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ORIGINAL ARTICLE

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LncRNA GACAT1 induces tongue squamous cell carcinoma migration and proliferation via miR-149

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Abstract

Recent studies have observed that lncRNAs (long non-coding RNAs) are involved in the progression of various tumours including tongue squamous cell carcinoma (TSCC). Recently, a new lnRNA, GACAT1, has been firstly identified in gastric cancer. However, its potential role in TSCC remains unknown. In this reference, we observed that GACAT1 was overexpressed in TSCC samples and cell lines. Of 25 TSCC specimens, GACAT1 expression was overexpressed in 18 patients (18/25, 72%) compared to non-tumour specimens. Ectopic expression of GACAT1 induced cell growth and migration and promoted epithelial to mesenchymal transition in TSCC. In addition, ectopic expression of GACAT1 decreased miR-149 expression in SCC1 cell. We observed that miR-149 expression was down-regulated in TSCC cell lines. Moreover, we observed that GACAT1 expression was negatively correlated with miR-149 expression. GACAT1 overexpression induced TSCC cell growth and migration via regulating miR-149 expression. These data provided that GACAT1 played an oncogenic role in the progression of TSCC partly through modulating miR-149 expression.

KEYWORDS

GACAT1, miR-149, tongue squamous cell carcinoma

1 | INTRODUCTION

Tongue squamous cell carcinoma (TSCC) represents the most frequent type of oral squamous cell carcinoma (OSCC) and is famous for its high potential of metastasis and proliferation.[1-5] TSCC usually leads to speech, deglutition and mastication malfunction.[6-8] Despite the advancement in radiotherapy, chemotherapy and surgery, the 5-year survival rate of this disease is still not satisfactory.[9-12] Survival rate improvement requires more understanding of initiation and progression of TSCC.[6,13,14] Therefore, more works should be performed to explain the molecular mechanisms and process, which may identify new effective targets for TSCC treatment.

Long non-coding RNAs (lncRNAs) are more than 200 nucleotides in length that can modulate gene expression in post-transcriptional or transcriptional level.[15-18] Recent reports have showed that lncRNAs play essential roles in several cellular functions including cell development, growth, apoptosis, differentiation, invasion and migration.[19-23] In addition, a number of studies suggested that lncRNAs were deregulated in various cancers such as colorectal cancer, breast cancer, osteosarcoma, hepatocellular carcinoma, bladder cancer and LSCC.[12,24-28] Recently, a new lnRNA, AC096655.1-002 (GACAT1), was originally found to be correlated with progression of gastric cancer, and expression of GACAT1 was decreased in gastric cancer.[29] Lower expression of CACAT1 was associated with TNM stages, lymph node metastasis, distant metastasis and differentiation.

However, Shi et al[30] reported that GACAT1 was overexpressed in gastric cancer samples and GACAT1 overexpression induced gastric cancer cell growth, migration and invasion. However, its role in TSCC development and the underlying molecular mechanisms has not been studied.

In the current study, our data observed that GACAT1 was overexpressed in TSCC samples and cell lines. Ectopic expression of GACAT1 induced cell growth and migration and promoted epithelial to mesenchymal transition (EMT) in TSCC.

2 | MATERIAL AND METHODS

2.1 | Clinical specimens

Samples of TSCC and their matched non-tumour were collected from cases undergoing surgery in our department of Jinan Stomatological Hospital. These specimens were immediately frozen in the liquid nitrogen. Written consent of this study was collected from each patient, and this protocol was confirmed with Institutional Review Board of Jinan Stomatological Hospital (No. 20170203).

2.2 | Cell cultured and transfection

Tca8113, SCC1, SCC-4 and SCC-15 TSCC cells were obtained from ATCC. These cells were kept in RPMI 1640 and penicillin, streptomycin and FBS. pcDNA3.1-GACAT1 and control plasmid, miR-149 mimic and scramble were collected from Shanghai GenePharma, and Lipofectamine 3000 (Invitrogen) was utilized for plasmid transfection.

