **P < 0.01, and ***P < 0.001.

CAL27 cells (Figure 2e). These results revealed that TUG1 knockdown inhibited OSCC cell proliferation and induced apoptosis.

Knockdown of TUG1 promoted cell migration and EMT and regulated the MAPK signaling pathway in OSCC cells

Given the effects on cell proliferation observed in OSCC cells, the impact of TUG1 knockdown on invasion was evaluated in these cell lines. Knockdown of TUG1 in SCC25 and CAL27 cells inhibited cell invasion (Figure 3a). Western blotting results showed that the expression of E-cadherin was upregulated, while that of N-cadherin was inhibited by TUG1 knockdown (Figure 3b). Thus, the MAPK pathway regulates cell proliferation, differentiation, and stress response [21,22]. To analyze the potential mechanism underlying the effect of TUG1 on OSCC cells, the expression of MAPK signaling pathway-related proteins was detected using western blotting. The results showed that p-p38 and p-JNK expression was markedly increased after TUG1 knockdown in OSCC cell lines (Figure 3c). Therefore, we concluded that TUG1 knockdown promotes cell migration and EMT and regulates the MAPK signaling pathway in OSCC cells.

TUG1 directly binds to miR-593-3p

In contrast to normal tissues, miR-593-3p expression was decreased in OSCC tissues (Figure 4a). Similar results were observed in OSCC cell lines (Figure 4b). We also mutated the predicted miR-593-3p-binding site in TUG1 (Figure 4c). miR-593-3p overexpression reduced the luciferase activity of TUG1-WT, without affecting that of TUG1-MUT, suggesting that miR-593-3p interacted with TUG1 at the predicted binding site (Figure 4c). A negative correlation was found between miR-593-3p and TUG1 expression in OSCC samples (Figure 4d). Collectively, the results indicate that TUG1 negatively interacts with miR-5590-3p in OSCC.

TUG1 regulates OSCC cell proliferation, apoptosis, and invasion and the MAPK signaling pathway by targeting miR-593-3p

CCK-8 assays showed that transfection with si-TUG1 significantly suppressed OSCC cell proliferation (Figure 5a, 5b), whereas transfection with miR-593-3p-inhibitor enhanced their proliferation (Figure 5a, 5b). We found that TUG1 knockdown promoted cell apoptosis, while the miR-593-3p-inhibitor reversed the apoptotic effects (Figure 5c). In addition, the Transwell assay indicated that TUG1 knockdown decreased cell invasion, whereas the miR-593-3p-inhibitor promoted it (Figure 5d). Similarly, E-cadherin expression was decreased, while that of N-cadherin was increased, as observed by western blotting (Figure 5e). TUG1 knockdown in transfected OSCC cells significantly increased p38 and JNK phosphorylation (Figure 5f), while transfection with the miR-

