European Review for Medical and Pharmacological Sciences 2020; 24: 4255-4262

MiR-802 inhibits the malignant biological behavior of oral squamous cell carcinoma by targeting proto-oncogene *MET*

H.-Y. XU[1], Q. DAI[1], Q.-X. CHEN[2], F. XIAO[3], Y.-H. DAI[1]

[1]Department of General Emergency, The Affiliated Stomatological Hospital of Nanchang University, The Key Laboratory of Oral Biomedicine, Jiangxi Province, Nanchang, China
[2]Department of Orthodontics, The Affiliated Stomatological Hospital of Nanchang University, The Key Laboratory of Oral Biomedicine, Jiangxi Province, Nanchang, China.
[3]Department of Endodontics, The Affiliated Stomatological Hospital of Nanchang University, The Key Laboratory of Oral Biomedicine, Jiangxi Province, Nanchang, China

Abstract. – OBJECTIVE: Oral squamous cell carcinoma (OSCC) is one of the frequently occurring malignancies, but effective treatments are lacking. It is believed that exploring new molecular targets could help us to improve the treatment of OSCC. Therefore, we hope to find a new miRNA target to control OSCC.

PATIENTS AND METHODS: qPCR and Western blots were used to test the expressions of miR-802 and target gene in OSCC tissues and cell lines. Luciferase reporter assay was performed to check whether miR-802 could directly target *MET*. CCK-8, wound healing, cell invasion, colony formation, and tumor growth assays were used to determine the functions of miR-802 and *MET* in the malignant biological behavior of OSCC.

RESULTS: The results suggested that miR-802 was low expressed in OSCC tissues and cell lines. Overexpression of miR-802 inhibited the cell viability, colony formation, migration and invasion of Tca8113 and SCC9 cells, and tumor growth *in vivo*. It was predicted that miR-802 might target the mRNA of proto-oncogene *MET*. Overexpressing miR-802 suppressed the expression of wild-type *MET* at both protein and mRNA levels in Tca8113 and SCC9 cells. Moreover, the expression of *MET* was high and significantly correlated with the low expression of miR-802 in OSCC tissues. Overexpression of *MET* in Tca8113 and SCC9 cells reduced the tumor-suppressive effects, which was induced by miR-802 overexpression.

CONCLUSIONS: MiR-802 suppresses the malignant biological behavior of OSCC by targeting proto-oncogene *MET*. This work provides a new potential molecular target for treating OSCC.

Key Words:
Oral squamous cell carcinoma, MiR-802, *MET*, Cell migration, Cell invasion.

Introduction

Oral squamous cell carcinoma (OSCC) is the most frequent malignancy of oral cancers in the world[1]. The occurrence of OSCC is mainly due to genetic mutations, caused by continued exposure to various risk factors, such as viral infections, tobacco, and alcohol. The malignant biological behavior, e.g., local lymph node metastasis, leads to the poor prognosis of OSCC[2]. However, the molecular mechanisms of OSCC development remain poorly known, which limits the treatment of OSCC.

Activation of several proto-oncogenes and deactivation of tumor suppressors are involved in the development of OSCC[3]. *MET* is a proto-oncogene encoding a tyrosine-protein kinase and participates in the occurrence and progression of many cancers[4]. *MET* expression is correlated with OSCC[5,6]. The high expression of *MET* may promote the malignant biological behavior of OSCC[6,7], but this needs validation *via* gene loss-of-function.

A microRNA (miRNA) is a small non-coding RNA that can regulate gene expression at both transcription and translation levels by interacting with the target mRNA[8]. MiRNAs can directly target oncogenes and play anti-tumor activity[9,10]. In OSCC cells, some miRNAs have been found to inhibit tumor growth by targeting several oncogenes and tumor suppressors[11-13]. Notably, *MET* is the target of a couple of miRNAs in OSCC[14,15], suggesting miRNA can function as a tumor suppressor in OSCC by regulating *MET* expression. Therefore, identifying new miRNAs that target *MET* may promote the treatment of OSCC.