2.3 | Quantitative RT-PCR

Total RNA of non-tumour and TSCC samples, cells were purchased with TRIzol kit (Invitrogen) following to instructions. Quantitative RT-PCR analysis was carried out to detect GACAT1, miR-149 and ki-67 expression using SYBR Green on the system of 7500 Real-Time PCR (Applied Biosystems). U6 was utilized as control for miR-149, and GAPDH was carried out as control for ki-67 and GACAT1. The primers for GACAT1 were 5′-ACCGGAGGAAAATCCCTAGC-3′ (Forward) and 5′-CCATAAAAGGGGCGGCTGT-3′ (reverse); primers for miR-149 were 5′-CATCCTTTCTGGCTC CGTGT-3′ (Forward) and 5′-GCGTGATTCGTGCTCGTATATC-3′ (reverse); primers for GAPDH were 5′-TGTTCGTCATGGGTGTGAAC-3′ (Forward) and 5′-ATGGCATGGACTGTGGTCAT-3′ (reverse). Ki-67, 5′-TCCTTTG GTGGGCACC TAAGACCTG-3′ (Forward) and 5′-TGATGGTT GAGGTCGT TCCTTGATG-3′ (reverse). E-cadherin, 5′-CGAGAGCT ACACGTTCAC GG-3′ (Forward) and 5′-CGAGA GCTACACGTT CACGG-3′ (reverse). Vimentin, 5′-GACGCC ATCAACACC GAGTT-3′ (Forward) and 5′-CTTTGTCGTT GGTTAGCTGGT-3′ (reverse).

2.4 | Cell proliferation and migration assay

Cell growth rates were determined with MTT analysis (Sigma). Cell was kept in the 96-well dish, and 10 μL was added to each well. After incubation for about 2 hours, the absorbance value at the 490 nm was read on the plate reader. For cell migration, wound scratch analysis was carried out. Pipette tip was utilized to create the cell wound. These treated cells were kept in the FBS-free medium. Image of the wound was taken at the 0 and 48 hours.

2.5 | Statistical analysis

Results were indicated as mean ± standard deviation. Student's *t* test was utilized to analysis the significance difference about these difference groups. The statistical analysis was carried out by SPSS $P < .05$ was defined as significance.

3 | RESULTS

3.1 | GACAT1 was overexpressed in TSCC samples and cell lines

As indicated in Figure 1A, we proved that expression of GACAT1 was increased in TSCC specimens compared to non-tumour specimens (Figure 1A). Of 25 TSCC specimens, GACAT1 expression was overexpressed in 18 patients (18/25, 72%) compared to non-tumour specimens (Figure 1B). We observed that GACAT1 expression was overexpressed in TSCC cell lines (Tca8113, SCC1, SCC-4 and SCC-15) compared to non-tumour specimen (Figure 1C).

3.2 | MiR-149 was down-regulated in TSCC samples and cell lines

We observed that miR-149 expression was down-regulated in TSCC cell lines (Tca8113, SCC1, SCC-4 and SCC-15) compared to non-tumour specimen (Figure 2A). As shown in Figure 2B, we proved that expression of miR-149 was decreased in TSCC specimens compared to non-tumour specimens. Of 25 TSCC specimens, miR-149 expression was decreased in 14 patients (14/25, 56%) compared to non-tumour specimens (Figure 2C). Moreover, we observed that GACAT1 expression was negatively correlated with miR-149 expression (Figure 2D).

3.3 | GACAT1 induced TSCC cell growth and migration

To further investigate the function role of GACAT1 in TSCC development, we induced GACAT1 expression in SCC1 cell through transfection with pcDNA-GACAT1 (Figure 3A). Ectopic

expression of GACAT1 enhanced SCC1 cell growth by using MTT assay (Figure 3B). Overexpression of GACAT1 increased ki-67 expression in SCC1 cell (Figure 3C). By using wound-healing analysis, we observed that GACAT1 overexpression promoted SCC1 cell migration (Figure 3D,E).

3.4 | GACAT1 promoted epithelial to mesenchymal transition in TSCC cell

Next, we observed that ectopic expression of GACAT1 induced the mesenchymal makers such as N-cadherin, Vimentin and Snail expression in the SCC1 cell (Figure 4A). Moreover, we indicated that elevated expression of GACAT1 decreased epithelial maker E-cadherin expression (Figure 4B). These data suggested that GACAT1 overexpression induced EMT transition in TSCC.

