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LncRNA MINCR activates Wnt/β-catenin signals to promote cell proliferation and migration in oral squamous cell carcinoma

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is a common type of malignant oral cancer with high recurrence. MYC-induced long non-coding RNA (MINCR) has been reported as a tumor suppressor in liver cancer and lung cancer. Whereas, it is unknown whether MINCR exerted function in OSCC progression. This study focused on its function and mechanism in OSCC. At first, the expression level of MINCR in OSCC tissues and cell lines as well as corresponding normal controls was evaluated by qRT-PCR assay. The relative high level of MINCR was observed in OSCC tissues and cell lines. The overall survival rate of OSCC patients with high or low level of MINCR was analyzed by using Kaplan-Meier method. In addition, functional assay revealed that MINCR knockdown significantly suppressed OSCC cell proliferation and invasion. Importantly, the effect of MINCR knockdown on Wnt/β-catenin signaling pathway was detected by luciferase reporter and western blot assays. It was found that MINCR knockdown obviously decreased the activity of Wnt/β-catenin pathway. Rescue assays were further used to validate the role of Wnt/β-catenin pathway in MINCR-mediated OSCC progression. The effects of MINCR knockdown on OSCC cell proliferation and migration were partly reversed by the activator of Wnt/β-catenin pathway (LiCl). Overall, our findings revealed that MINCR may be an oncogene in OSCC via modulation of Wnt/β-catenin pathway.

1. Introduction

Oral squamous cell carcinoma (OSCC) is a common oral cancer [24]. About 500, 000 people die of oral cancer annually [14]. Due to the malignant growth and regional metastasis, OSCC severely affects the health of patients [1]. Currently, smoking and alcohol abuse have been considered as the main etiological factors in OSCC. Although the oral examination is easy to get, more than 60% of OSCC cases still undiagnosed until advanced stage [26].

Recently, studies demonstrated that the etiology of OSCC were closely connected with proto-oncogene activation and over-expression [2]. Longer than 200 nucleotides, long non-coding RNAs (lncRNAs) are a type of non-protein coding RNA transcripts [15]. Numerous reports revealed that lncRNAs involved in various biological processes [19]. Dysregulation of lncRNAs has been regarded as a potential diagnostic target in many malignancies, such as prostate, gastric and lung cancers. For example, overexpression of HULC promotes tumor growth and is associated with the poor prognosis [30]. LncRNA MT1JP inhibited gastric cancer cell proliferation and migration via regulating MT1JP/miR-214-3p/RUNX3 axis [25]. Moreover, lncRNA NEAT1 serve as an oncogene to promote cell proliferation and invasion via miR365/RGS20 axis in oral squamous cell carcinoma [5]. However, the specific function of MINCR in OSCC remains unclear. In the present, we examined the expression pattern of MINCR in OSCC tissues and cell lines. The overall survival of OSCC patients with high or low level of MINCR. The effects of MINCR knockdown on cell proliferation and migration.

Wnt/β-catenin signaling pathway is a classical pathway which plays a key role in cell signal transduction [3]. Reports showed that β-catenin can connected with TCF/LEF transcription factor to activate downstream target gene, causing cell proliferation, migration and invasion [13]. Moreover, reports have shown that lncRNAs can promote cell growth and metastasis via activating Wnt/β-catenin signaling pathway [4,10,12,29]. The interaction between MINCR and Wnt/β-catenin pathway was analyzed in OSCC cells. Finally, rescue assays were conducted in TSCCA cell. Taken together, our research findings suggested that MINCR exerted oncogenic role in OSCC via Wnt/β-catenin signaling pathway.

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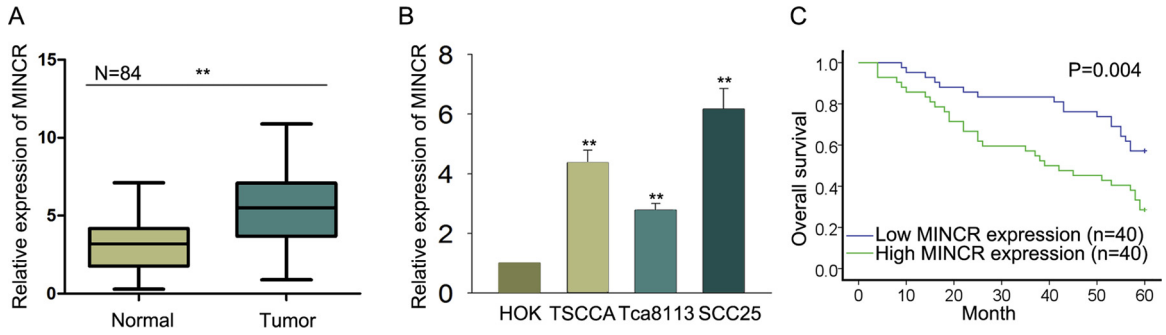