Corresponding Author: Yinhua Dai, MD; e-mail: xiangrikui126@139.com

In this work, we found miR-802 exhibited low expression in OSCC tissues and cell lines. Transfecting miR-802 mimics in OSCC cells inhibited the malignant biological behavior, such as cell viability, migration, and invasion. Moreover, *MET* was identified as the target of miR-802 and mediated the anti-tumor activity of miR-802. Therefore, we argue that this study provides a new miRNA target for treating OSCC.

Patients and Methods

Quantitative Real-Time PCR (qPCR)

The human samples of normal and OSCC tissues were obtained from the patients in The Affiliated Stomatological Hospital of Nanchang University. All the patients agree with the sample collection. This investigation was approved by the Institutional Ethics Committee of Nanchang University. According to the manufacturer's protocols, total RNA was extracted using TRIzol (Invitrogen, Carlsbad, CA, USA), and cDNA was synthesized using SuperScript II Reverse Transcriptase (Invitrogen, Carlsbad, CA, USA). qPCR was performed with the corresponding primers (Table I) using an ABI Quant Studio6 system (Applied Biosystems, Foster City, CA, USA). The relative expression of miRNA was normalized to *U6* expression, but that of *MET* was normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) expression. The $2^{-\Delta\Delta CT}$ method was used to analyze the qPCR results based on three biological replicates and three technical replicates.

Cell Culture and the Transfection of MiRNA and Plasmids

Tca8113, SCC9, SCC25, and CAL27 cell lines were purchased from American Type Culture Collection (ATCC; Manassas, VA, USA), and HN12, HSU3, and FADU cell lines were obtained from the Committee of the Type Culture Collection of the Chinese Academy of Sciences (Shanghai, China). Cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS; Hyclone, South Logan, UT, USA), 100 U/ml penicillin, and 100 μg/ml streptomycin, and maintained at 37°C in a humidified 5% CO_2 incubator. The miR-802 mimics (5′-CAGUAACAAAGAUUCAUCCUUGU-3′) and miRNA-negative control (AgomiR-NC, 5′-CAGUACUUUUGUGUAGUACAA-3′) were synthesized by the GenePharma Company (Shanghai, China). Transfection of miRNAs and the plasmids expressing *MET* was performed using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions.

Cell Counting Kit-8 (CCK-8) Assay

The CCK-8 assay was performed to detect cell viability. Briefly, cells were seeded in a 96-well plate. After the transfection of miRNA or plasmids, the cells were treated with CCK-8 reagent (#C0038, Beyotime, Haimen, Jiangsu, China) according to the manufacturer's method. Finally, the absorbance was measured at 450 nm with a microplate reader.

Colony Formation Assay

Two hundred cells were seeded into per well of a 6-well plate and cultured in DMEM containing 10% FBS. After 10-day incubation, the cells were washed with phosphate-buffered saline (PBS) and fixed with 4% paraformaldehyde and then stained with 0.5% crystal violet. Colonies with more than 50 cells were counted under a microscope (Olympus, Tokyo, Japan).

Wound Healing Assay

A wound healing assay was performed to test cell motility. When the cells grew to 90% confluent, a wound was generated by scratching the cell monolayer with a 200-μL pipette tip. To avoid cell proliferation, we used a DMEM medium containing 1% FBS to culture the cells after wound generation. Wound distance was imaged and measured after a 48-h incubation period.

Table I. Primers used in qPCR.

Gene/miRNA	Forward primer (5′-3′)	Reverse primer (5′-3′)
miR-802	CGTTGTGTAGCTTATCAGACTG	AATGGTTGTTCTCCACACTCTC
U6	CTCGCTTCGGCAGCACA	AACGCTTCAGGAATTTGCGT
MET	CCCCACCCTTTGTTCAG	TCAGCCTTGTCCCTCCT
GAPDH	AAGGTGAAGGTCGGAGTCAAC	GGGGTCATTGATGGCAACAATA

Cell Invasion Assay

Cell invasion assay was performed using the transwell chamber (Millipore Corporation, Billerica, MA, USA). 1.0×10^4 cells in serum-free medium were seeded into the upper chamber precoated with Matrigel (BD Biosciences, Bedford, MA, USA). DMEM with 10% FBS was filled into the lower chamber. After 48-h incubation, cells that had invaded through the membrane were fixed in 4% paraformaldehyde and stained with 0.5% crystal violet. The invaded cells were imaged and counted under a microscope (Olympus, Tokyo, Japan).