3.5 | GACAT1 suppressed miR-149 expression in TSCC cell

Ectopic expression of GACAT1 decreased miR-149 expression in SCC1 cell (Figure 5A). We observed that the expression of miR-149 was significantly up-regulated in the SCC1 cell via transfection with miR-149 mimic (Figure 5B). Elevated expression of miR-149 suppressed the GACAT1 expression in SCC1 cell (Figure 5C).

3.6 | GACAT1 induced TSCC cell growth and migration via regulating miR-149

We next induced the expression of miR-149 through transfection with miR-149 mimic in the GACAT1-overexpressing SCC1 cell. We observed that ectopic expression of miR-149 decreased cell proliferation in the GACAT1-overexpressing SCC1 cell (Figure 6A). We showed that elevated expression of miR-149 suppressed ki-67 expression in the GACAT1-overexpressing SCC1 cell (Figure 6B). Moreover, we observed that miR-149 overexpression decreased cell migration in GACAT1-overexpressing SCC1 cell (Figure 6C,D).

4 | DISCUSSION

In this study, we observed that GACAT1 was overexpressed in TSCC samples and cell lines. Of 25 TSCC specimens, GACAT1 was overexpressed in 18 patients (18/25, 72%) compared to

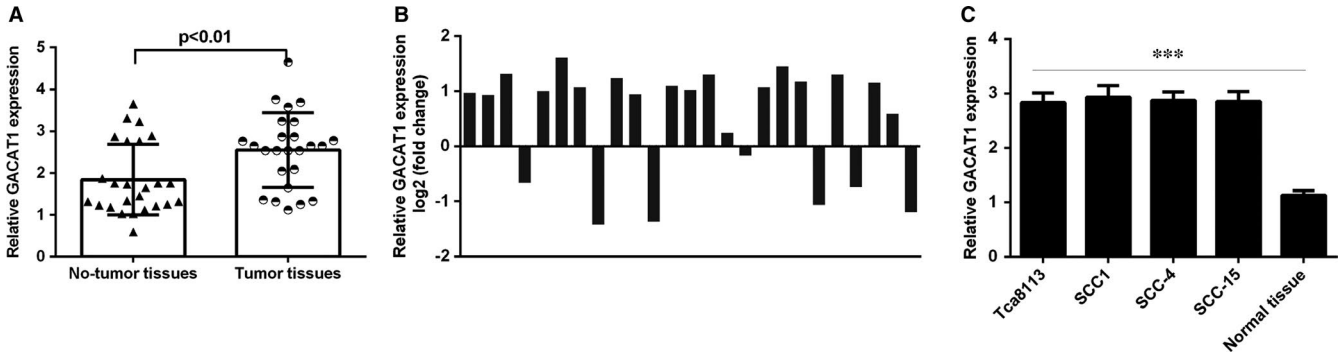

FIGURE 1 GACAT1 was overexpressed in TSCC samples and cell lines. A, The GACAT1 expression was detected by using qRT-PCR analysis. B, Of 25 TSCC specimens, GACAT1 expression was overexpressed in 18 patients (18/25, 72%) compared to non-tumour specimens. C, The GACAT1 expression in TSCC cell lines (Tca8113, SCC1, SCC-4 and SCC-15) and one non-tumour specimen was detected by qRT-PCR assay. $^{***}P < .001$