Fig. 1. The expression level of lncRNA MINCR in OSCC is associated with the prognosis. (A) The expression of MINCR in OSCC tissues and paired adjacent normal tissues. (B) Relative expression of MINCR in three different OSCC cell lines (TSCCA, Tca8113, SCC25) and one human oral keratinocytes (HOK). (C) Overall survival rate of OSCC patients with high or low level of MINCR (P = 0.004). $^{*}P < 0.05$, $^{**}P < 0.01$.

Table 1
Correlation between the expression of MINCR and clinical features of patients with oral squamous cell carcinoma. (n = 84).

Variable	MINCR Expression		P-value
	low	high	
Age			
< 60	20	22	0.827
≥60	22	20	
Gender			
Male	26	28	0.820
Female	16	14	
Lymph Node Metastasis			
Absent	22	11	0.025*
Present	20	31	
Tumor Size			
≤5.0	26	23	0.658
> 5.0	16	19	
TNM Stage			
I–II	23	8	0.001**
III–IV	19	34	
Distant metastasis			
Absent	25	10	0.002**
Present	17	32	
Differentiation			
well	9	12	0.615
Moderate, Poor	33	30	
Peritoneum Dissemination			
Absent	13	11	0.810
Present	29	31	

Low/high by the sample mean. Pearson χ^2 test. $^{*}P < 0.05$ was considered statistically significant.

2. Material and methods

2.1. Tissues sample

OSCC tissues and paired normal tissues were collected from patients who were diagnosed with OSCC in Nanjing First Hospital, Nanjing Medical University. Informed consent was obtained from each patient. And this study was approved by the ethical committee of Nanjing First Hospital.

2.2. Cell culture

Human OSCC cell lines (TSCCA, Tca8113, SCC25) and one human oral keratinocytes (HOK) were commercially obtained from the Chinese Academy of Sciences (Shanghai, China). Cell lines were cultured in DMEM/F12 medium (Invitrogen, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (Life Technologies, Carlsbad, CA, USA), penicillin (100 U/mL), and streptomycin (100 mg/mL) at 37 °C with 5% CO_2.

2.3. Cell transfection

Short-hairpin RNA (shRNA) specially targeted to MINCR (sh-MINCR) and control shRNA (sh-NC) were all synthesized and obtained from GenePharma (Shanghai, China) and transfected into SCC25 and TSCCA cells. Cell transfection was measured by using Lipofectamine 2000 (Invitrogen–Life Technologies, Carlsbad, CA, USA). After 48 h, cells were collected for subsequent experiments.

2.4. Quantitative real-time PCR

Total RNAs were extracted from OSCC tissues and cell lines by using Trizol reagent (Invitrogen, Carlsbad, CA, USA) following the manufacturer's instructions. The concentration and quality of RNA were measured by NanoDrop 2000 (Quawell, San Jose, CA, USA). High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA) was used for lncRNA MINCR transcription. Quantitative real-time PCR was determined by using TaqMan Universal Master Mix II. The results were analyzed by the $2^{-\Delta\Delta Ct}$ method. GAPDH was used as internal control. qRT-PCR was performed to detect the MINCR expression.

2.5. CCK-8

After transfection, cells (2×10^3) were cultured in five 96-well plates for 24, 36, 48, 72, 96 h. 10 μl CCK-8 solution was added into each well. Cells were incubated at 37 °C for 2 h. The absorbance was detected by a microplate reader at 450 nm (Bio-TekInstruments Inc., Winooski, VT, USA).

2.6. Colony formation assay

Cells were added into 6-well plates (1×10^3 cells/well) and cultured in DMEM with 10% FBS. After two weeks, colony cells were washed with PBS, fixed with methanol for 30 min and stained with 1% crystal violet. At last, colony numbers were counted manually.

2.7. Cell cycle analysis

Cells were harvested by standard trypsinization procedure. Then, cells were washed with PBS and fixed with 70% ethanol at 4 °C overnight. Furthermore, cells were incubated with RNase at room temperature and stained with Propidium Iodide Solution (Cytognos S. L, Salamanca, Spain) for 30 min. Cells were collected and measured by using a Cytomics FC500 flow cytometer (Beckman Coulter, Fullerton, CA, USA).

