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LncRNA PRNCR1 aggravates the malignancy of oral squamous cell carcinoma by regulating miR-326/FSCN1 axis

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Abstract. – OBJECTIVE: The important regulatory mechanism of lncRNA PRNCR1 has been emphasized in malignant tumors. However, the role of lncRNA PRNCR1 remains unclear in oral squamous cell carcinoma (OSCC). The purpose of this study is to reveal the role of lncRNA PRNCR1 in OSCC.

PATIENTS AND METHODS: RT-qPCR was used to detect mRNA expression. The functional mechanism of lncRNA PRNCR1 in OSCC was investigated by CCK-8, transwell and Luciferase reporter assays.

RESULTS: LncRNA PRNCR1 was upregulated in OSCC and promoted cell proliferation, migration and invasion. LncRNA PRNCR1 directly binds to miR-326. The mutual inhibition between the expressions of lncRNA PRNCR1 and miR-326 was identified in OSCC. In addition, miR-326 restrained cell proliferation, migration and invasion in OSCC. Further, miR-326 directly targets FSCN1. FSCN1 expression was positively regulated by lncRNA PRNCR1 in OSCC. And FSCN1 promoted the progression of OSCC and aggravated the carcinogenic effect of lncRNA PRNCR1 in OSCC.

CONCLUSIONS: LncRNA PRNCR1 promotes the progression of OSCC by functioning as a miR-326 'sponge' to upregulate FSCN1 expression.

Key Words:
PRNCR1, Oral squamous cell carcinoma, MiR-326, FSCN1.

Introduction

In recent years, oral cancer has been threatening our health and is one of the most serious oral diseases. Oral cancer is more common in men, and the most common is oral squamous cell carcinoma (OSCC)[1]. The etiology of oral cancer is unclear and may be related to long-term smoking and alcohol abuse, poor oral hygiene, malnutrition, leukoplakia and erythema[2]. Oral cancer should be easier to detect than cancers elsewhere, but this is not the case. Taking the most common tongue cancer among oral cancer as an example, stage I patients account for only 10.9% to 25.4%[3]. In addition, the 5-year survival rate of OSCC patients with early oral cancer can reach more than 60%[4]. Therefore, early detection and treatment are very important for OSCC patients.

Long non-coding RNAs (lncRNAs) have been proven to be important regulators of various diseases, including cancers, and their key roles have also been determined in OSCC. In particular, lncRNA KCNQ1OT1 promoted cell migration and inhibited apoptosis by regulating the miR-185-5p/Rab14 axis in OSCC[5]. LINC01234 facilitated the growth and invasiveness of OSCC by regulating the miR-637/NUPR1 axis[6]. LncRNA PRNCR1 has been widely reported to participate in human diseases. Notably, lncRNA PRNCR1 was upregulated and played an oncogenic role in breast can-

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cer[7]. Upregulation of lncRNA PRNCR1 in colorectal cancer promoted cell proliferation and cell cycle progression[8]. In addition, lncRNA PRNCR1 has been reported to promote the development of eclampsia by regulating the MAPK signaling pathway[9]. However, the regulatory mechanism of lncRNA PRNCR1 in OSCC is still unclear and needs to be investigated.

LncRNAs participates in tumorigenesis by acting as a 'sponge' of miRNA. Here, miR-326 was found to have a binding site with lncRNA PRNCR1. Abnormal expression of miR-326 has been detected in breast cancer[10] and glioma[11]. In addition, miR-326 has been proposed to act as a tumor suppressor in human prostate cancer by targeting Mucin1[12]. Besides, lncRNA PCAT1 is a new serum-based biomarker that can enhance cell growth by sponging miR-326 in esophageal squamous cell carcinoma[13]. However, the relationship between lncRNA PRNCR1 and miR-326 has not been confirmed in previous studies.

It has been reported that lncRNA PRNCR1 can interact with HEY2 to abolish miR-448-mediated growth inhibition in non-small cell lung cancer[14]. In this study, we investigated how lncRNA PRNCR1 regulates fascin actin-bundling protein 1 (FSCN1) in OSCC. Upregulation and carcinogenesis of FSCN1 have been found in gastric cancer and lung cancer[15,16]. LncRNA PCAT-1 has been reported to promote the tumorigenesis of prostate cancer by regulating FSCN1 through miR-145-5p[17]. In addition, down-regulation of miR-326 has been found to be associated with poor prognosis in gastric cancer patients and promoted the growth and metastasis of gastric cancer by targeting FSCN1[18]. Therefore, the regulatory mechanism of lncRNA PRNCR1/miR-326/FSCN1 was explored in OSCC.