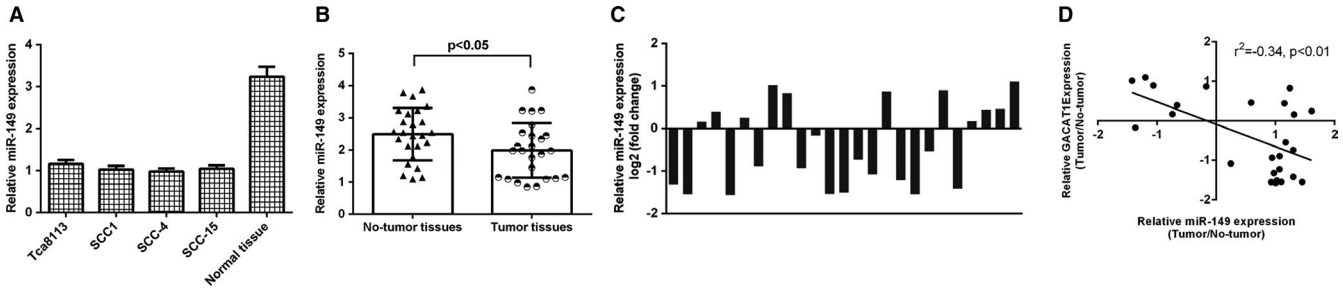

FIGURE 2 miR-149 was down-regulated in TSCC samples and cell lines. A, The miR-149 expression in TSCC cell lines (Tca8113, SCC1, SCC-4 and SCC-15) and one non-tumour specimen was detected by qRT-PCR assay. B, The expression of miR-149 was decreased in TSCC specimens compared to non-tumour specimens. C, Of 25 TSCC specimens, miR-149 expression was decreased in 14 patients (14/25, 56%) compared to non-tumour specimens. D, GACAT1 expression was negative correlated with miR-149 expression