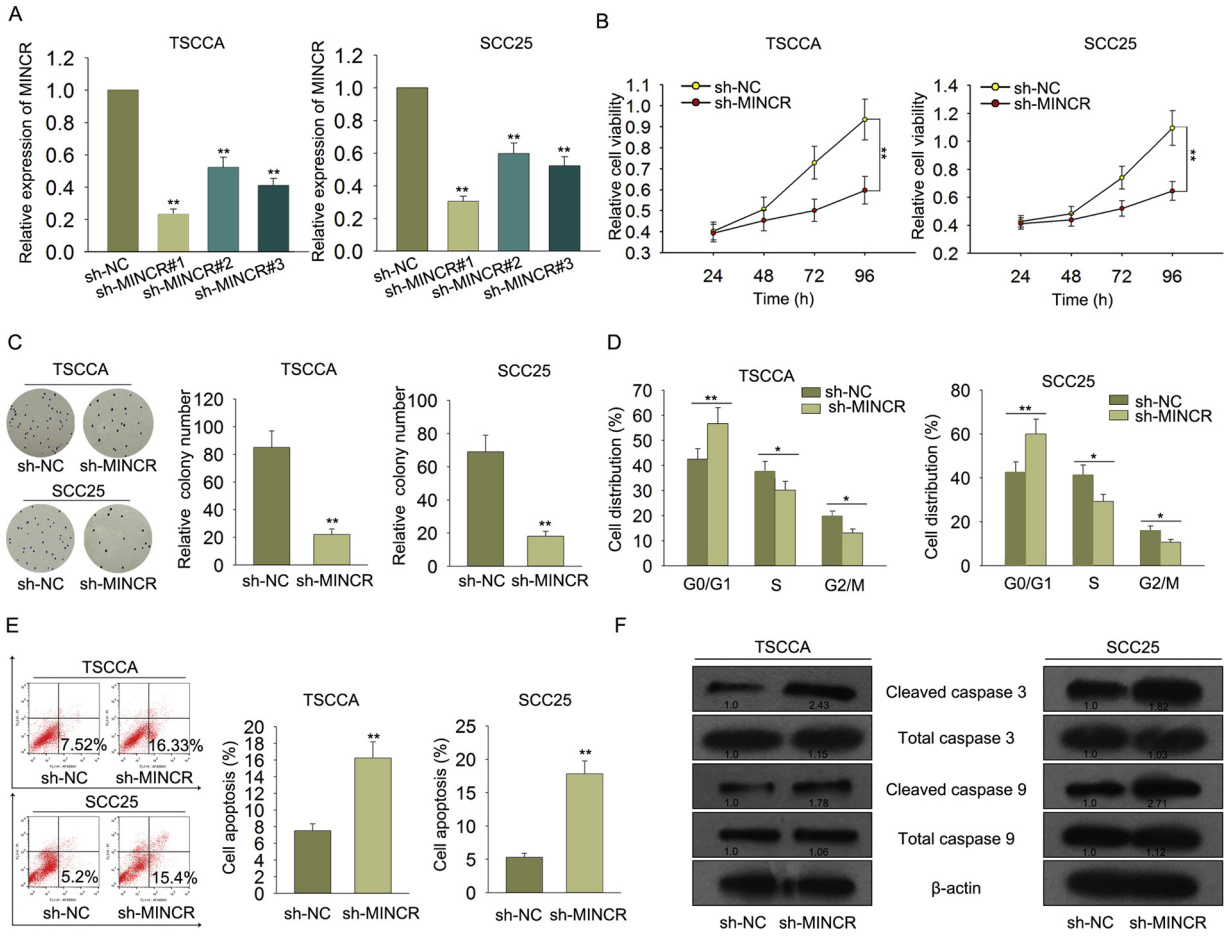

Fig. 2. MINCR knockdown inhibited OSCC cell proliferation and induced apoptosis. (A) The transfection efficiency for MINCR knockdown in TSCCA and SCC25 cells. (B–C) Cell viability and colony formation in TSCCA and SCC25 cells transfected with sh-MINCR or sh-NC. (D) Cell cycle analysis in TSCCA and SCC25 cells transfected with sh-MINCR or sh-NC. (E) Cell apoptosis in TSCCA and SCC25 cells transfected with sh-MINCR or sh-NC. (F) The protein levels of total caspase 3, total caspase 9, cleaved caspase 3 as well as cleaved caspase 9 in indicated cells. β-actin was utilized as the internal control. $^{*}P < 0.05$, $^{**}P < 0.01$.