Patients and Methods

Clinical Tissues

Thirty-five patients diagnosed with OSCC (mean age: 53 years, ranging from 28 to 77 years; 21 males and 14 females) without any pre-operative radiotherapy or chemotherapy were recruited. All histological diagnoses analyses were conducted in Yantaishan Hospital. All specimens were confirmed by pathological examinations. Patients' inclusion criteria: (1) patients who were diagnosed as OSCC through pathological biopsies; (2) patients who had a complete medical record; (3) patients who were willing to join the study and signed informed consent. Patients' exclusion criteria: (1) patients failed to cooperate with researchers; (2) patients who were diagnosed with multiple diseases; (3) patients who were treated before admission. There were 14 cases of T1, 11 cases of T2, 12 cases of T3, and 22 cases of T4. According to clinical Tumor Node Metastasis (TNM) staging, there were 5 cases in stage I, 18 cases in stage II, and 12 cases in stage III. In addition, according to the squamous cell carcinoma staging method, 13 cases were classified as highly differentiated squamous cell carcinoma, 7 cases as moderately differentiated squamous cell carcinoma, and 15 cases as poorly differentiated squamous cell carcinoma. Tumor samples were obtained mostly from the cheek areas of the mouth, and adjacent normal tissues were collected from the same patient. All participants provided written informed consents. These tissues were frozen in liquid nitrogen and stored at −80 °C. This study was approved by the Institutional Ethics Committee of Yantaishan Hospital and performed following the World Medical Association Declaration of Helsinki ("World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects", 2013).

Cells Culture

The human normal oral epithelial cell line NHOK and the OSCC cell lines SCC-4 and Cal-27 were obtained from the American Type Culture Collection (ATCC; Manassas, VA, USA). These cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% FBS (5% CO_2, 37°C).

Cell Transfection

PRNCR1 vector, PRNCR1 and FSCN1 siRNA, miR-326 mimics were purchased from GenePharma (Shanghai, China). Cal-27 cells grown at 70-80% confluence were transfected with the vectors or oligonucleotides by using Lipofectamine 2000 (Thermo Fisher Scientific, Waltham, MA, USA).

RNA Isolation, Reverse Transcription and RT-qPCR

Total RNA was extracted using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). The PrimeScript RT reagent kit (TaKaRa, Dalian, China) was used for first strand DNA synthesis. PrimeScript RT reagent kit (TaKaRa, Dalian, China) and primers were used for RT-qPCR assay. GAPDH or U6 was used as an internal control. The

expressions of lncRNA PRNCR1, miR-326 and FSCN1 were quantified with the $2^{-\Delta\Delta cq}$ method. The primers used in our work were as follows: PRNCR1 forward, 5'-CCA GAT TCC AAG GGC TGA TA-3', and reverse, 5'-GAT GTT TGG AGG CAT CTG GT-3'; miR-326, forward, 5'-GGC GCC CAG AUA AUG CG-3', reverse, 5'-CGT GCA GGG TCC GAG GTC-3'; U6, forward primer: 5'-CTC GCT TCG GCA GCA CA-3', reverse primer: 5'-AAC GCT TCA CGA ATT TGC GT-3'; FSCN1 forward, 5'-CAC AGG CAA ATA CTG GAC GGT-3', reverse, 5'-CCA CCT TGT TAT AGT CGC AGA AC-3'; GAPDH forward, 5'-ACA TCG CTC AGA CAC CAT G-3', reverse, 5'-TGT AGT TGA GGT CAA TGA AGG G-3'.

Dual-Luciferase Reporter Assay

The pmiR-GLO vector (Promega, Beijing, China) with the 3'-UTR of wild-type or mutant PRNCR1 or FSCN1 was transfected into Cal-27 cells with miR-326 mimics. After 48 h, the Luciferase activity was measured by the Dual-Luciferase reporter gene assay system (Promega, Madison, WI, USA).

Cell Counting Kit-8 (CCK-8) Assay

The transfected Cal-27 cells (4×10^3 cells/well) were seeded into 96-well plates and incubated in DMEM medium for 24, 48, 72 or 96 h, respectively. Next, the cells were incubated with 10 μL CCK-8 reagents for 4 h. After shaking for 10 min, a spectrophotometer (Bio-Rad, Hercules, CA, USA) was used to measure the absorbance at 490 nm to reflect cell proliferation.

Transwell Assay

The transfected Cal-27 cells (4×10^3 cells/well) were placed in the upper chamber with 8 μm pore size (Corning Inc., Corning, NY, USA). The upper chamber was pre-coated with Matrigel (BD Biosciences, San Jose, CA, USA) for cell invasion assay. Lower chamber was added with DMEM medium containing 10% FBS. After 24 h of incubation, the moving cells were stained with 0.1% crystal violet. Observation and photographing were performed by a light microscope.

Statistical Analysis

The data were analyzed by using SPSS 19.0 (IBM, Armonk, NY, USA) or GraphPad Prism 6. Data are expressed as mean ± SD. The differences were analyzed by using Student's *t*-test or one-way ANOVA. $p< 0.05$ was considered significant.