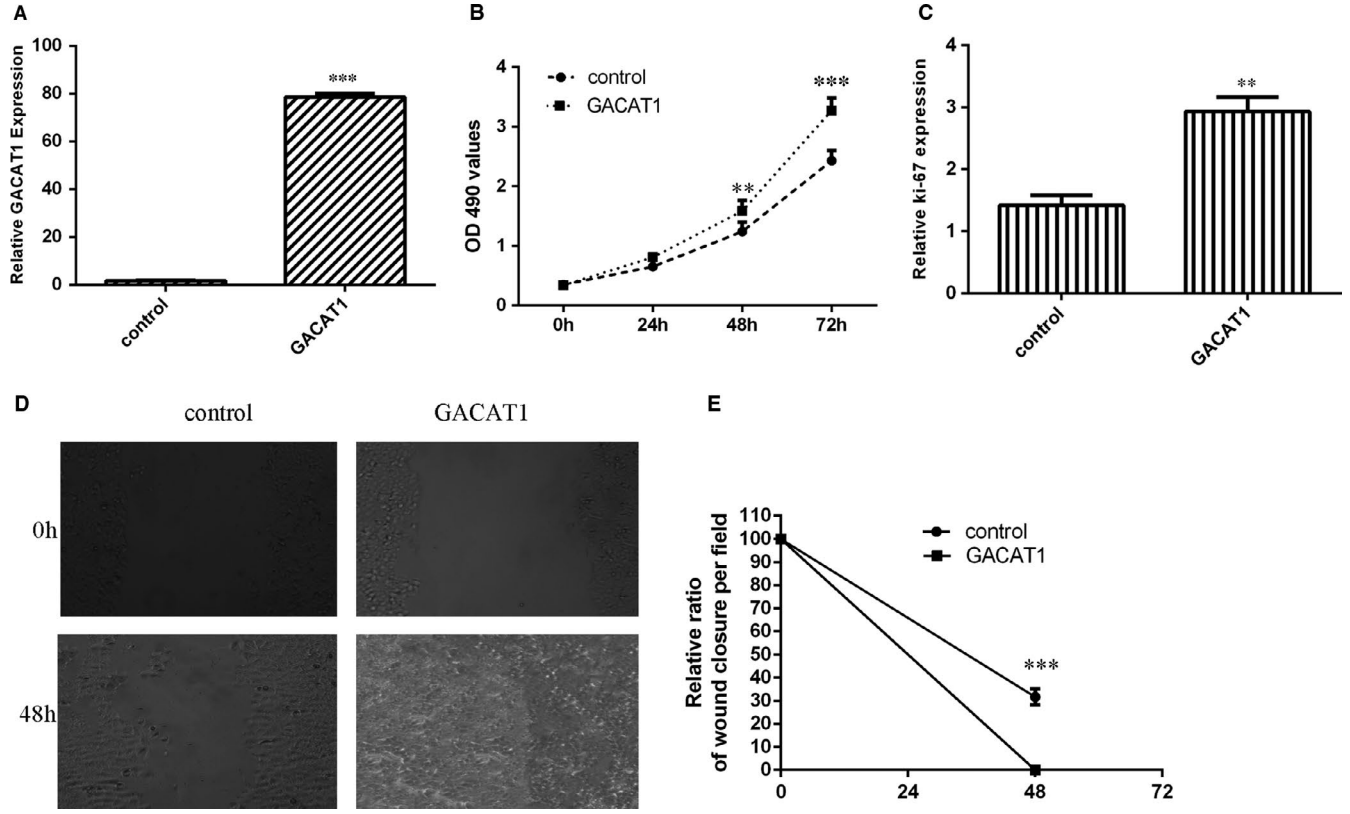

FIGURE 3 GACAT1 induced TSCC cell growth and migration. A, The expression of GACAT1 was determined by qRT-PCR assay. B, Ectopic expression of GACAT1 enhanced SCC1 cell growth by using MTT assay. C, Overexpression of GACAT1 increased the ki-67 expression in the SCC1 cell. D, GACAT1 overexpression promoted the SCC1 cell migration by using wound-healing analysis. E, The relative wound closure was shown. $^{**}P < .01$ and $^{***}P < .001$

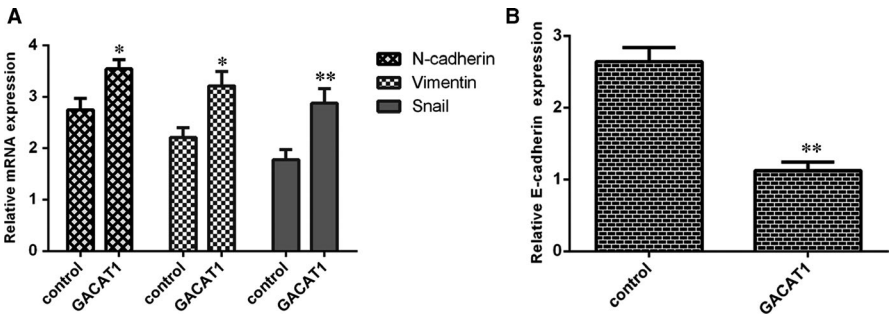

FIGURE 4 GACAT1 promoted epithelial to mesenchymal (EMT) transition in TSCC cell. A, Ectopic expression of GACAT1 induced the mesenchymal makers such as N-cadherin, Vimentin and Snail expression in the SCC1 cell. B, Elevated expression of GACAT1 decreased epithelial maker E-cadherin expression. $^{*}P < .05$ and $^{**}P < .01$

non-tumour specimens. Ectopic expression of GACAT1 induced TSCC cell growth and migration and promoted EMT in TSCC cell. In addition, ectopic expression of GACAT1 decreased miR-149 expression in SCC1 cell. We observed that miR-149 expression was down-regulated in TSCC cell lines. Moreover, we observed that GACAT1 expression was negatively correlated with miR-149 expression. GACAT1 overexpression induced TSCC cell growth and migration via regulating miR-149 expression. These data provided that GACAT1 played an oncogenic role in the progression of TSCC partly through modulating miR-149 expression.

Previous reports showed that lncRNAs acted critical roles in TSCC initiation, metastasis and growth. LncRNA H19 promoted TSCC invasion and migration through sponging miR-let-7.[31] Knockdown of lncRNA TUC338 inhibited TSCC cell growth and increased cell apoptosis.[32] LncRNA NKILA suppressed invasion and migration of TSCC cell through inhibiting epithelial-mesenchymal transition.[33] Recently, Zhong et al[34] showed that GACAT1 was decreased in NSCLC tissues, and knockdown of GACAT1 inhibited cell growth and promoted apoptosis via suppressing miR-422a. Wang et al[35] indicated that GACAT1 induced breast tumour progression via sponging miR-875-3p. However, its role and mechanism in TSCC development have not been studied. We firstly studied the expression level of GACAT1 in TSCC samples and cell lines. We proved that expression of GACAT1 was increased in TSCC specimens and cells. Furthermore, we indicated that ectopic expression of GACAT1 induced TSCC cell growth and migration and promoted EMT in TSCC