2.8. Analysis of cell apoptosis

Cells were transfected with sh-MINCR or sh-NC in six-well plates. After 48 h transfection. TSCCA and SCC25 cells were stained with Annexin V-FITC and propidium iodide (PI; BD Biosciences, San Jose, CA, USA). Flow cytometry analysis (Cytomics FC500; Beckman Coulter, Miami, FL, USA) was used to measure early and late apoptosis cells.

2.9. Migration and invasion assay

48 h after transfection, cells were plated in the upper of the chamber in serum-free medium. For migration assay, the lower chamber was suffused with medium and stained with 10% FBS. For invasion assay, cells without FBS were plated in the upper chamber, which was pre-coated with Matrigel. Next, the lower chamber was filled with complete medium. The cells of the upper membrane were removed and washed by PBS and fixed in 4% paraformaldehyde solution. After that, cells were stained with 0.1% crystal violet for 30 min. The invasive or migratory cells were counted under a microscope.

2.10. Western blot analysis

Total protein was isolated from OSCC cell lines with RIPA lysis buffer (Beyotime, Shanghai, China). The protein concentration was measured by BCA Protein Assay Reagent Kit (Beyotime, China). The protein was subjected to 10% SDS-PAGE and then transferred into PVDF membranes (Millipore, MA, USA). The membrane was then blocked in 5% skim milk and incubated with the primary antibodies overnight at 4℃. Primary antibody included anti-β-catenin (1:5000), anti-c-myc (1:2000), anti-Cyclin D1 (1:2000), anti-β-actin (1:5000). The secondary antibody conjugated to horseradish peroxidase was adopted to incubate for 2 h at room temperature. Antibodies used in this experiment were obtained from Abcam (Cambridge, USA). Protein bands were visualized by using the ECL detecting system (Applygen, Beijing). β-actin was used as an internal reference.

2.11. Dual luciferase reporter assays

Cells were incubated in 96-well plates and transferred into TCF/β-catenin reporter plasmid (Promega, USA) and 10 ng Renilla in accordance with the protocol of Lipofectamine 2000 transfection system. After 48 h transfection, firefly and Renilla luciferase activities were detected from the cell lysates via the dual-luciferase reporter assay system (Promega, Madison, WI).

2.12. Statistical analysis

Statistical analysis was measured by using SPSS 17.0 (SPSS, Inc. Chicago, IL, USA). All results were presented as mean ± standard deviation (SD). Each experiment was performed in triplicate. The statistical difference was calculated using Student's *t*-test and one-way ANOVA. The survival rate of OSCC patients was measured by the Kaplan-Meier method and log rank test. P value < 0.05 indicates a statistical significance.