Results

LncRNA PRNCR1 Promotes Cell Proliferation and Motility in OSCC

Abnormal expression of lncRNA PRNCR1 was observed in OSCC tissues and cells. It was found that the expression of lncRNA PRNCR1 in OSCC tissues was higher than that in normal tissues (Figure 1A). In addition, upregulation of lncRNA PRNCR1 was also detected in SCC-4 and Cal-27 OSCC cell lines compared with NHOK cells (Figure 1B). Due to the significant difference in the expression of lncRNA PRNCR1 in Cal-27 cells, Cal-27 cells were used for further experiments. In order to explore the role of lncRNA PRNCR1 in OSCC, PRNCR1 siRNA was transfected into Cal-27 cells. We found that the expression of PRNCR1 expression was significantly reduced by its siRNA (Figure 1C). Additionally, knockdown of PRNCR1 inhibited cell proliferation (Figure 1D). Similarly, the downregulation of PRNCR1 also inhibited cell migration and invasion in Cal-27 cells (Figure 1E, 1F). Based on the above results, lncRNA PRNCR1 is considered to promote the proliferation, migration and invasion of OSCC cells.

PRNCR1 can act as a ceRNA in OSCC Cells by Binding with MiR-326

The starBase version 2.0 (http://starbase.sysu.edu.cn/) predicts that miR-326 is a potential target of lncRNA PRNCR1 (Figure 2A). To verify this prediction, a Dual-Luciferase reporter assay was designed in Cal-27 cells. The Luciferase activity of wt-PRNCR1 was significantly reduced by miR-326 mimics. But the miR-326 mimics had almost no effect on mut-PRNCR1 Luciferase activity in Cal-27 cells (Figure 2B). At the same time, the expression of miR-326 was inhibited by PRNCR1 vector and enhanced by PRNCR1 siRNA in Cal-27 cells (Figure 2C). In addition, miR-326 mimics inhibited PRNCR1 expression, while miR-326 inhibitor promoted PRNCR1 expression in Cal-27 cells (Figure 2D). The results show that lncRNA PRNCR1 can directly bind to miR-326. And the expressions of lncRNA PRNCR1 and miR-326 are reciprocally inhibited in OSCC cells.

MiR-326 Restrains the Aggressive Behaviors of OSCC by Interacting with LncRNA PRNCR1

We found that miR-326 expression in OSCC tissues was decreased compared with normal tissues (Figure 3A). The expression of miR-326

