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MiR-1290 targets CCNG2 to promote the metastasis of oral squamous cell carcinoma

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Abstract. – OBJECTIVE: MicroRNAs (miRNAs) have been demonstrated to be involved in the pathogenesis of various human cancers, including oral squamous cell carcinoma (OSCC). Here, we designed this study to explore the potential effect of miR-1290 on tumorigenesis of OSCC.

PATIENTS AND METHODS: The expressions of miR-1290 and cyclin G2 (CCNG2) in OSCC were observed by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). Dual-Luciferase Reporter Assay was performed to confirm the relationship between miR-1290 and CCNG2. The functions of miR-1290 and CCNG2 were analyzed using transwell assay. The Western blot analysis was used to detect epithelial-mesenchymal transition (EMT).

RESULTS: Upregulation of miR-1290 and downregulation of CCNG2 were identified in OSCC. And upregulation of miR-1290 was associated with clinicopathological characteristics and poor prognosis in OSCC patients. Moreover, the downregulation of miR-1290 inhibited cell metastasis and EMT in OSCC cells. Furthermore, CCNG2 was a direct target of miR-1290. Its expression was inversely regulated by miR-1290 in OSCC cells. At the same time, the suppressive effect of CCNG2 was observed in OSCC. Furthermore, overexpression of CCNG2 weakened the promoted effect of miR-1290 on cell metastasis in OSCC.

CONCLUSIONS: MiR-1290 promoted cell metastasis and EMT, inhibiting CCNG2 expression in OSCC.

Key Words:
Oral squamous cell carcinoma, MiR-1290, Metastasis, Prognosis, CCNG2.

Introduction

Oral squamous cell carcinoma (OSCC) is one of the most common malignant tumors in the head and neck. The tumorigenesis of OSCC is closely related to the patient's bad habits, such as smoking and drinking[1]. Moreover, cervical lymph node metastasis and distant organ metastasis are the main causes of high mortality in OSCC[2]. The main treatments for OSCC include surgical resection, radiotherapy, chemotherapy, and traditional Chinese medicine[3]. However, the 5-year survival rate for OSCC patients still remains approximately 50%, and OSCC has no effective preventive measures[4]. Therefore, early detection and diagnosis are keys in the OSCC's prevention and treatment.

MicroRNAs (miRNAs) have been proposed to regulate biological processes by affecting corresponding gene expression[5]. Abnormal expressions of miRNAs have been demonstrated to be involved in the pathogenesis of many human cancers[6]. In OSSC, miR-101[7], miR-137[8], miR-186[9] and miR-375[10] were reported to be downregulated and acted as tumor suppressors. In contrast, it had been reported that miR-497 was upregulated in OSCC, which enhanced cell metastasis through regulating SMAD7[11]. Now, the role of miR-1290 has attracted our attention. It has been reported that miR-1290 can be used as a novel diagnostic and prognostic biomarker in human colorectal cancer[12]. Moreover, upregulation of miR-1290 had been observed in non-small cell lung cancer[13], pancreatic cancer[14], ovarian cancer[15], and acute lymphoblastic leukemia[16]. However, the specific function of miR-1290 in OSCC is still unclear and requires in-depth research.

The dysregulation of Cyclin G2 (CCNG2) had been identified in human oral cancer[17], which was associated with OSCC tumor size[18]. An abnormal expression of CCNG2 had been examined in kidney cancer[19], esophageal cancer[20], and nasopha-

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ryngeal carcinoma[21]. In addition, CCNG2 was found to promote cell cycle arrest in breast cancer cells and was associated with patient survival[22]. Furthermore, CCNG2 can be used as a novel independent prognostic marker for pancreatic cancer[23]. Besides that, CCNG2 had been verified as a direct target of miR-125b in lung cancer [24]. However, the interaction between miR-1290 and CCNG2 has not been fully elucidated in OSCC.

In the current work, we observed the expressions of miR-1290 and CCNG2 in OSCC. The effect of miR-1290 and CCNG2 on cell metastasis was also investigated. These findings will help to understand the role of miR-1290 and CCNG2 in OSCC.

Patients and Methods

Clinical Tissues

Forty-seven pairs of surgical OSCC specimens and adjacent normal tissues were obtained from the Affiliated Yantai Yuhuangding Hospital of Qingdao University. All OSCC patients involved in this study provided the written informed consent. Moreover, these patients with OSCC did not receive any treatment prior to surgery. The tissues were then frozen in liquid nitrogen and stored in a -80°C refrigerator for further experiment. The investigation was approved by the Institutional Ethics Committee of The Affiliated Yantai Yuhuangding Hospital of Qingdao University.

Cell Culture and Transfection

The normal human oral keratinocytes (NHOK) and Cal-27, SCC-9, SCC-25, Tca-8113 cell lines were used for this experiment. These cell lines were purchased from American Type Culture Collection (Manassas, VA, USA). Next, these cell lines were seeded in Dulbecco's Modified Eagle's Medium (DMEM) medium (Gibco, Rockville, MD, USA) containing 10% fetal bovine serum (FBS; Gibco, Rockville, MD, USA) and incubated at 37°C in an atmosphere with 5% CO_2.

MiR-1290 mimic or inhibitor, and CCNG2 siRNA were purchased from GenePharma (Shanghai, China). They were severally transferred into OSCC cells with Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) following the manufacturers' protocols.

Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

Total RNA containing miRNA was extracted using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) to quantify miR-1290 expression in OSCC tissues and cell lines. QRT-PCR was performed using SYBR Premix Ex Taq II (TaKaRa, Otsu, Shiga, Japan) on ABI 7500 Fast Real-Time PCR system (Applied Biosystems, Foster City, CA, USA). U6 and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) were used as controls for miR-1290 and CCNG2. The $2^{-\Delta\Delta Ct}$ method was used to calculate their relative expression levels. The primers used were: miR-1290 forward, 5'-ACA CTC CAG CTG GGT GGA TTT TTG GAT C-3' and reverse, 5'-CTC AAC TGG TGT C-3'; GAPDH forward, 5'-CGG AGT CAA CGG ATT TGG TCG TAT-3' and reverse, 5'-AGC CTT CTC CAT GGT GGT GAA GAC-3'; CCNG2 forward, 5'-AAG AAG AGA GAT TCC AAC C-3' and reverse, 5'-CCA GCA AAA AAG AAC AGA C-3'; U6 forward, 5'-TTC CTC CGC AAG GAT GAC ACG C-3', U6 reverse, 5'-GTG CAG GGT CCG AGG T-3'.

Dual Luciferase Assay

The 3'-untranslated region (3'-UTR) of wild or mutant CCNG2 was inserted into the pmirGLO luciferase vector (Promega, Madison, WI, USA) for the luciferase reporter assay. Next, the above vector and miR-1290 mimics were transfected into Tca-8113 cells. Finally, the luciferase activity was analyzed using a dual luciferase assay system (Promega, Madison, WI, USA).

Transwell Assays for Cell Migration and Invasion

Cell migration and invasion were evaluated using transwell chambers (8 μm pore size; Millipore, Billerica, MA, USA) in 24-well plates. First, 1×10^5 OSCC cells were placed in the upper chamber. Moreover, the lower chamber was filled with 10% FBS. The upper chamber with Matrigel (BD, Biosciences, Bedford, MD, USA) was used for invasion assay. These cells were incubated at 37°C for 18 or 24 h, respectively for migration and invasion assays. Finally, they were stained with 0.1% crystal violet. A microscope was used to count migrated and invading cells.

Western Blot Analysis

Protein samples were obtained using radioimmunoprecipitation assay (RIPA) lysis buffer (Beyotime, Shanghai, China). The protein was then separated by 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). Next, the protein was incubated with 5% non-fat milk in polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA) at room temperature. The membrane was incubated with rabbit monoclonal anti-CCNG2 (1:2000; Abcam,

Cambridge, MA, USA) and rabbit monoclonal anti-GAPDH antibody (1:1000; Epitomics, Burlingame, CA, USA) overnight at 4°C. After that, the protein was incubated with goat polyclonal anti-rabbit IgG secondary antibody (1:2000; Abcam, Cambridge, MA, USA). Finally, protein expression levels were measured using enhanced chemiluminescence (ECL, Pierce, Rockford, IL, USA). In addition, antibodies against Vimentin, E-cadherin and N-cadherin were obtained from Abcam (Cambridge, MA, USA).

Statistical Analysis

Data were analyzed by Statistical Product and Service Solutions (SPSS) 19.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 6 (GraphPad Software, Inc., San Diego, CA, USA). Differences were calculated according to the Chi-squared test. Comparison between groups was done using One-way ANOVA test followed by Post-Hoc Test (Least Significant Difference). The relationship between miR-1290 expression and survival rate in OSCC patients was performed by the Kaplan-Meier method with log-rank test. $p<0.05$ was defined as a significant difference.

Results

Upregulation of miR-1290 and Downregulation of CCNG2 Were Identified in OSCC

First, miR-1290 expression levels were observed in OSCC tissues. The expression of miR-1290 in OSCC tissues was found to be higher than that in normal tissues (Figure 1A). Moreover, miR-1290 expression was also observed in the Cal-27, SCC-9, SCC-25, Tca-8113 cell lines and NHOK cells (control). The results of the qRT-PCR experiment showed that the expression of miR-1290 was apparently increased in the Cal-27, SCC-9, SCC-25, and Tca-8113 cell lines compared to NHOK cells (Figure 1B). Besides that, CCNG2 levels were also detected in OSCC cells. In contrast, CCNG2 expressions were decreased in both