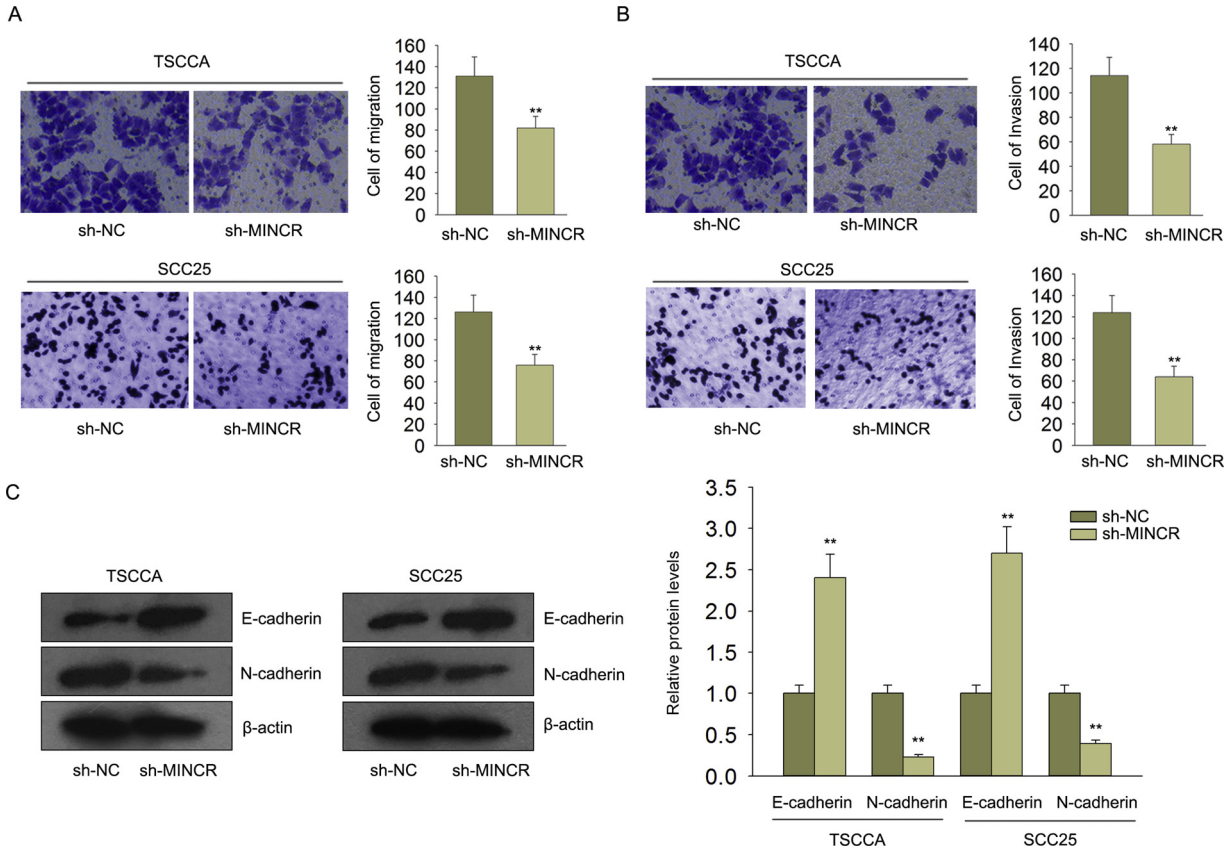

Fig. 3. Silencing of MINCR suppressed cell migration and invasion in OSCC. (A-B) The migratory and invasive cells were measured in TSCCA and SCC25 cells transfected with sh-MINCR or sh-NC. Scale bar = 100 μm. (C) The protein levels of E-cadherin and N-cadherin in TSCCA and SCC25 cells after transfection. β-actin was utilized as an internal control. $^{**}P < 0.01$.

3. Results

3.1. The expression level of lncRNA MINCR in OSCC is associated with the prognosis

At first, we analyzed the expression pattern of MINCR in OSCC tissues and cell lines using qRT-PCR examination. Results showed that MINCR was remarkably upregulated in both OSCC tissues (Fig. 1A, P = 0.005) and cell lines (Fig. 1B, P < 0.01). In addition, 80 pairs of OSCC tissues was stratified into two groups in accordance with the sample median. The association between MINCR expression and the clinicopathological features was analyzed. As illustrated in Table 1, the level of MINCR is correlated with lymph node metastasis, TNM stage and distant metastasis. Kaplan-Meier analysis revealed a negative correlation between the MINCR expression and the overall survival of OSCC patients (Fig. 1C, P = 0.004). Therefore, we hypothesized the potential regulatory role of MINCR in OSCC progression.

3.2. MINCR knockdown inhibited OSCC cell proliferation and induced apoptosis

For functional assays, MINCR was silenced in TSCCA and SCC25 cells by transfecting with MINCR-specific shRNAs (sh-MINCR#1, sh-MINCR#2, sh-MINCR#3). As shown in Fig. 2A, the expression level of MINCR was decreased efficiently (P < 0.01). Subsequently, loss-of function assays were conducted in MINCR-downregulated OSCC cells. As presented in Fig. 2B, cell viability was obviously impaired in TSCCA (P = 0.003) and SCC25 cells (P = 0.005). Colony formation assay also reflected the inhibitory effect of silenced MINCR on OSCC cell proliferation (Fig. 2C, P = 0.001, P = 0.006). Furthermore, we detected the role of MINCR in regulating cell cycle progress and cell apoptosis. According to flow cytometry analysis, MINCR knockdown induced cell cycle arrest in G0/G1 phase (Fig. 2D, P < 0.01, P < 0.05) and induced cell apoptosis (Fig. 2E, P = 0.005, P = 0.006). Additionally, western blot assay demonstrated that inhibition of MINCR remarkably increased the protein level of cleaved caspase 3 and cleaved caspase 9 in TSCCA and SCC25 cells (Fig. 2F, P < 0.01). These results indicated that MINCR knockdown inhibited OSCC cell growth.