Tumor Growth Assay

All animal experiments were approved by the Institutional Animal Ethical Committee of Nanchang University, China, and conformed to the National Institutes of Health guidelines on the ethical use of animals. Male nude mice aged 4-5 weeks (about 15-25 g) were purchased from Shanghai Sippr-BK Laboratory Animal (Shanghai, China). Mice were randomly divided into two groups, which injected with Tca8113 cells overexpressing miR-802 mimics and negative control miRNA, respectively. The length and width of tumors were measured weekly. When the tumors reached 2.0 cm in diameter, they were excised. Furthermore, the tumor volume was calculated using the reported formula $(a\times b^2)\times0.5$[16].

Luciferase Reporter Assay

Forty-eight hours after the transfection of miRNAs and reporter plasmids, cells were lysed with passive lysis buffer. Subsequently, the samples were subjected to Dual-Luciferase assay using the Dual-Luciferase Reporter Assay Kit (Promega, Madison, WI, USA) and a microplate reader. The data was analyzed based on three replicates.

Western Blots

Total protein was extracted using radioimmunoprecipitation assay buffer (RIPA; 30 mM Tris-HCl pH 7.4, 150 mM NaCl, and 1% NP-40) containing proteinase inhibitor cocktail (Sigma-Alrdich, St. Louis, MO, USA). The protein sample was mixed with sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) loading buffer and boiled at 95°C for 5 min. About 50 μg of total protein per sample was subjected to SDS-PAGE. Proteins were transferred to polyvinylidene difluoride (PVDF) membrane, and the membrane was then blocked in 5% skim milk powder. The primary antibodies, including antibodies of *MET* (Abcam, Cambridge, MA, USA, Catalog No. ab51067) and GAPDH (Abcam, Catalog No. ab181602), were used to incubate the membrane overnight at 4°C with a 1:1000 dilution. Then, a horseradish peroxidase (HRP)-conjugated goat anti-rabbit antibody (Abcam, Catalog No. ab6721) was used as the secondary antibody to incubate the membrane for 1 h at room temperature. Target bands were visualized by using an enhanced chemiluminescence kit (Pierce Biotechnology, Rockford, IL, USA) according to the manufacturer's instructions. Protein bands were quantified by densitometric analysis and the relative gray was calculated by normalizing to GAPDH level.

Statistical Analysis

All data were analyzed by SPSS 17.0 software (Chicago, IL, USA) and GraphPad Prism 5 Demo software (San Diego, CA, USA). The values were expressed as the mean± standard error. Significant differences were calculated using the Student's *t*-test based on three biological replicates. $p < 0.05$ was considered statistically significant.

Results

MiR-802 Is Significantly Downregulated In OSCC Tissues and Cell Lines

To investigate the potential relationship between miR-802 and OSCC, we analyzed the expression levels of miR-802 in OSCC tissues and cell lines. qPCR results suggested that miR-802 was low expressed in the 50 OSCC tissues, compared with that of in the normal tissues (Figure 1A). Similarly, miR-802 exhibited lower expression in a couple of OSCC cell lines, including Tca8113, SCC9, SCC25, CAL27, HN12, HSU3, and FADU, than that of in the normal human oral keratinocytes (NHOK) cells (Figure 1B). Hence, the miR-802 expression is suppressed in OSCC tissues and cell lines.