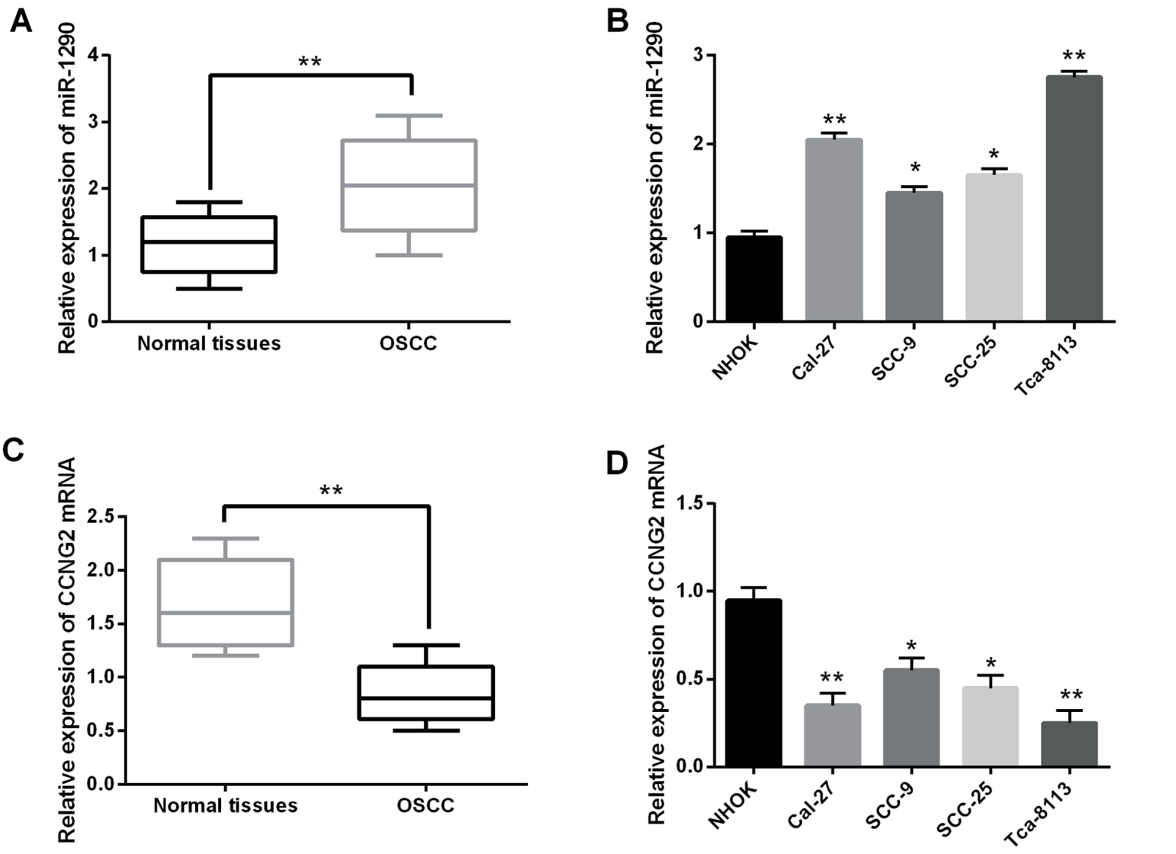

Figure 1. Upregulation of miR-1290 and downregulation of CCNG2 were identified in OSCC. **A,** The mRNA expressions of miR-1290 in OSCC tissues. **B,** The expression of miR-1290 in Cal-27, SCC-9, SCC-25, Tca-8113 cell lines and NHOK cells (control) **C,** The mRNA expressions of CCNG2 in OSCC tissues. **D,** The expression of CCNG2 in Cal-27, SCC-9, SCC-25, Tca-8113 cell lines and NHOK cells (control). *$p<0.05$, **$p<0.01$).

OSCC tissues and cell lines (Figure 1C, 1D). The findings reflected that the abnormal expressions of miR-1290 and CCNG2 might be related to tumorigenesis of OSCC.

Upregulation of miR-1290 Was Associated with Clinic-Pathological Characteristics and Poor Prognosis of the OSCC Patients

Next, the correlation between miR-1290 levels and clinicopathological characteristics was analyzed in OSCC patients. As shown in Table I, the high expression of miR-1290 was found to be significantly associated with both the TNM stage (p=0.021) and the lymph node metastasis (p=0.0002). Hence, we presumed that an abnormal expression of miR-1290 might be involved in the development of OSCC. Furthermore, the survival analysis indicated that low miR-1290 expression was significantly associated with longer overall survival in OSCC patients (p=0.0124; Figure 2). Based on these results, miR-1290 was found to be associated with clinicopathological characteristics and prognosis in OSCC patients.

Downregulation of miR-1290 Repressed Cell Migration and Invasion in OSCC

MiR-1290 mimics or inhibitor was then transfected into Tca-8113 cells to explore its biological role in OSCC. We found that miR-1290 mimics significantly promoted its expression in Tca-8113 cells (Figure 3A), while miR-1290 inhibitor reduced its expression (Figure 3B). Besides that, transwell assay suggested that a downregulation of miR-1290 suppressed migration and invasion of Tca-8113 cells. In contrary, (an) upregulation of miR-1290 promoted cell migration and invasion in OSCC (Figure 3C, 3D). Briefly, the overexpression of miR-1290 promoted cell migration and invasion in OSCC.

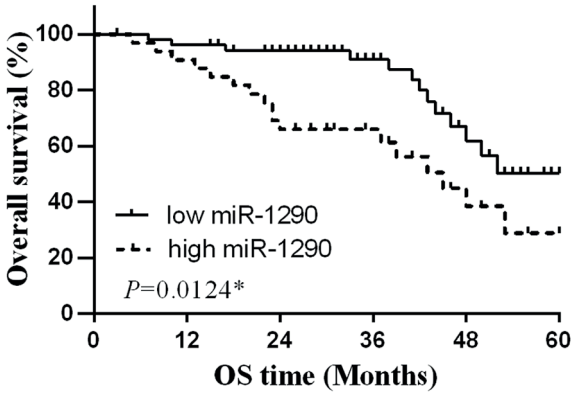

Figure 2. MiR-1290 could predict the prognosis of OSCC patients. High miR-1290 expression patients showed a shorter OS (*p<0.05).

Table I. Relationship between miR-1290 expression and their clinic-pathological characteristics of OSCC patients.