3.3. Silencing of MINCR suppressed cell migration and invasion in OSCC

Transwell assays were applied to analyze the influences of MINCR knockdown on cell migration and invasion. As expected, both migration and invasion were efficiently suppressed by the knockdown of MINCR (Fig. 3A–B, P < 0.01). Furthermore, western blot assay elucidated that silencing of MINCR obviously increased the protein level of E-cadherin, but decreased the N-cadherin protein level (Fig. 3C, P < 0.01). These findings indicated that MINCR knockdown suppressed the capacity of OSCC cells to migrate and invade.

3.4. MINCR activated the Wnt/β-catenin signaling pathway in OSCC cells

Wnt/β-catenin signaling pathway plays crucial role in lncRNAs-mediated tumor progression [12,28]. Luciferase reporter assays showed that MINCR knockdown significantly decreased the luciferase activity of TOP flash, while the luciferase activity of FOP exhibited no significant difference, indicating that MINCR knockdown attenuated the activity of signaling pathway (Fig. 4A, P < 0.01). Then, we investigated the levels of Wnt/β-catenin pathway factors in MINCR-downregulated OSCC cells. The results showed that inhibition of MINCR expression dramatically reduced the mRNA and protein levels of β-catenin, cyclin D1 and c-myc in TSCCA and SCC25 cells (Fig. 4B–C,

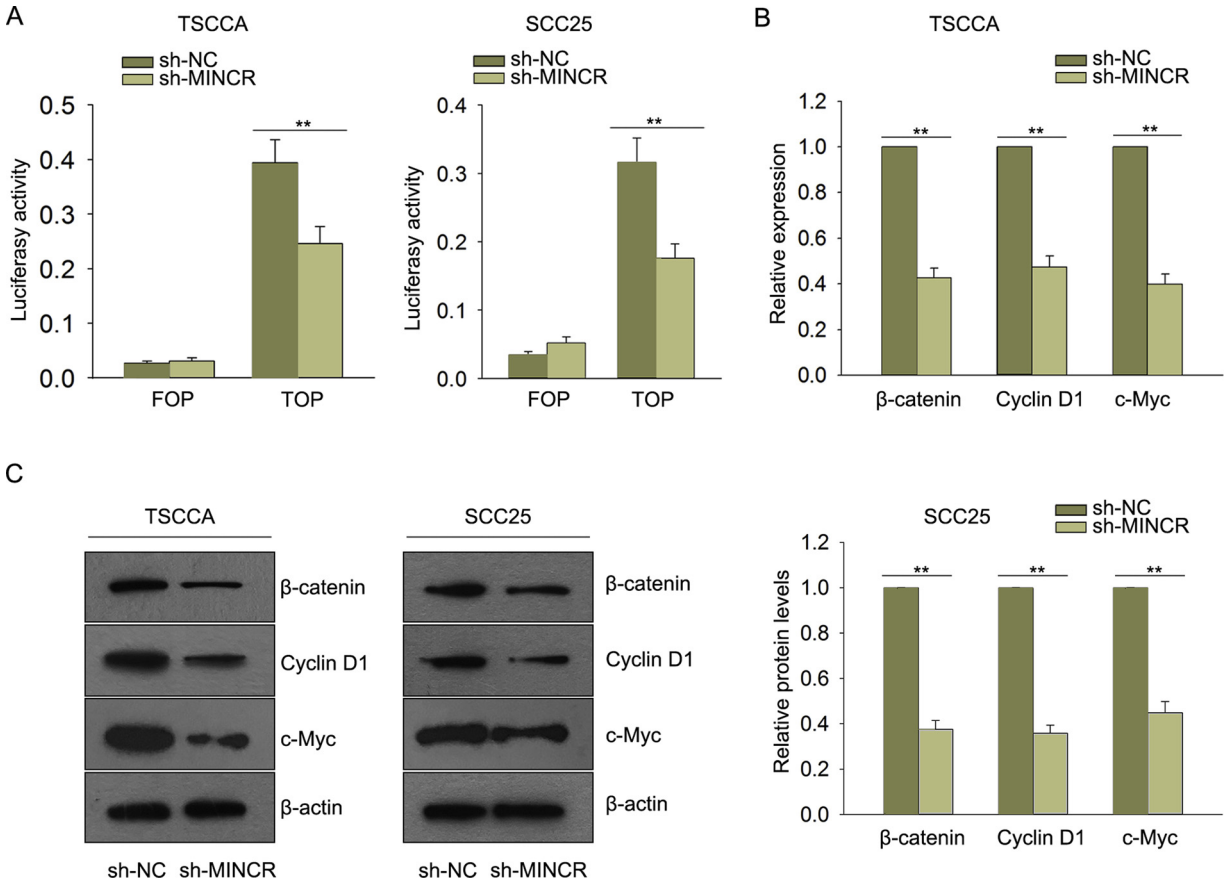

Fig. 4. MINCR activated the Wnt/β-catenin signaling pathway in OSCC cells. (A) The activity of TOP flash and FOP flash in indicated TSCCA and SCC25 cells. (B–C) The mRNA and protein levels of β-catenin, cyclin D1, and c-myc in MINCR-downregulated TSCCA and SCC25 cells. β-actin was utilized as internal control. $^{**}P < 0.01$.