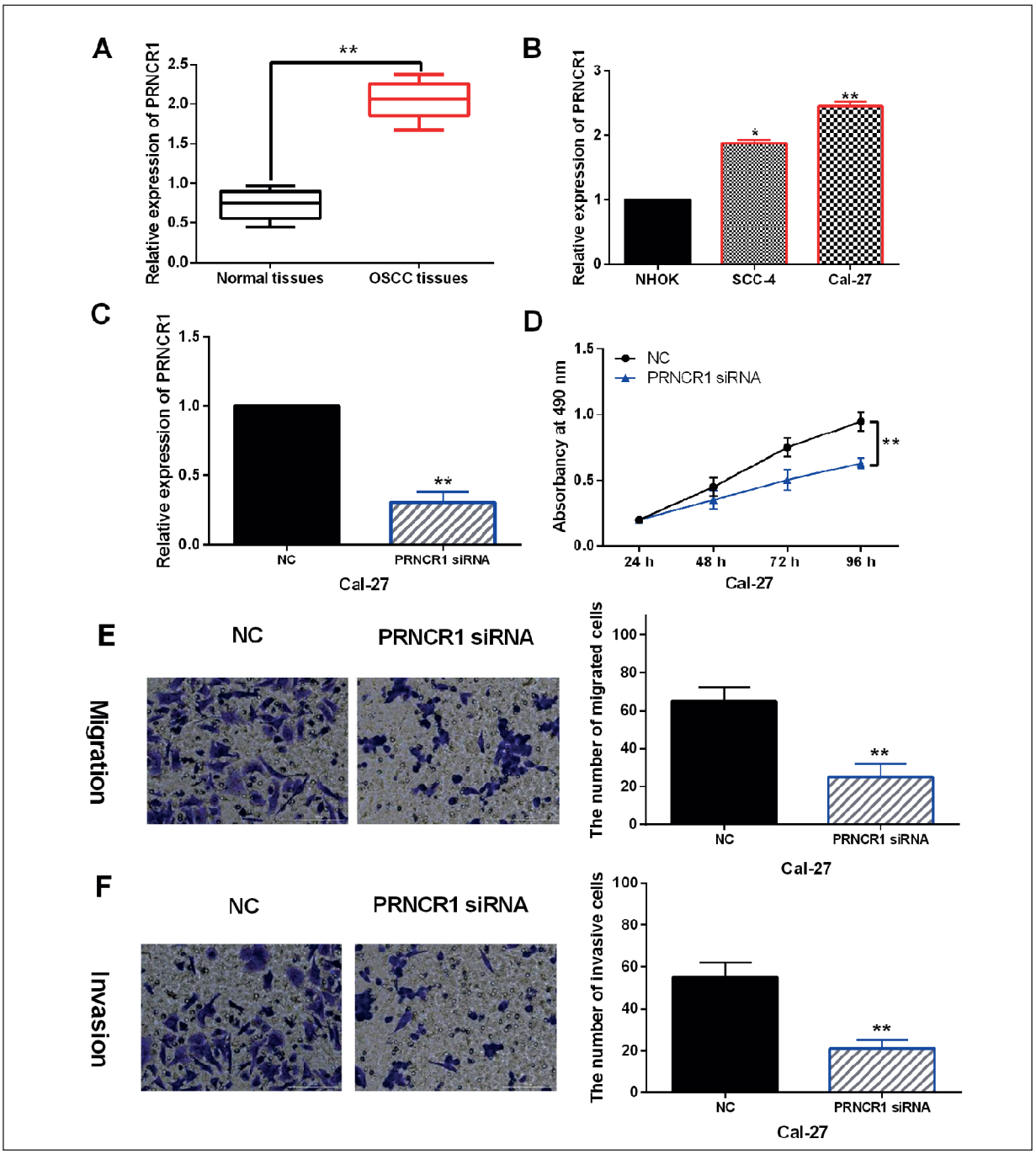

Figure 1. LncRNA PRNCR1 promotes cell proliferation and motility in OSCC. **A**, LncRNA PRNCR1 expression in OSCC tissues and normal tissues (**B**) LncRNA PRNCR1 expression in SCC-4, Cal-27 and NHOK cells (**C**) LncRNA PRNCR1 expression in Cal-27 cells with its siRNA (**D**, **E**, **F**) Cell proliferation, migration and invasion in Cal-27 cells with PRNCR1 siRNA (200×) *p<0.05, **p<0.01

was negatively correlated with lncRNA PRNCR1 expression in OSCC tissues (Figure 3B). At the same time, downregulation of miR-326 was found in SCC-4 and Cal-27 OSCC cell lines compared with NHOK cells (Figure 3C). To explore the function of miR-326 and its interaction with lncRNA PRNCR1, miR-326 mimics and lncRNA PRNCR1 vector were transfected into Cal-27 cells. RT-qPCR showed that miR-326 mimics increased its expression in Cal-27 cells, but the

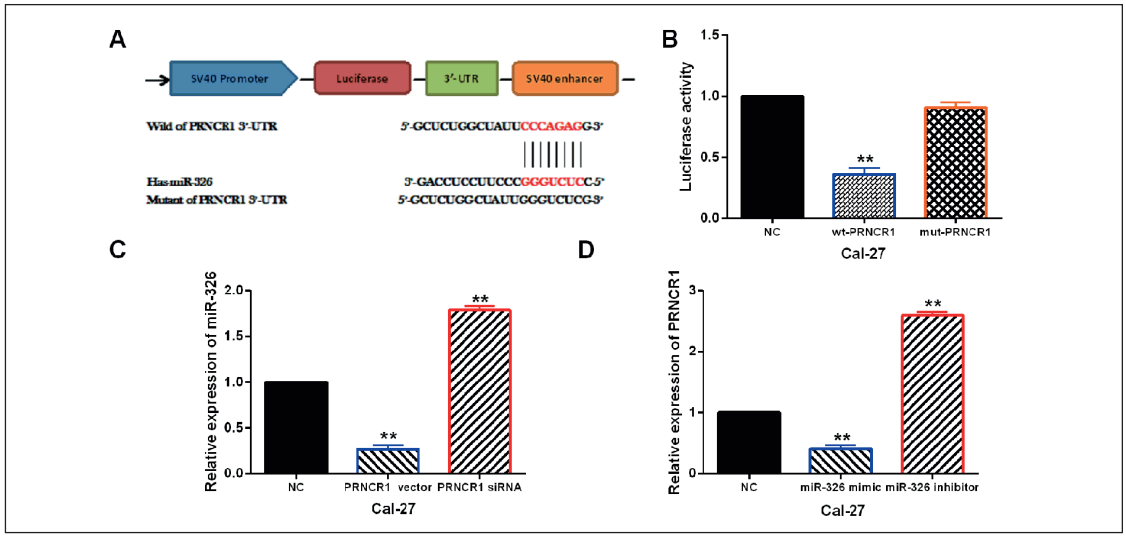

Figure 2. PRNCR1 can act as a ceRNA in OSCC cells by binding with miR-326. **A**, The binding site between lncRNA PRNCR1 and miR-326 **B**, Luciferase reporter assay (**C**) MiR-326 expression regulated by lncRNA PRNCR1 siRNA or vector in Cal-27 cells (**D**) LncRNA PRNCR1 expression in Cal-27 cells containing miR-326 mimics or inhibitor $^{**}p<0.01$.