Overexpression of MiR-802 Inhibits OSCC Cell Proliferation, Migration, and Invasion In Vitro As Well As Tumor Growth In Vivo

The low expression of miR-802 in OSCC tissues let us ask whether miR-802 could inhibit the malignant biological behavior of OSCC. To test this, we overexpressed miR-802 in OSCC cell lines, including Tca8113 and SCC9, by transfecting synthetic miR-802 mimics. qPCR

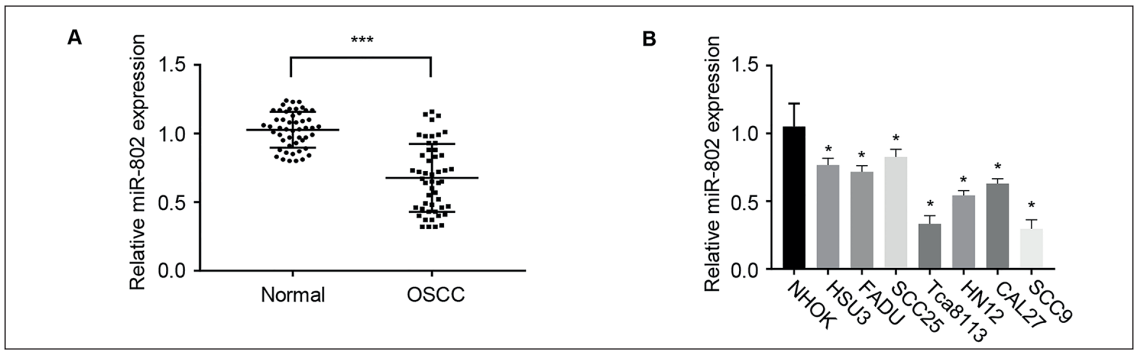

Figure 1. Expression of miR-802 in OSCC tissues and cell lines. **A**, qPCR showing miR-802 expression in the 50 OSCC tissues and normal tissues. **B**, MiR-802 expression in the OSCC cell lines, including Tca8113, SCC9, SCC25, CAL27, HN12, HSU3, FADU, and the normal human oral keratinocytes (NHOK) cells. Significant differences were analyzed by Student's *t*-test (* $p < 0.05$, *** $p < 0.001$).

suggested that the transfection of miR-802 significantly upregulated the miR-802 levels in the cells (Figure 2A). CCK-8 assays indicated that miR-802 mimics decreased the cell viability of Tca8113 and SCC9 (Figure 2B). Colony formation assays showed that overexpressing miR-802 reduced the colony number of the cells (Figure 2C). Wound healing assay indicated