Characteristics	Cases	miR-1290		p-value
		High	Low	
Age (years)				0.142
≥ 60	25	15	10	
< 60	22	14	8	
Gender				0.042
Male	27	17	10	
Female	20	12	8	
Differentiation				0.078
Well/moderately	32	20	12	
poorly	15	9	6	
Tumor location				0.235
Buccal cancer	5	3	2	
Oropharyngeal cancer	10	6	4	
Tongue cancer	20	12	8	
Gingival cancer	12	=	4	
Positive lymph node metastasis				0.0002*
No	34	21	13	
Yes	13	8	5	
TNM stage				0.021*
I/II	37	25	12	
III/IV	10	4	6	

Statistical analyses were performed by the χ^2-test. *p<0.05 was considered significant.

MiR-1290 overexpression promoted EMT in OSCC cells

Subsequently, expression levels of EMT markers were examined to further detect the effect of miR-1290 on OSCC cell metastasis. The results suggested that an upregulation of miR-1290 blocked the expression of the epithelial marker E-cadherin and promoted the expressions of N-cadherin and Vimentin in OSCC cells (Figure 4A). In contrast, a downregulation of miR-1290 enhanced E-cadherin levels and decreased N-cadherin and Vimentin levels (Figure 4B). Therefore, we considered that an overexpression of miR-1290 promoted EMT in OSCC cells.

CCNG2 was a target gene of miR-1290 in OSCC cells

Further, target genes of miR-1290 were searched from the TargetScan database (http://www.targetscan.org/vert_71/). In particular, CCNG2 was found to have binding sites with miR-1290 (Figure 5A). Next, we performed luciferase reporter

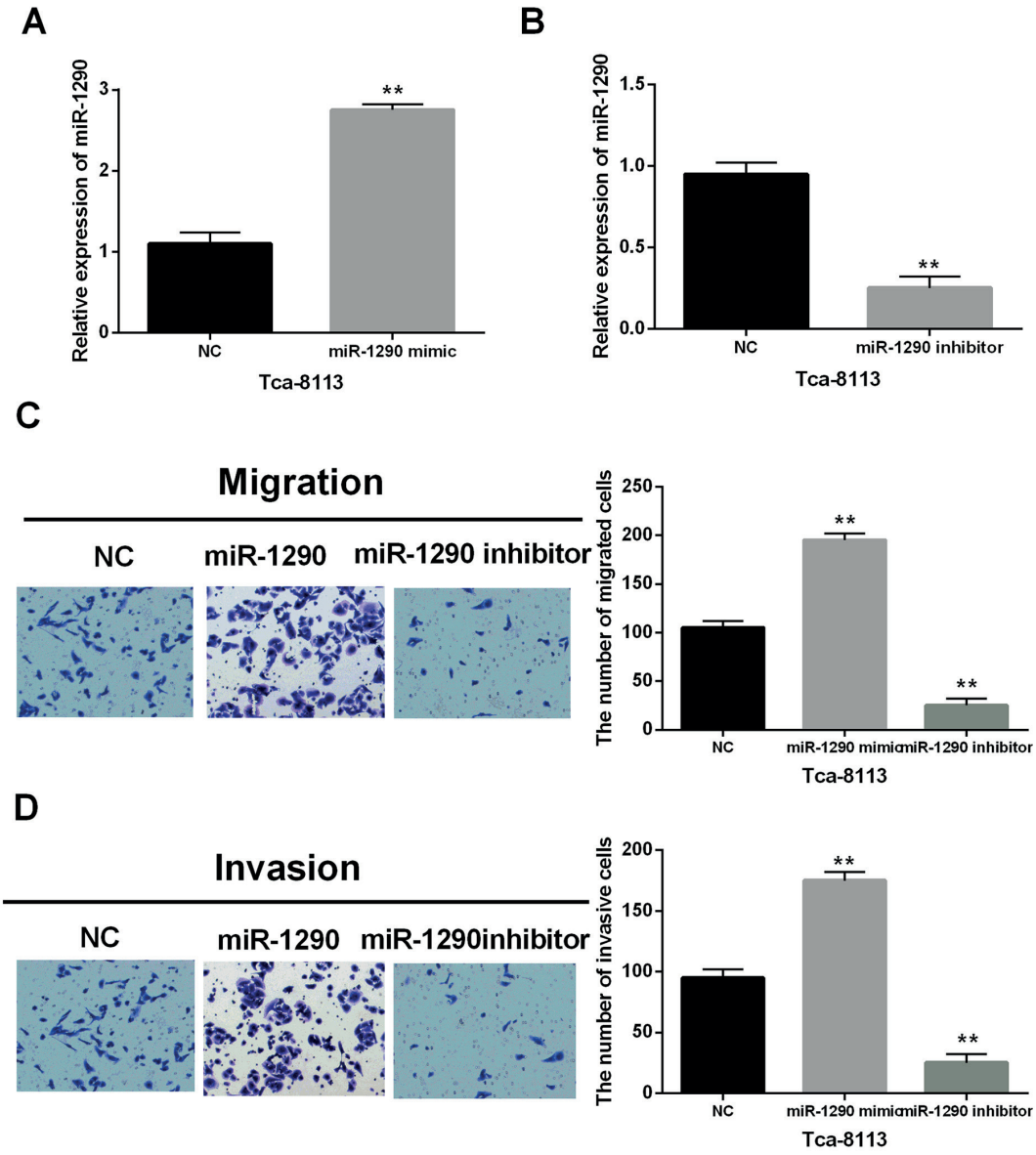

Figure 3. Downregulation of miR-1290 repressed cell migration and invasion in OSCC. **A-B,** The expression of miR-1290 in Tca-8113 cells with miR-1290 mimics or inhibitor. **C-D,** Cell migration and invasion in cells with miR-1290 mimics or inhibitor (magnification: 40×). (**$p<0.01$).