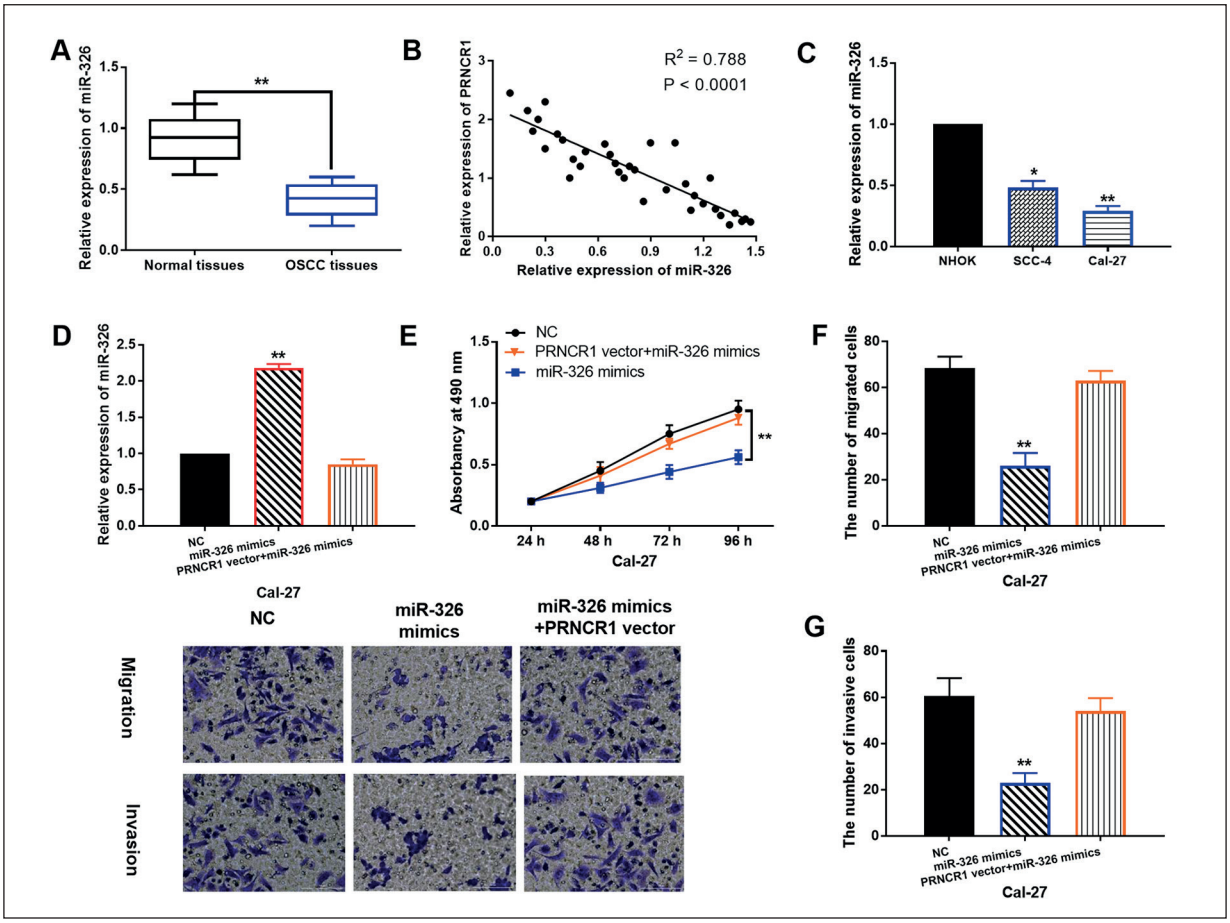

Figure 3. MiR-326 restrains the aggressive behaviors of OSCC by interacting with lncRNA PRNCR1. **A**, MiR-326 expression in OSCC tissues and normal tissues (**B**) MiR-326 was negatively correlated with lncRNA PRNCR1 in OSCC tissues. **C**, MiR-326 expression in SCC-4, Cal-27 and NHOK cells (**D**) MiR-326 expression in Cal-27 cells with miR-326 mimics and PRNCR1 vector. (**E**, **F**, **G**) Cell proliferation, migration and invasion in Cal-27 cells with miR-326 mimics and PRNCR1 vector (200×) $^{**}p<0.01$.

lncRNA PRNCR1 vector reduced this increase in miR-326 expression (Figure 3D). Additionally, CCK-8 showed that miR-326 overexpression inhibited the proliferation of Cal-27 cells. And upregulation of PRNCR1 attenuated the inhibitory effect of miR-326 on cell proliferation (Figure 3E). Transwell assay showed that miR-326 overexpression inhibited cell migration and invasion in Cal-27 cells. The reverse effect of PRNCR1 vector on cell migration and invasion was also found in Cal-27 cells with miR-326 mimics (Figure 3F, 3G). Taken together, miR-326 inhibits cell proliferation, migration and invasion in OSCC. And upregulation of PRNCR1 can weaken the anti-tumor effect of miR-326 in OSCC.