$P < 0.01$). Taken together, high level of MINCR is positively correlated with the activity of Wnt/β-catenin signaling in OSCC.

3.5. MINCR activated the Wnt/β-catenin signaling to promote cell proliferation, migration and invasion

To determine whether Wnt/β-catenin signaling involved in MINCR-mediated OSCC progression, we treated MINCR-downregulated OSCC cells with 20 mol LiCl (Wnt/β-catenin signaling activator). Intriguingly, the cell proliferation that was impaired by the knockdown of MINCR was drastically recovered by the treatment with LiCl (Fig. 5A–B, $P < 0.05$, $P < 0.01$). Moreover, the invasive and migratory abilities of MINCR-downregulated TSCCA cell were recovered by treating with LiCl (Fig. 5C–D, $P < 0.05$, $P < 0.01$). Western blot assay demonstrated that the increased protein level of E-cadherin and decreased protein level of N-cadherin caused by sh-MINCR were attenuated by treating with LiCl (Fig. 5E, $P < 0.05$, $P < 0.01$). Therefore, we identified the involvement of Wnt/β-catenin signaling pathway in MINCR-mediated OSCC progression.

4. Discussion

OSCC accounts for 80%–90% of head and neck cancer [22]. OSCC is characterized by keratin generation, squamous differentiation, growth and metastasis [7]. The five-year survival of OSCC patients is only 50%, indicating the poor prognosis [21]. Recently, the abnormal expression or dysfunctional activity of lncRNAs have been investigated in numerous tumor [6]. LncRNAs can participate in the initiation and progression of malignant tumors [11,27]. The aberrant expression of lncRNAs is found to be correlated with cell proliferation and migration [18]. Moreover, aberrantly expressed lncRNAs is correlated with the overall survival of cancer patients and can be taken as the novel prognostic biomarkers in the treatment of tumors [8,16]. MINCR was identified as a differentially expressed lncRNA in gallbladder cancer [23]. To our knowledge, this study is the first time to elucidate the role of MINCR in OSCC. At first, we determined the upregulation of MINCR in OSCC tissues and cell lines. The prognostic potential of MINCR in OSCC patients was analyzed. Intriguingly, high level of MINCR indicated the low overall survival of OSCC patients, suggesting the potential prognostic influence of MINCR. In order to detect the biological function of MINCR in OSCC cells, we designed and carried out loss-of function assays. MINCR knockdown inhibited OSCC cell proliferation and induced cell cycle arrest in G0/G1 stage. Furthermore, silencing of MINCR in TSCCA and SCC25 cells suppressed cell migration and invasion. These findings revealed that MINCR acted as an oncogene in OSCC.

Wnt/β-catenin signaling pathway can regulate various cancer progression, which related to tumorigenesis [23]. Reports have showed that Wnt/β-catenin signaling accelerates tumor progression in nasopharyngeal carcinoma and esophageal squamous carcinoma [9]. Furthermore, FOXD2-AS1 overexpression contributed to cell proliferation, migration and invasion of non-small cell lung cancer through Wnt/β-catenin signaling pathway [20]. In this study, we examined the whether MINCR regulates the activity of Wnt/β-catenin signaling pathway in OSCC. When the Wnt/β-catenin signaling pathway was activated, β-catenin gathered in nucleus to promote cells loss of epithelial phenotype. This process was closely connected with tumor growth and metastasis [17]. To explore the molecular mechanism of MINCR in OSCC cells, we measured the activity of Wnt/β-catenin signaling pathway by luciferase reporter analysis. Results showed that MINCR knockdown