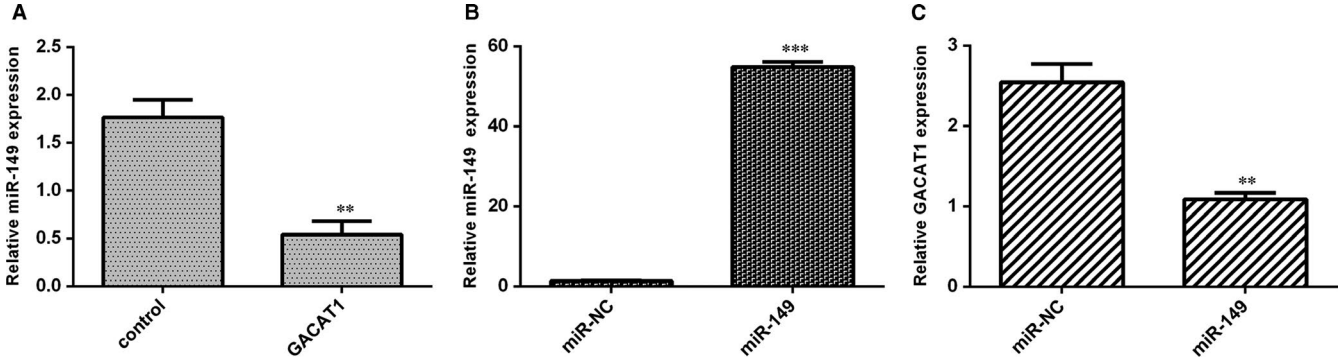

FIGURE 5 GACAT1 suppressed miR-149 expression in TSCC cell. A, Ectopic expression of GACAT1 decreased miR-149 expression in SCC1 cell. B, Expression of miR-149 was significantly up-regulated in the SCC1 cell via transfection with miR-149 mimic. C, Elevated expression of miR-149 suppressed the GACAT1 expression in SCC1 cell. $^{**}P < .01$ and $^{***}P < .001$