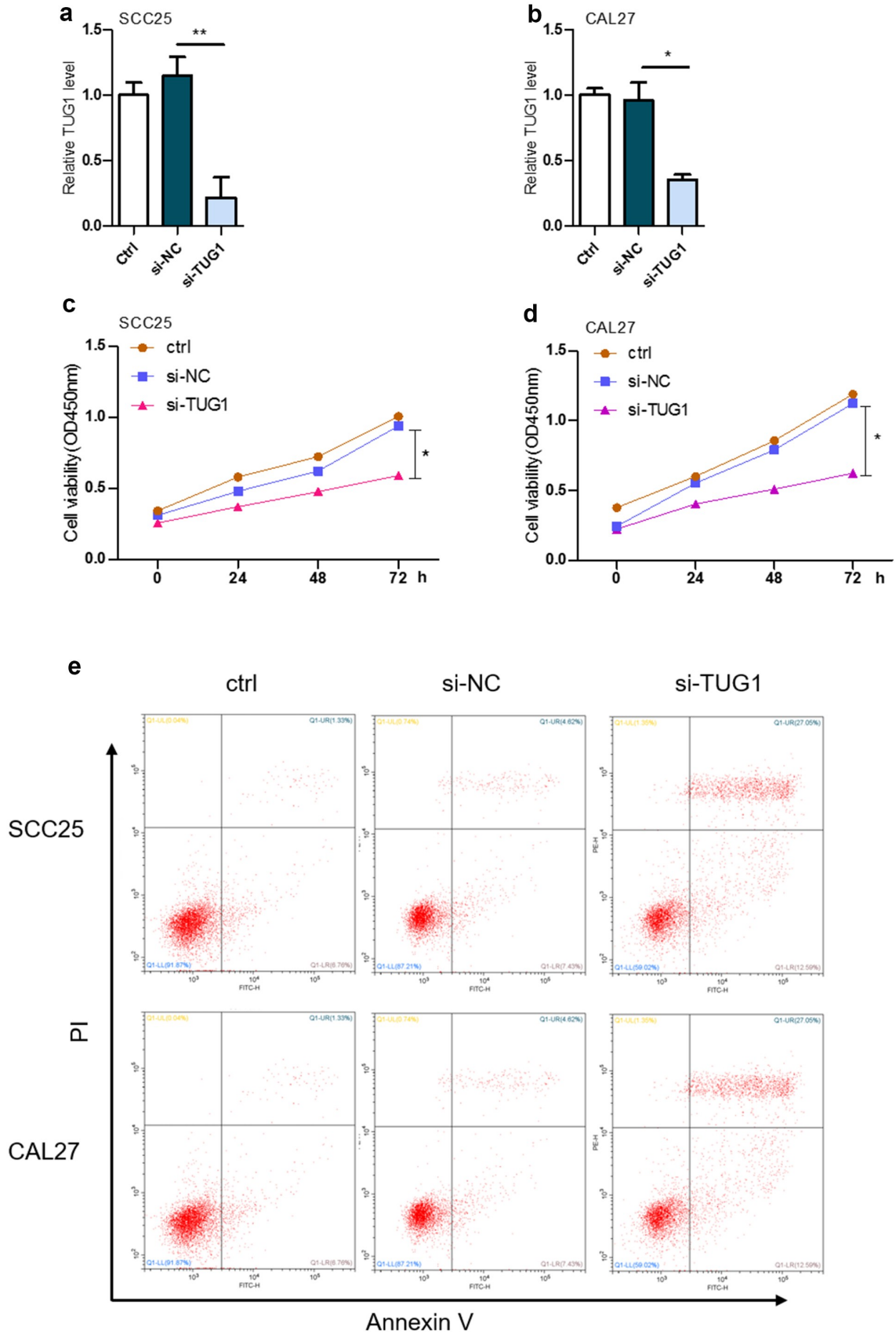

Figure 2. Knockdown of TUG1 inhibits OSCC cell proliferation and promotes their apoptosis.

A-B. Verification of the knockdown efficiency of siRNA targeting the binding sites of TUG1 in SCC25 and CAL27 cells (n = 3). C-D. SCC25 and CAL27 cell proliferation at 24, 48, and 72 h was assessed using CCK-8 assay (n = 3). E. SCC25 and CAL27 cell apoptosis was detected using Annexin V/PI assay (n = 3). *P < 0.05 and **P < 0.01.