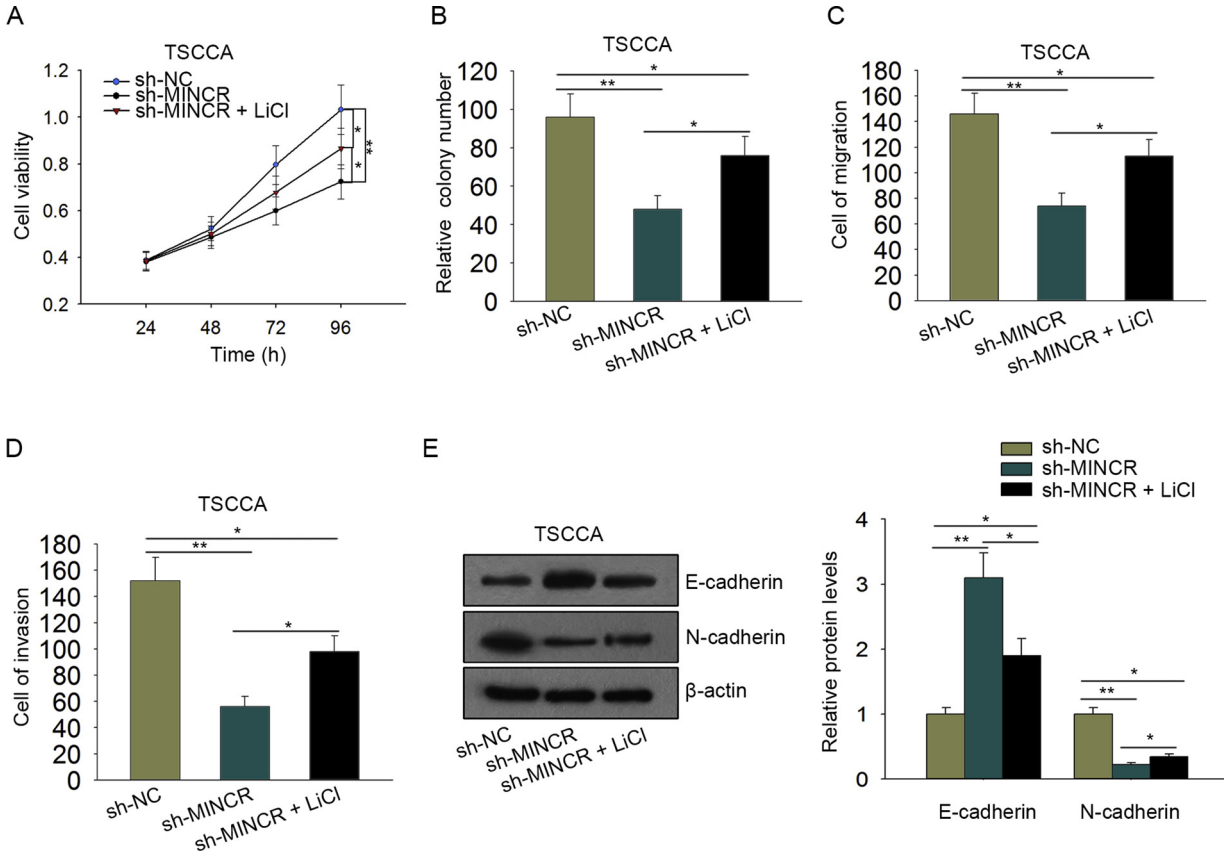

Fig. 5. MINCR activated the Wnt/β-catenin signaling to promote cell proliferation, migration and invasion. (A–B) Cell proliferation that was impaired by the knockdown of MINCR was drastically recovered by the treatment with LiCl. (C–D) The invasive and migratory abilities of MINCR-downregulated TSCCA cell were recovered by treating with LiCl. (E) The increased protein level of E-cadherin and decreased protein level of N-cadherin caused by sh-MINCR were attenuated by treating with LiCl. $^{*}P < 0.05$, $^{**}P < 0.01$.

significantly decreased the activity of TOP flash. Western blot assay also demonstrated that MINCR knockdown decreased the mRNA and protein levels of β-catenin, Cyclin D1 as well as c-myc. Finally, rescue assay demonstrated that activation of Wnt/β-catenin signaling pathway obviously reversed the suppressive effect of MINCR knockdown on OSCC cellular activities.

In conclusion, MINCR was upregulated in OSCC and promoted cell proliferation, migration as well as invasion. MINCR could activate the Wnt/β-catenin signaling pathway. MINCR activated the Wnt/β-catenin signaling pathway to promote OSCC cell proliferation and migration. Although we examined the effects of MINCR on the activity of TOP/FOP flash and the levels of pathway factors, the specific mechanism between MINCR and Wnt/β-catenin signaling pathway still need to be further detected. In conclusion, MINCR activates Wnt/β-catenin signaling pathway to promote OSCC cell proliferation and migration. MINCR may serve as a potential prognostic biomarker and therapeutic target for OSCC.

Conflicts of authors

None.

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