FSCN1 is a Direct Target of MiR-326

The TargetScan database predicts that FSCN1 has a binding site for miR-326 (http://www.targetscan.org, Figure 4A). We found that miR-326 mimics reduced the Luciferase activity of wt-FSCN1, but had little effect on the Luciferase activity of mut-FSCN1 (Figure 4B). At the same time, miR-326 mimics inhibited FSCN1 expression, while miR-326 inhibitor promoted FSCN1 expression in Cal-27 cells (Figure 4C). Then, upregulation of FSCN1 was found in OSCC tissues compared with normal tissues (Figure 4D). A negative correlation between miR-326 and FSCN1 expression was found in OSCC tissues (Figure 4E). We also found that FSCN1 expression was positively correlated with lncRNA PRNCR1 expression in OSCC tissues (Figure 4F). Therefore, miR-326 directly targets FSCN1. And FSCN1 expression can be positively regulated by lncRNA PRNCR1 in OSCC.

LncRNA PRNCR1 Serves as an Oncogene in OSCC by Regulating FSCN1

To confirm whether FSCN1 participates in OSCC tumorigenesis or interacts with lncRNA PRNCR1, FSCN1 siRNA and lncRNA PRNCR1

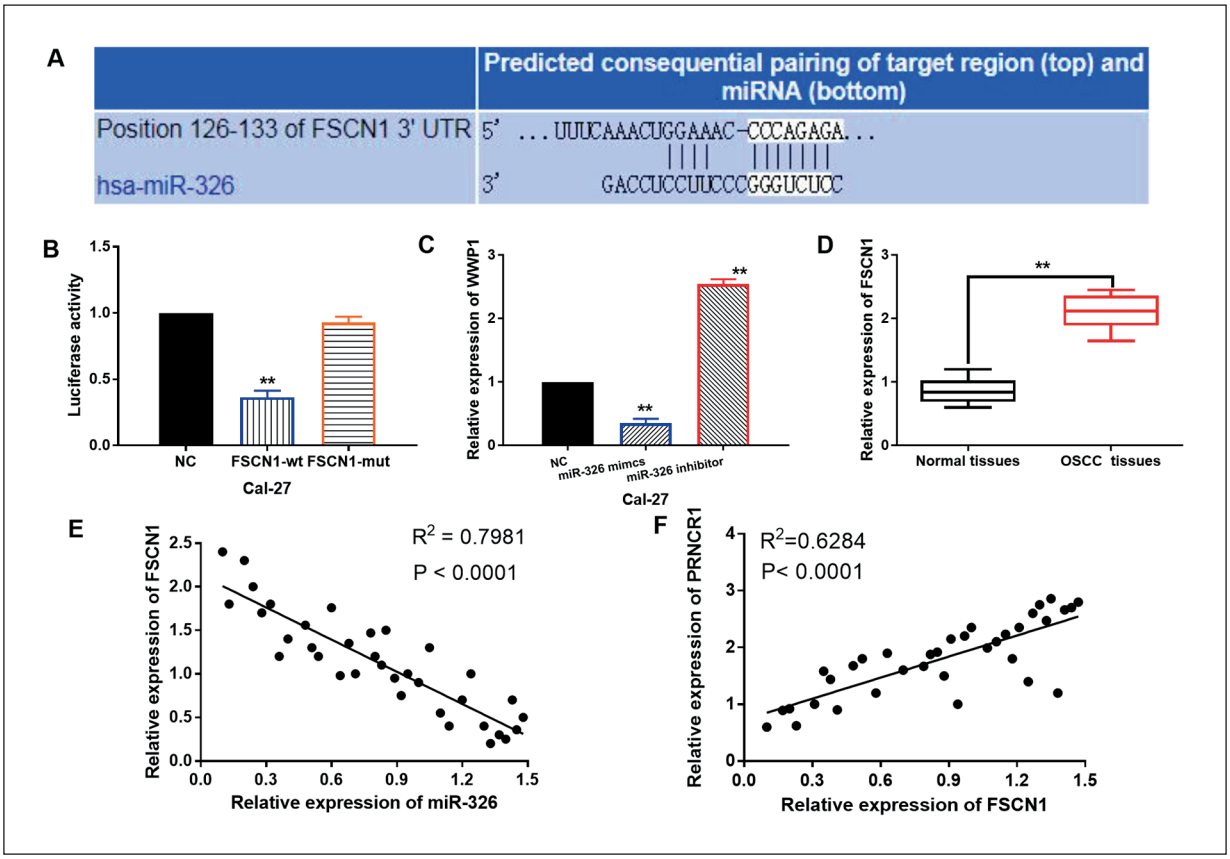

Figure 4. FSCN1 is a direct target of miR-326. **A**, The binding site between FSCN1 and miR-326 **B**, Luciferase reporter assay (**C**) FSCN1 expression regulated by miR-326 mimics or inhibitor in Cal-27 cells (**D**) FSCN1 expression in OSCC tissues and normal tissues (**E**) MiR-326 was negatively correlated with FSCN1 expression in OSCC tissues. **F**, LncRNA PRNCR1 expression was positively correlated with FSCN1 in OSCC tissues $^{**}p<0.01$.

vector were transfected into Cal-27 cells. We found that the lncRNA PRNCR1 vector increased FSCN1 expression. FSCN1 siRNA inhibited the increase of FSCN1 expression in Cal-27 cells (Figure 5A). Functionally, upregulation of PRNCR1 promoted cell proliferation, while knockdown of FSCN1 restored the promotion of cell proliferation in Cal-27 cells (Figure 5B). Additionally, up-regulation of PRNCR1 also promoted cell migration and invasion. FSCN1 siRNA eliminated the promoting effect of PRNCR1 on cell migration and invasion in Cal-27 cells (Figure 5C, 5D). These results indicate that FSCN1 can promote the progression of OSCC and aggravate the carcinogenic effect of lncRNA PRNCR1 in OSCC.

Discussion

Cell viability and motility are important biological activities in the pathogenesis of OSCC. Many lncRNAs have been reported to regulate cell viability and motility in OSCC, such as FEZF1-AS1 and OIP5-AS1[19,20]. However, the role of lncRNA PRNCR1 in OSCC is unclear.