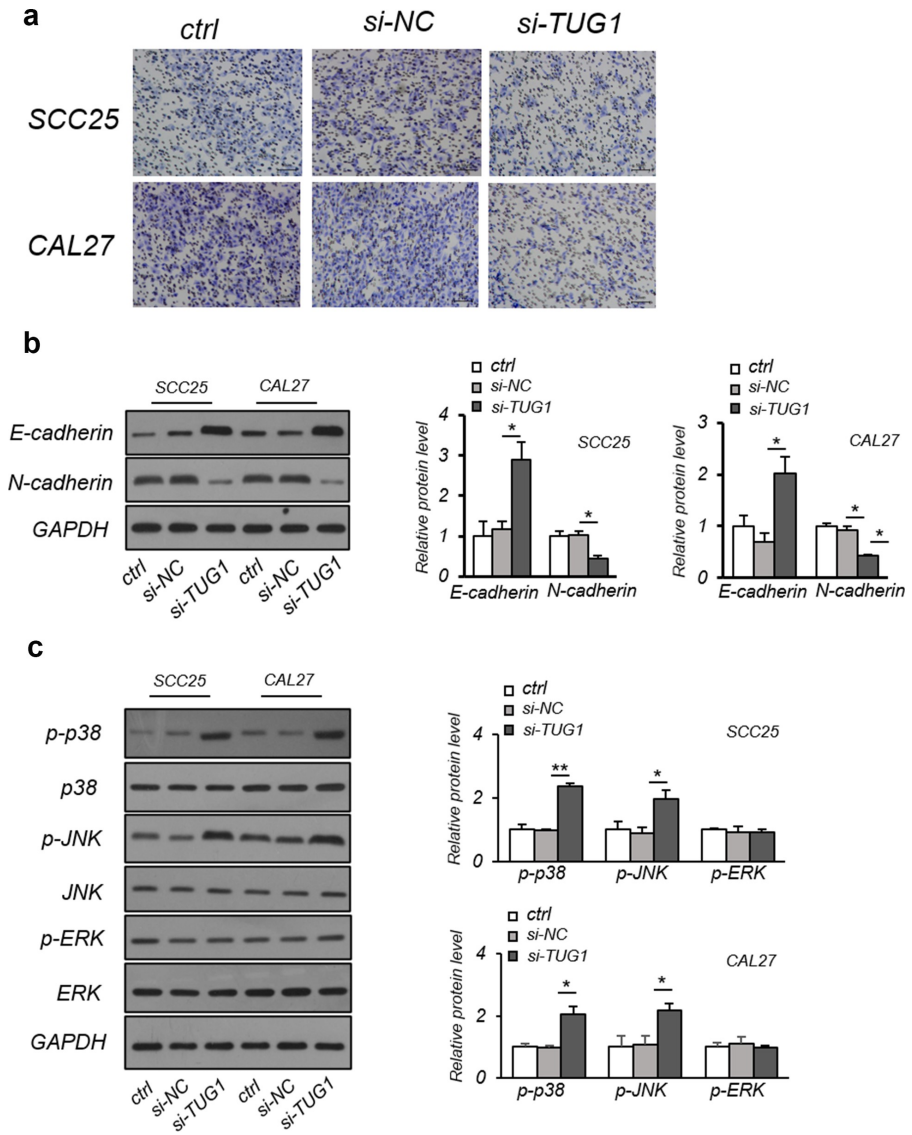

Figure 3. Knockdown of TUG1 promotes OSCC cell migration and EMT and regulates the MAPK signaling pathway.

A. SCC25 and CAL27 cell invasion was detected using Transwell assay (n = 3). B. Expression of the following EMT markers detected using western blotting: E-cadherin, N-cadherin, and GAPDH (n = 3). C. Expression of the following MAPK signaling pathway-related proteins detected using western blotting: p38, JNK, and ERK (n = 3).

593-3p inhibitor reversed these trends (Figure 5f). These results indicate that TUG1 in OSCC cells regulates their proliferation, apoptosis, invasion, and the MAPK signaling pathway by targeting miR-593-3p.

Knockdown of TUG1 restrained tumor growth of OSCC cells in vivo

In vitro studies results indicated that depletion of TUG1 might inhibited tumor growth in OSCC cells. To further validate the conclusion, xenograft tumor models were utilized. We constructed a SCC25 cell line with stable TUG1 deficiency (si-TUG1) and a control cell line (si-NC). The results manifested that TUG1 knockdown notably impeded the tumor growth, exhibited as declined tumor volume (Figure 6a). Moreover, the mean weights of the excised tumors were lower in si-TUG1 group mice compared with in control mice (Figure 6b). All these data suggested that knockdown of TUG1 inhibits OSCC tumor growth in vivo.