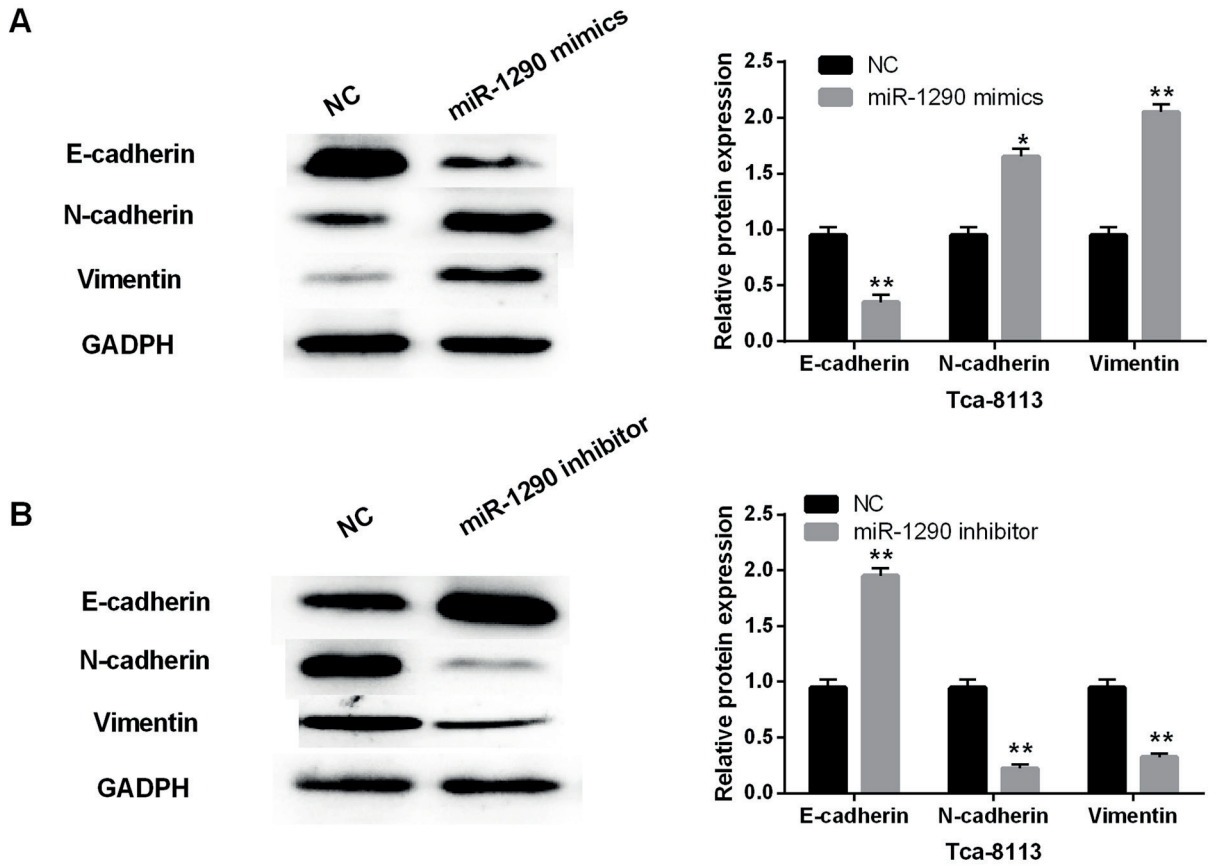

Figure 4. MiR-1290 overexpression promoted EMT in OSCC cells. **A-B,** The expression of E-cadherin, N-cadherin and Vimentin in Tca-8113 cells with miR-1290 mimics or inhibitor (*p<0.05, **p<0.01)

assay to confirm their relationship. As we predicted, miR-1290 mimics significantly blocked the luciferase activity of wild-type CCNG2 (CCNG2-Wt). However, the luciferase activity of mutant CCNG2 (CCNG2-Mut) was not affected by miR-1290 (Figure 5B). Furthermore, it was examined that CCNG2 expression was inversely correlated with miR-1290 expression in OSCC tissues (R^2=0.6406, p<0.0001, Figure 5C). Moreover, the overexpression of miR-1290 significantly reduced CCNG2 mRNA and protein expressions, while the downregulation of miR-1290 promoted them (Figure 5D, 5E). Taken together, CCNG2 was a direct target of miR-1290 and was negatively regulated by miR-1290 in OSCC cells.

The suppressive function of CCNG2 was observed in OSCC.

Next, CCNG2 siRNA was transfected into Tca-8113 cells to analyze its role in OSCC. We found that CCNG2 expression was reduced by CCNG2 siRNA (Figure 6A). Moreover, CCNG2 siRNA inhibited the expression of the epithelial marker E-cadherin and promoted expressions of N-cadherin and Vimentin (Figure 6B). Besides that, the transwell assay showed that CCNG2 siRNA promoted cell migration and invasion in OSCC (Figure 6C, 6D). These results implied that CCNG2 played a suppressive effect on cell metastasis in OSCC cells.