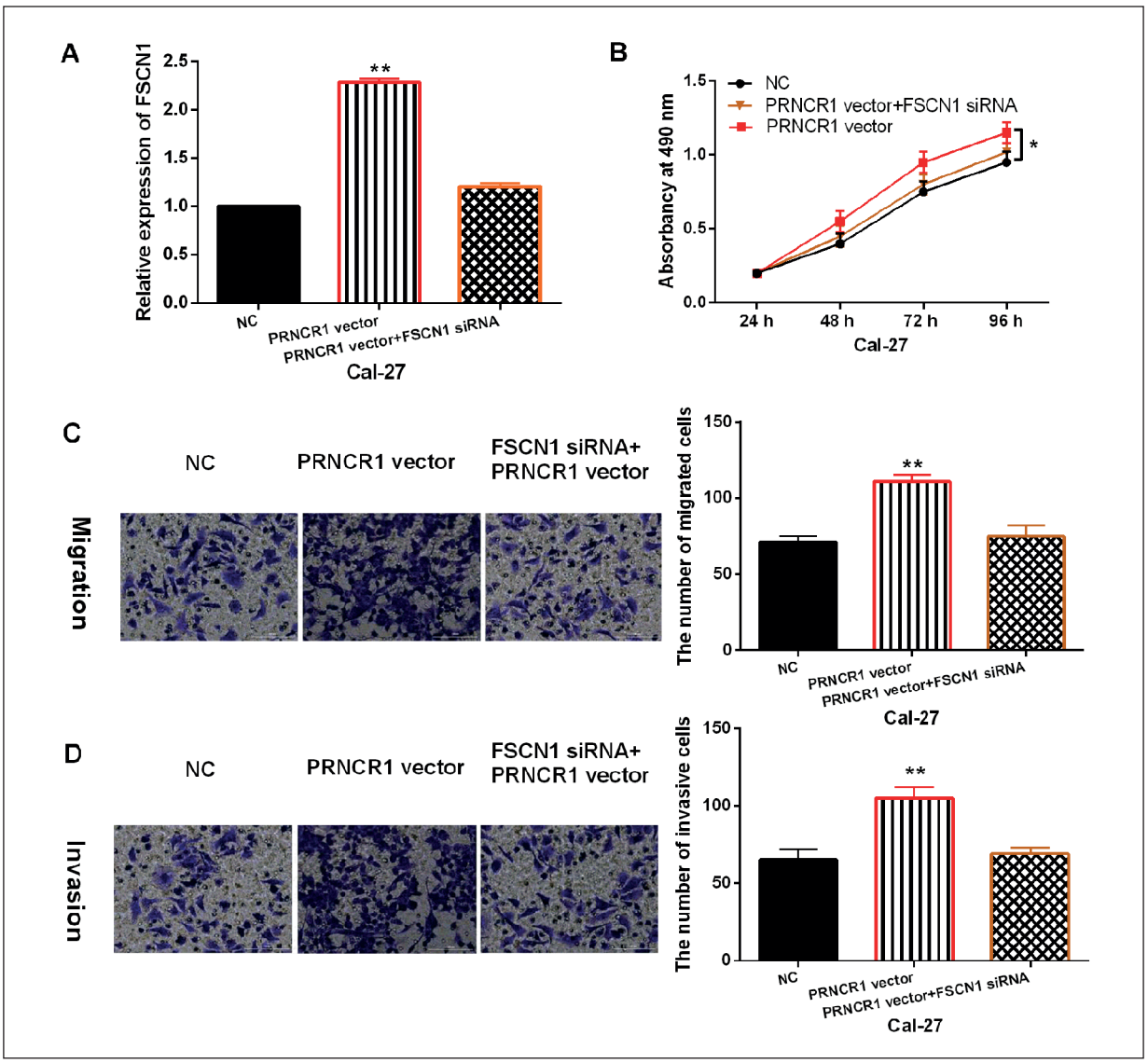

Figure 5. LncRNA PRNCR1 serves as an oncogene in OSCC by regulating FSCN1. **A**, FSCN1 expression in Cal-27 cells with FSCN1 siRNA and lncRNA PRNCR1 vector (**B, C**, **D**) Cell proliferation, migration and invasion in Cal-27 cells with FSCN1 siRNA and lncRNA PRNCR1 vector (200×) *p<0.05, **p<0.01.

Previous studies[21,22] have shown that lncRNA PRNCR1 was upregulated in gastric cancer and colorectal cancer. Functionally, lncRNA PRNCR1 has been found to promote cell proliferation and cell cycle in colorectal cancer[8]. In addition, upregulation of PRNCR1 promoted cell migration and invasion in breast cancer[7]. In this study, upregulation of PRNCR1 was also found in OSCC. The knockdown of PRNCR1 inhibited OSCC cell proliferation, migration and invasion. These results are consistent with previous studies. All these findings imply that lncRNA PRNCR1 acts as a tumor promoter in the development of OSCC.

To further elucidate the regulatory mechanism of lncRNA PRNCR1 in OSCC, miR-326 was confirmed to be the target of lncRNA PRNCR1. Moreover, the mutual inhibition between the expressions of lncRNA PRNCR1 and miR-326 was found in OSCC. The same interaction between miR-326 and other lncRNAs has also been detected in human cancers, such as HOTAIR and TDRG1[23,24]. In addition, we found that the expression of miR-326 was reduced in OSCC. Overexpression of miR-326 inhibited cell proliferation, migration and invasion in OSCC. MiR-326 has been proven to be a promising cancer biomarker[25]. Similar to our results, downregulation of miR-326 was found in melanoma[26]. MiR-326 was found to inhibit gastric cancer tumor growth and endometrial cancer cell metastasis[27,28]. These results indicate that miR-326 serves as a tumor suppressor in OSCC, which has not been reported in