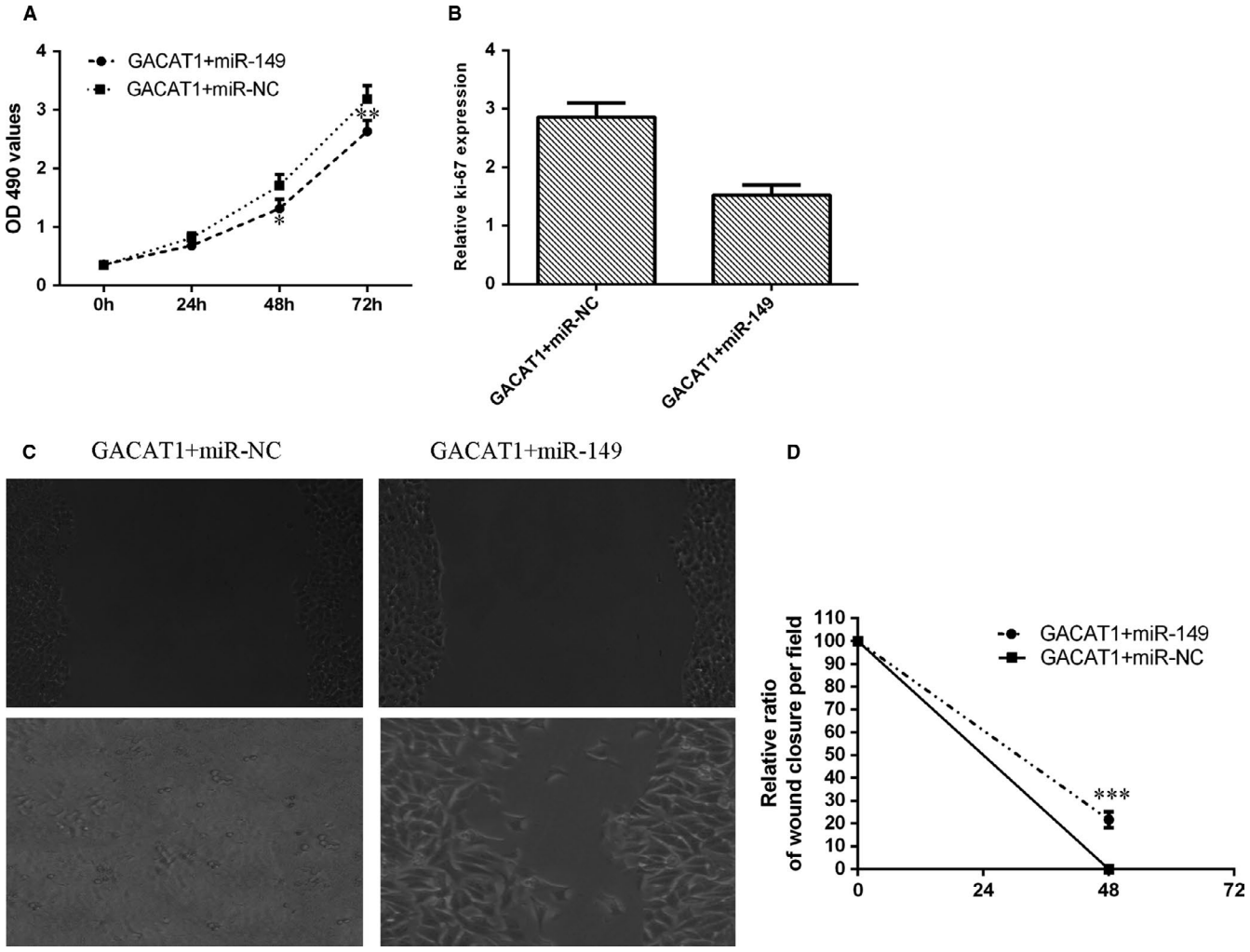

FIGURE 6 GACAT1 induced TSCC cell growth and migration via miR-149. A, The cell proliferation was determined by using MTT assay. B, The mRNA expression of ki-67 was measured by using qRT-PCR analysis. C, The SCC1 cell migration in the different groups was measured by using wound-healing analysis. D, The relative wound closure was shown. $^{*}P < .05$; $^{**}P < .01$ and $^{***}P < .001$

cell. However, more TSCC samples are needed in our further work. Thus, these data indicated that GACAT1 may act as one oncogene in tumorigenicity of TSCC cell and provided one potential therapeutic strategy for TSCC.

Increasing studies have suggested that lncRNAs function as ceRNA to modulate tumour progression.[36-38] For instance, Ren and colleagues demonstrated that lncRNA CRNDE increased TSCC cell invasion and growth via down-regulating miR-384

expression.[39] Zhang et al[40] showed that KCNQ1OT1 modulated cisplatin resistance and proliferation through regulating miR-211-5p in tongue cancer. Ma et al[41] reported that lncRNA GIHCG enhanced TSCC cell proliferation, cycle and migration via regulating miR-429. Zuo and colleagues found that lncRNA CASC15 induced TSCC progression via modulating miR-33a-5p expression.[42] In addition, previous report showed that GACAT1 overexpression induced gastric cancer cell proliferation, migration and invasion through modulating miR-149 expression.[30] In line with this, we found that ectopic expression of GACAT1 decreased miR-149 expression in SCC1 cell. Moreover, GACAT1 overexpression induced TSCC cell growth and migration via regulating miR-149 expression. Previous reports showed that miR-149 played critical roles in tumour development. MiR-149-5p suppressed medullary thyroid carcinoma cell invasion and proliferation via targeting GIT1.[43] Moreover, miR-149 inhibited growth and induced sensitivity of ovarian tumour cell to cisplatin through targeting XIAP.[44] MiR-149 sensitizes oesophageal tumour cell to the cisplatin via regulating DNA polymerase β expression.[45] Thus, our results suggested that GACAT1 promoted TSCC progression via modulating miR-149 and its target genes.

Together, we described that GACAT1 was overexpressed in TSCC samples and cell lines. GACAT1 overexpression induced TSCC cell growth and migration via regulating miR-149 expression. These data implied that GACAT1 played an oncogenic role in the progression of TSCC partly through modulating miR-149 expression.

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CONFLICT OF INTEREST

There is no conflict of interest.

AUTHOR CONTRIBUTIONS

Xueling Wang: Conceptualization (equal); Investigation (equal); Resources (equal); Software (equal); Writing-original draft (equal); Writing-review & editing (equal). **Zuode Gong:** Writing-review & editing (equal). **Long Ma:** Software (equal); Writing-review & editing (equal). **Qibao Wang:** Conceptualization (equal); Funding acquisition (equal); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

Research data are not shared.

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