Overexpression of CCNG2 Weakened the Carcinogenesis of miR-1290 in OSCC.

Finally, CCNG2 vector and miR-1290 mimics were co-transfected into Tca-8113 cells to further explore their interaction. CCNG2 rescue experiments showed that CCNG2 vector restored the decreased expression of CCNG2 induced by miR-1290 mimics in Tca-8113 cells (Figure 7A, 7B). Similarly, overexpression of CCNG2 weakened the promoted effect of miR-1290 on cell migration and invasion in Tca-8113 cells (Figure 7C, 7D). In short, overexpression

of CCNG2 weakened the carcinogenic effect of miR-1290 in OSCC.

Discussion

In this investigation, we found that miR-1290 targeted CCNG2 to promote tumorigenesis of OSCC. First, upregulation of miR-1290 and downregulation of CCNG2 were identified in OSCC. Upregulation of miR-1290 was associated with TNM stage and lymph node metastasis in OSCC patients. Second, downregulation of miR-1290 repressed cell metastasis and EMT in OSCC cells. Furthermore, miR-1290 directly targeted CCNG2 and negatively regulated its expression in OSCC cells. The suppressive effect of CCNG2 was also observed in OSCC. Besides that, the overexpression of CCNG2 weakened the carcinogenic effects of miR-1290 in OSCC. In addition, high miR-1290 expression was also found to predict poor prognosis in OSCC patients.

In previous studies, miR-1290 had been identified as a potential prognostic biomarker for both esophageal squamous cell carcinoma (ESCC)[25] and non-small cell lung cancer[26], matching our results. Moreover, Xiao et al[27] demonstrated that miR-1290 promoted cell proliferation and invasion *via* modulating SOCS4 in lung adenocarcinoma. It was also found that miR-1290 promoted cancer progression through targeting NFIX in ESCC[28]. However, miR-1290 was found to inhibit cell viability and cell cycle progression in non-small cell lung carcinoma cells[29]. In our study, the

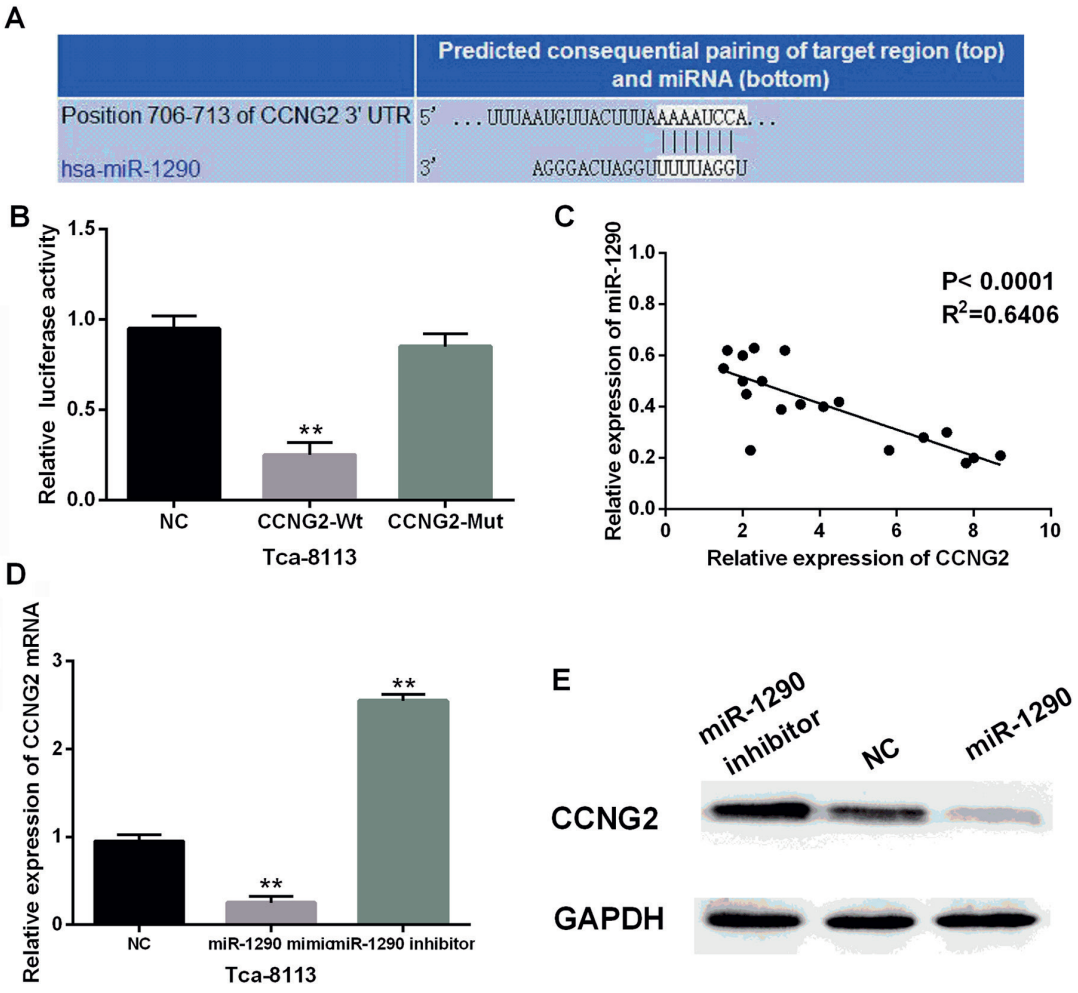

Figure 5. CCNG2 was a target gene of miR-1290 in OSCC cells. **A,** The binding sites between miR-1290 and CCNG2. **B,** Luciferase reporter assay. **C,** The correlation between miR-1290 and CCNG2. **D-E,** The mRNA and protein expression of CCNG2 in cells containing miR-1290 mimics or inhibitor. (**p<0.01).