previous studies. In addition, upregulation of PRNCR1 was found to weaken the anti-tumor effect of miR-326 in OSCC. This indicates that lncRNA PRNCR1 promotes the progression of OSCC by downregulating miR-326. Similarly, lncRNA SNHG3 was also proposed to promote hepatocellular tumorigenesis by targeting miR-326[29]. Further, it was found that FSCN1 is a direct target of miR-326 and involved in the development of OSCC by interacting with lncRNA PRNCR1.

In this study, upregulation of FSCN1 was found in OSCC tissues. At the same time, a positive correlation was found between FSCN1 and lncRNA PRNCR1 expression in OSCC. More importantly, FSCN1 can promote the progression of OSCC and aggravate the carcinogenic effect of lncRNA PRNCR1 in OSCC. Upregulation and carcinogenesis of FSCN1 have also been found in hepatocellular carcinoma and gastric cancer[30,31]. Additionally, lncRNA ROR promoted the metastasis and invasion of esophageal squamous cell carcinoma cells by regulating miR-145/FSCN1[32]. This study also shows that lncRNA PRNCR1 promotes the aggressive behaviors of OSCC by regulating miR-326/FSCN1. In addition, miR-326 was found to directly target FSCN1 and negatively regulate FSCN1 expression in OSCC. This indicates that lncRNA PRNCR1 upregulates FSCN1 expression in OSCC by inhibiting miR-326 expression. As far as we know, this conclusion was firstly reported in our study.

Conclusions

In summary, lncRNA PRNCR1 acts as a miR-326 'sponge' to trigger FSCN1 expression, thereby promoting the progression of OSCC. This indicates that lncRNA PRNCR1 is an important regulator in OSCC. Although this study still has some limitations, we will perform further experiments to perfect this research in the future.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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