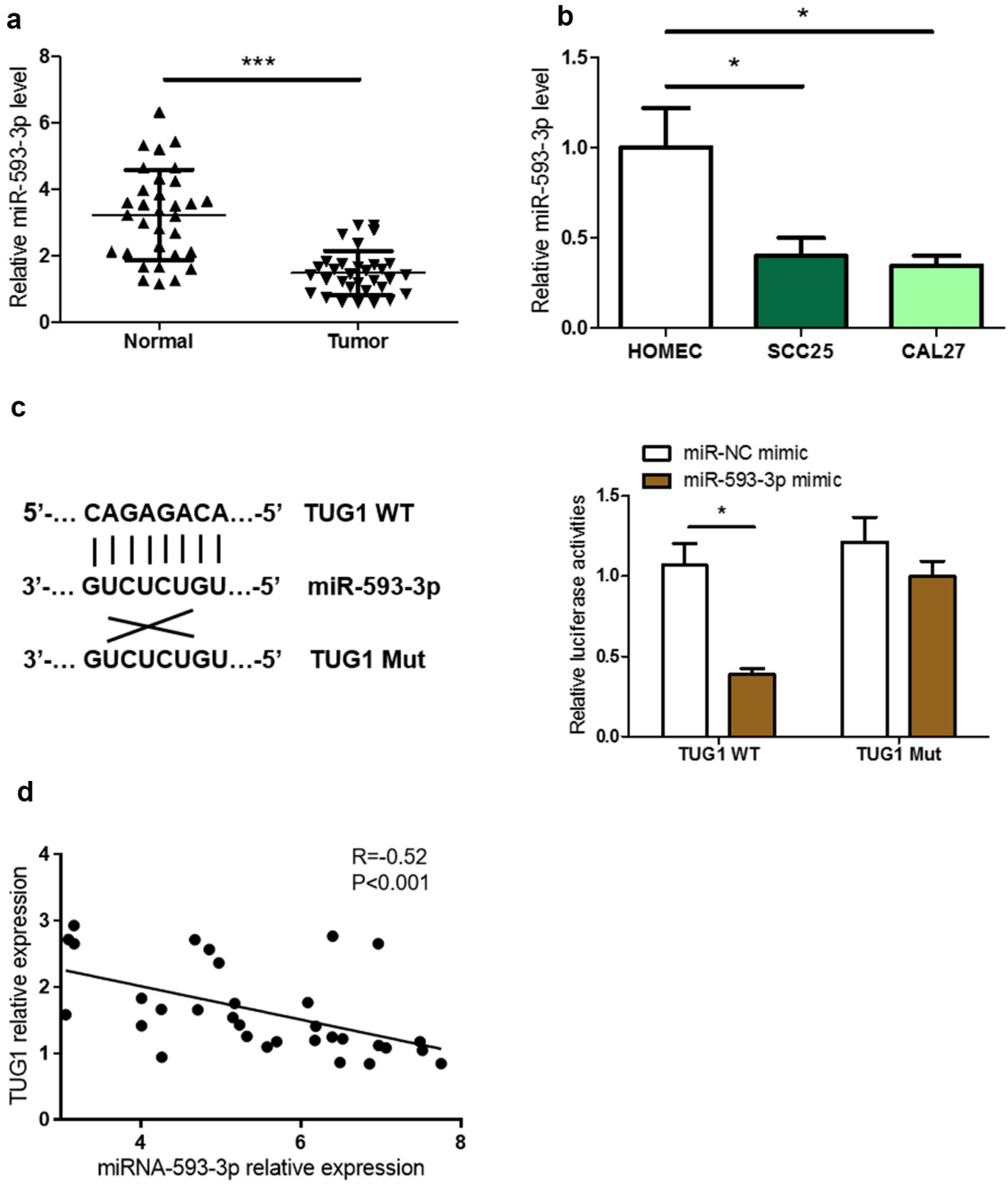

Figure 4. TUG1 directly binds to miR-593-3p.

A. OSCC and normal tissues were collected, and miR-593-3p expression was detected in them using RT-qPCR. B. OSCC and HOMEC cells were collected, and miR-593-3p expression was detected in them using RT-qPCR (n = 3). C. Bioinformatics analysis of the interaction between TUG1 and miR-593-3p. The relative luciferase activity in TUG1-WT and TUG1-MUT cells after transfection with miR-593-3p mimics or NC (n = 3). D. Negative correlation between TUG1 and miR-593-3p expression in OSCC tissues based on Pearson's correlation curve. *P < 0.05 and ***P < 0.001.

Discussion

We found that TUG1 was overexpressed and could mediate miR-593-3p/MAPK signaling in OSCC tissues and cells. Knockdown of TUG1 reduced the viability, impaired invasiveness, and enhanced apoptosis of OSCC cells. However, miR-593-3p knockdown in OSCC cells reversed these effects. The experimental results suggested that TUG1 and miR-593-3p could serve as promising markers and