upregulation of miR-1290 was examined to promote cell migration, invasion, and EMT in OSCC. The same effect of miR-1290 was also identified in glioma[30]. It was also reported that miR-1290 was a novel potential oncomiR in laryngeal carcinoma[31]. All of these studies indicated that miR-1290 was a tumor promoter in some human cancers. We also verified that CCNG2 was a direct target of miR-1290.

CCNG2 had been suggested to regulate cancer progression, such as cell proliferation and cell cycle[32]. It was reported that CCNG2 was downregulated in gastric carcinoma, which was associated with malignant transformation[33]. Here, downregulation of CCNG2 was also measured in OSCC. Besides that, CCNG2 was identified to inhibit EMT by blocking the Wnt/β-catenin signaling pathway[34], which was consistent with our findings. Moreover, CCNG2 had been shown to be a direct target gene of some miRNAs, such as miR-378[35] and miR-1246[36]. Especially, miR-1246 was found to promote cell growth and metastasis in colorectal cancer *via* targeting CCNG2[37]. In addition, miR-93 exerted a carcinogenic effect in laryngeal squamous cell carcinoma by suppressing CCNG2 expression[38]. Similarly, miR-1290 also promoted cell metastasis and EMT through regulating CCNG2 expression in OSCC.

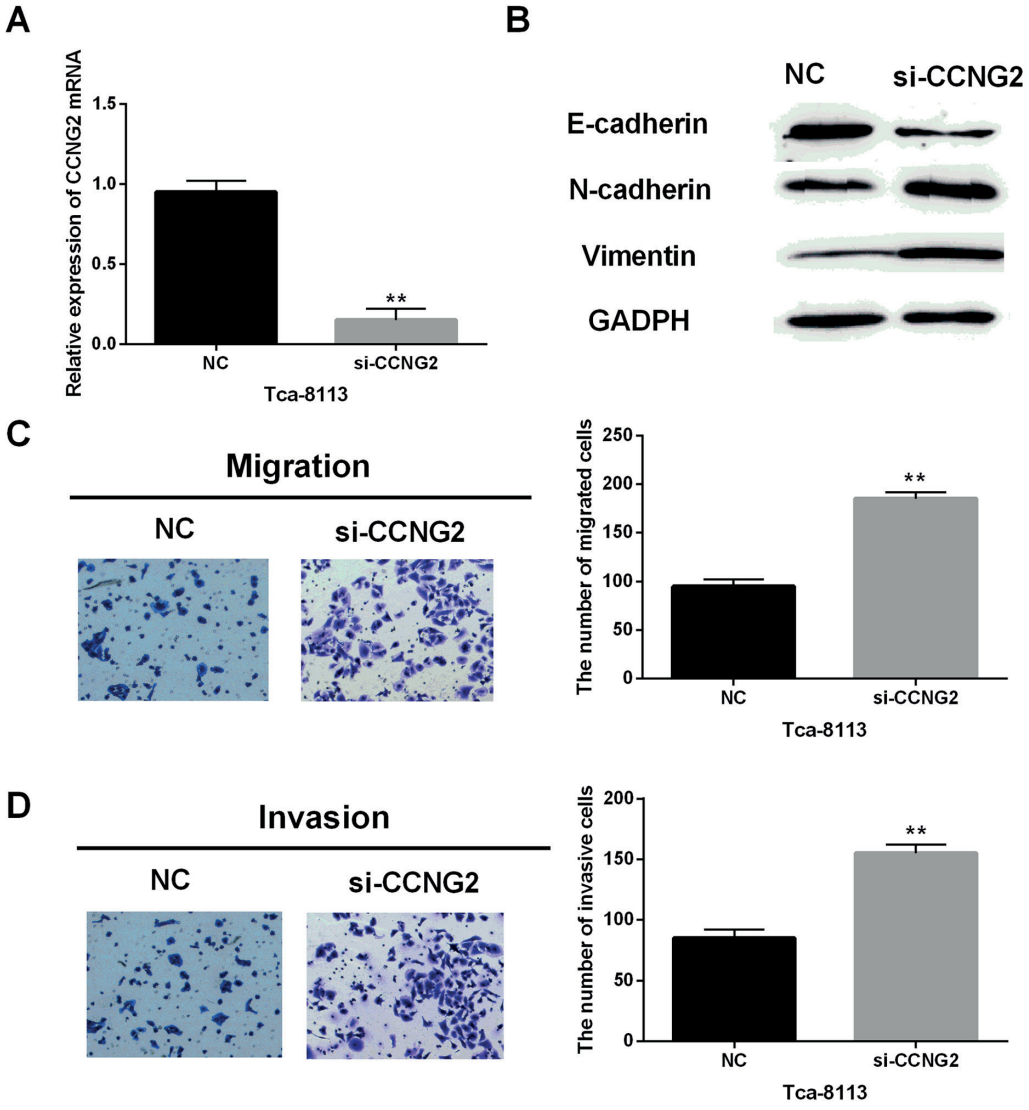

Figure 6. The suppressive function of CCNG2 was observed in OSCC. **A,** The expression of CCNG2 in cells containing CCNG2 siRNA. **B,** Western blot analysis of E-cadherin, N-cadherin and Vimentin in Tca-8113 cells with CCNG2 siRNA. **C, D,** Cell migration and invasion analysis of Tca-8113 cells with CCNG2 siRNA (magnification: 40×). (**p<0.01).

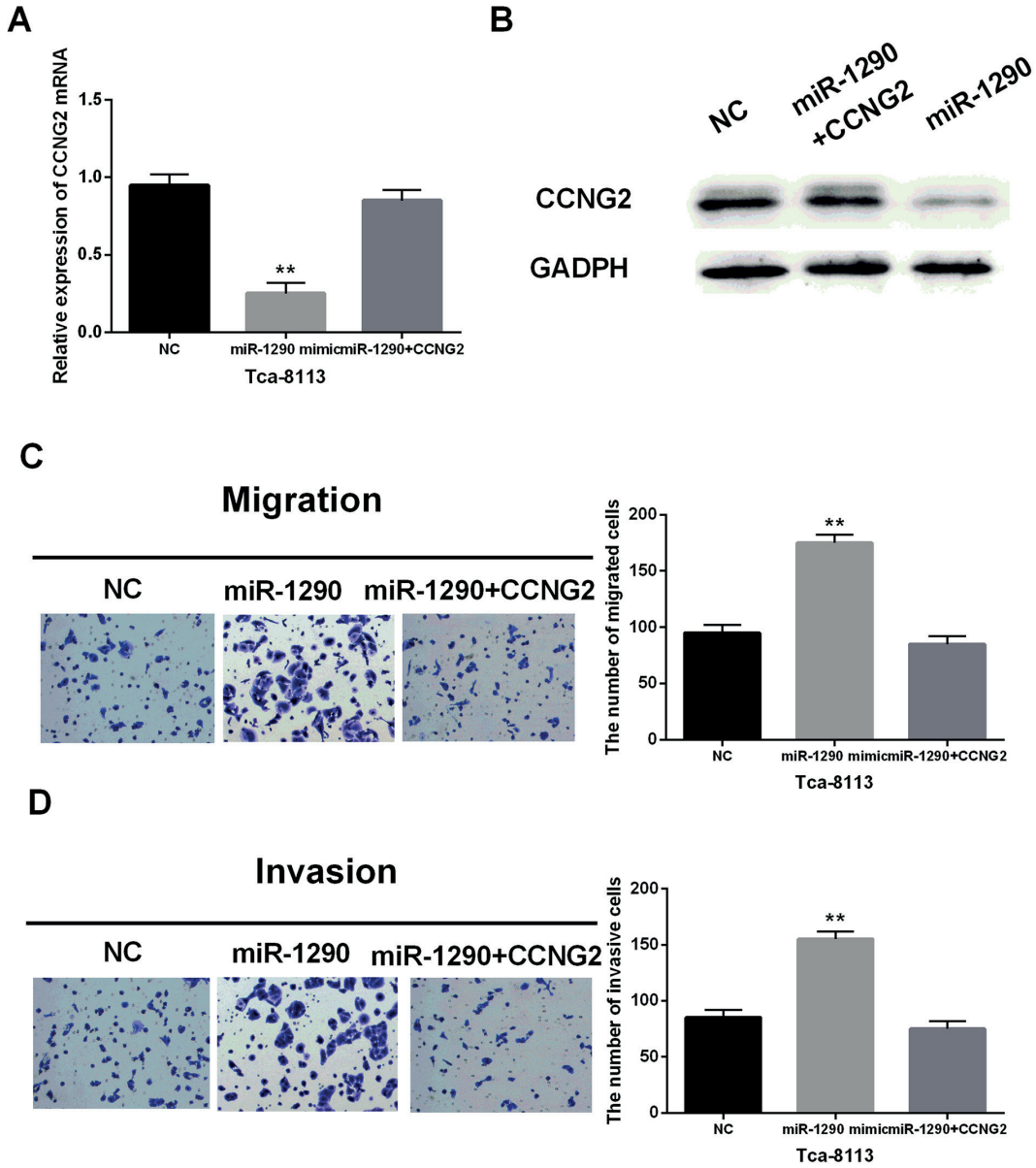

Figure 7. Overexpression of CCNG2 weakened the carcinogenesis of miR-1290 in OSCC. **A-B,** The mRNA and protein expressions of CCNG2 in cells containing CCNG2 vector and miR-1290 mimics. **C-D,** Cell migration and invasion in cells containing CCNG2 vector and miR-1290 mimics (magnification: 40×). (**p<0.01).

Conclusions

We identified an upregulation of miR-1290 and a downregulation of CCNG2 in OSCC. Moreover, miR-1290 was found to promote cell migration, invasion and EMT in OSCC through directly suppressing CCNG2 expression. Briefly, we considered that miR-1290 targeted CCNG2 to promote cell metastasis in OSCC.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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