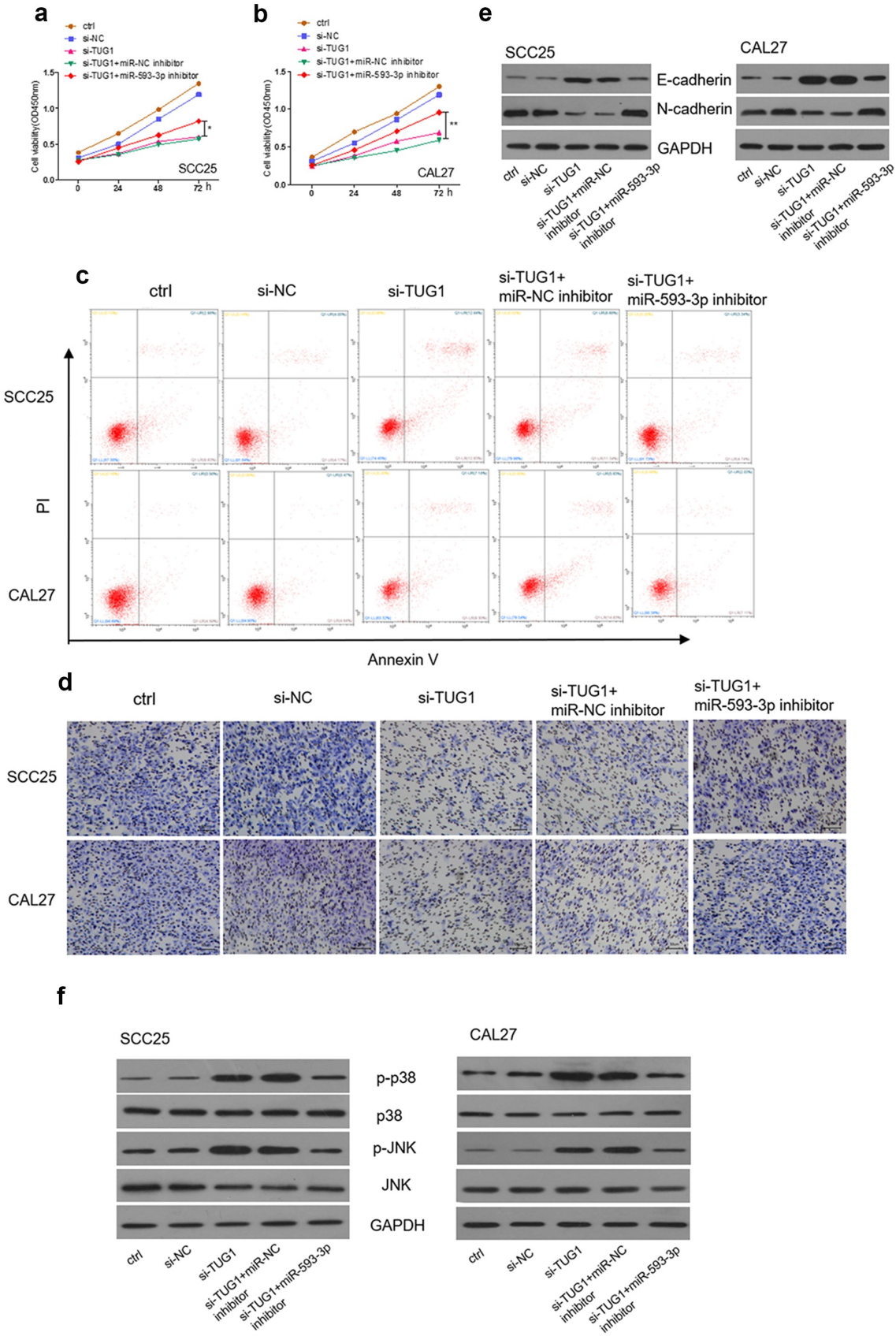

Figure 5. TUG1 regulates OSCC cell proliferation, apoptosis, and invasion and the MAPK signaling pathway by targeting miR-593-3p. A-B. Proliferation of SCC25 and CAL27 cells co-transfected with si-TUG1 and miR-593-3p inhibitor at 24, 48, and 72 h using CCK8 assay (n = 3). C. Apoptosis in SCC25 and CAL27 cells co-transfected with si-TUG1 and miR-593-3p inhibitor detected using Annexin V/PI assay (n = 3). D. Transwell assay detected the invasion of SCC25 and CAL27 cells transfected with si-TUG1 and miR-593-3p inhibitor (n = 3). E. EMT markers E-cadherin, N-cadherin and GAPDH in SCC25 and CAL27 cells si-TUG1 and miR-593-3p inhibitor (n = 3). F. MAPK signaling related proteins p38, JNK and ERK in SCC25 and CAL27 cells si-TUG1 and miR-593-3p inhibitor (n = 3). *P < 0.05 and **P < 0.01.

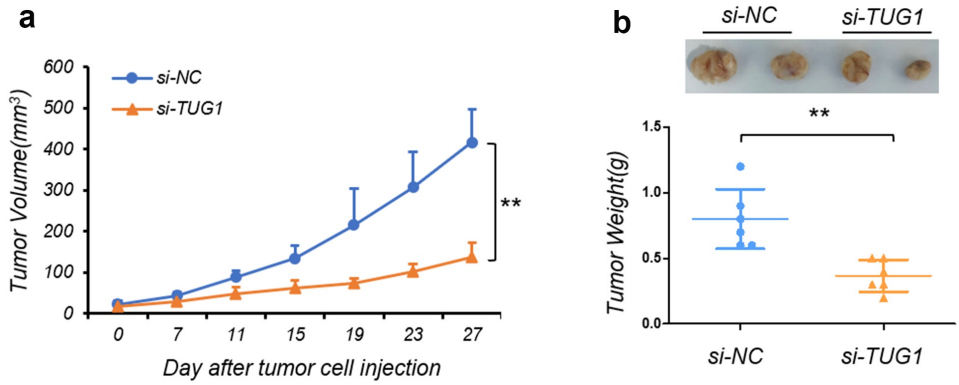

Figure 6. Knockdown of TUG1 restrained tumor growth in a SCC25 xenograft nude mouse model.
A. Tumor growth curve represented by the average tumor volumes of TUG1 knockdown of xenografts derived from SCC25 cells. *P < 0.05. B. Images of the gross tumors and average weights of tumors from nude mice from si-NC and si-TUG1 group. *P < 0.05.

targets for OSCC treatment. Subsequently, an in vivo study was conducted to confirm the role of TUG1 as a potent therapeutic target against OSCC.

Recent studies have shown that TUG1 regulates the formation of human tumors [13,23]. We found that TUG1 expression was elevated in OSCC cells and tissues. TUG1 knockdown significantly inhibited OSCC cell activity as well as EMT while enhancing apoptosis. Accordingly, we propose that TUG1, a pro-tumor factor, plays a key role in the development of OSCC.

Notably, previous studies indicated that some lncRNAs can function as a miRNA sponge to affect the levels of gene expression. For example, lncRNA-PCAT1 targeting miR-145-5p facilitates osteogenic differentiation of adipose-derived stem cells [24]. It is reported that TUG1 regulated the development of OSCC and served as ceRNA sponging miR-524-5p [25]. We demonstrated that TUG1 knockdown prevented the proliferation and invasion of OSCC cells. Subsequently, we investigated whether TUG1 acts as a miRNA sponge to exert its function. Through luciferase reporter assays, we found that miR-593-3p repressed the expression of the TUG1 reporter gene by complementary binding. Moreover, we found that miR-593-3p was negatively correlated with TUG1 expression in OSCC samples. Taken together, we concluded that TUG1 functioned as a ceRNA by sponging miR-593-3p, thus promoting the proliferation and invasion of OSCC cells.

Cell proliferation and invasion both contribute to cancer occurrence, during which the MAPK signaling pathway is vital [26,27]. MAPK, p38, JNK, and ERK are all members of the MAPK family. Wen et al. reported that p38 MAPK signaling is involved in the proliferation of breast cancer cells [28]. Zou et al. showed that the p38 MAPK signaling pathway should be targeted during cancer therapy [29]. Moreover, Zhu et al. reported that galectin-1 induces metastasis in human ovarian cancer cells through the MAPK JNK/p38 signaling pathway [30]. Therefore, these results suggest that the MAPK JNK/p38 signaling pathway may be a target for many types of cancers.

Conclusion

In our study, we found that only the expression of p-p38 and p-JNK was elevated after TUG1 knockdown in OSCC cell lines. TUG1 suppresses p38 and JNK phosphorylation by inhibiting miR-593-3p expression.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethical approval

This study was approved by the ethics committee of Zhongnan Hospital of Wuhan University.

Author contributions

Lei Jiang and Bo Cheng conceived the study and designed the experiments. Bing Zhou and Dongjie Fu contributed to the data collection, performed the data analysis and interpreted the results. Lei Jiang wrote the manuscript; Bo Cheng revised the article. All authors read and approved the final manuscript.

Informed consent from participants

All patients signed an informed consent form.

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