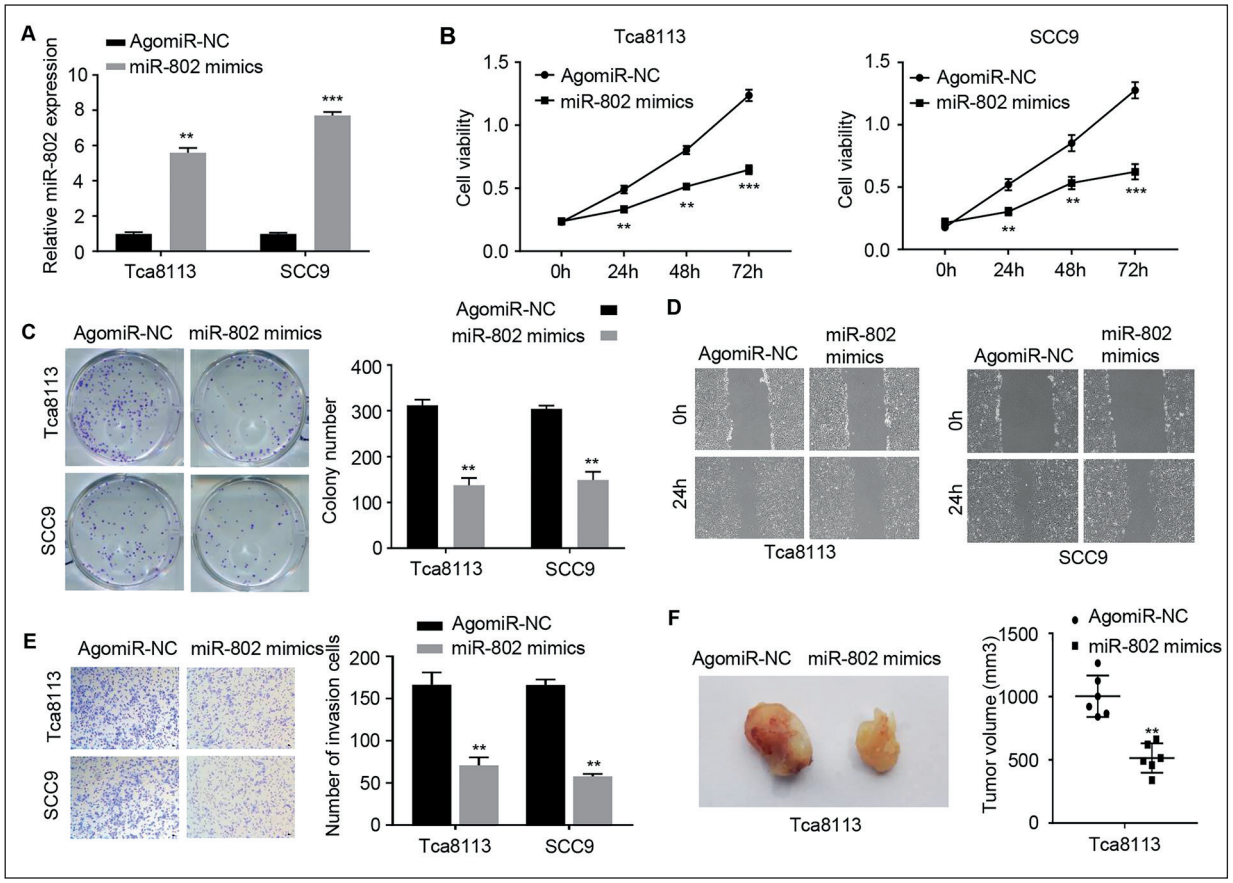

Figure 2. Anti-tumor activity of miR-802 in OSCC cells. **A**, Overexpressing miR-802 in Tca8113 and SCC9 cells by transfecting miR-802 mimics. The control cells received an equal amount of negative control miRNA (AgomiR-NC). **B**, Cell viability was determined in Tca8113 and SCC9 cells by the CCK-8 method. **C**, Colony formation in Tca8113 and SCC9 cells after miR-802 mimic transfection (magnification, ×20). **D**, Wound healing assay showing the cell migration in Tca8113 and SCC9 cells (magnification, ×10). **E**, Transwell assay showing the cell invasion (magnification, ×20). **F**, Tumor growth was analyzed in nude mice by injecting miR-802-transfecting Tca8113 cells. Significant differences were analyzed by Student's *t*-test (** $p < 0.01$, *** $p < 0.001$).

that high expression of miR-802 restrained cell migration (Figure 2D). Moreover, the transwell assay showed that transfecting miR-802 mimics inhibited cell invasion (Figure 2E). Injecting Tca8113 cells transfected with miR-802 mimics in nude mice significantly reduced the tumor size (Figure 2F). These data suggested that miR-802 restrains OSCC cell proliferation, migration, and invasion *in vitro,* as well as tumor growth *in vivo.*

MiR-802 Suppresses the Expression of Proto-Oncogene MET In OSCC Cells By Targeting the 3'-UTR of MET

To determine the mechanism by which miR-802 regulates the malignant biological behavior of OSCC, we investigated the possible target of miR-802. Of note, it is predicted that miR-802 may directly bind to the 3'-UTR of proto-oncogene *MET* (Figure 3A), which has been found participating in the progression of OSCC[6,17,18]. Luciferase reporter assay showed that transcription of wild-type *MET* was significantly suppressed by miR-802 (Figure 3A). However, miR-802 had no visible effect on the transcription of *MET* when the predicted binding site of *MET* mRNA was mutated. We then tested whether miR-802 could regulate the expression of endogenous *MET.* The results showed that miR-802 inhibited the expression of *MET* at both mRNA and protein levels in Tca8113 and SCC9 cells (Figure 3B and C). Furthermore, we found *MET* exhibited higher expression in OSCC tissues, compared with the normal tissues (Figure 3D). The high expression of *MET* was significantly correlated with the low expression of miR-802 (Figure 3E). These data suggested that *MET* is a target of miR-802 in OSCC cells.

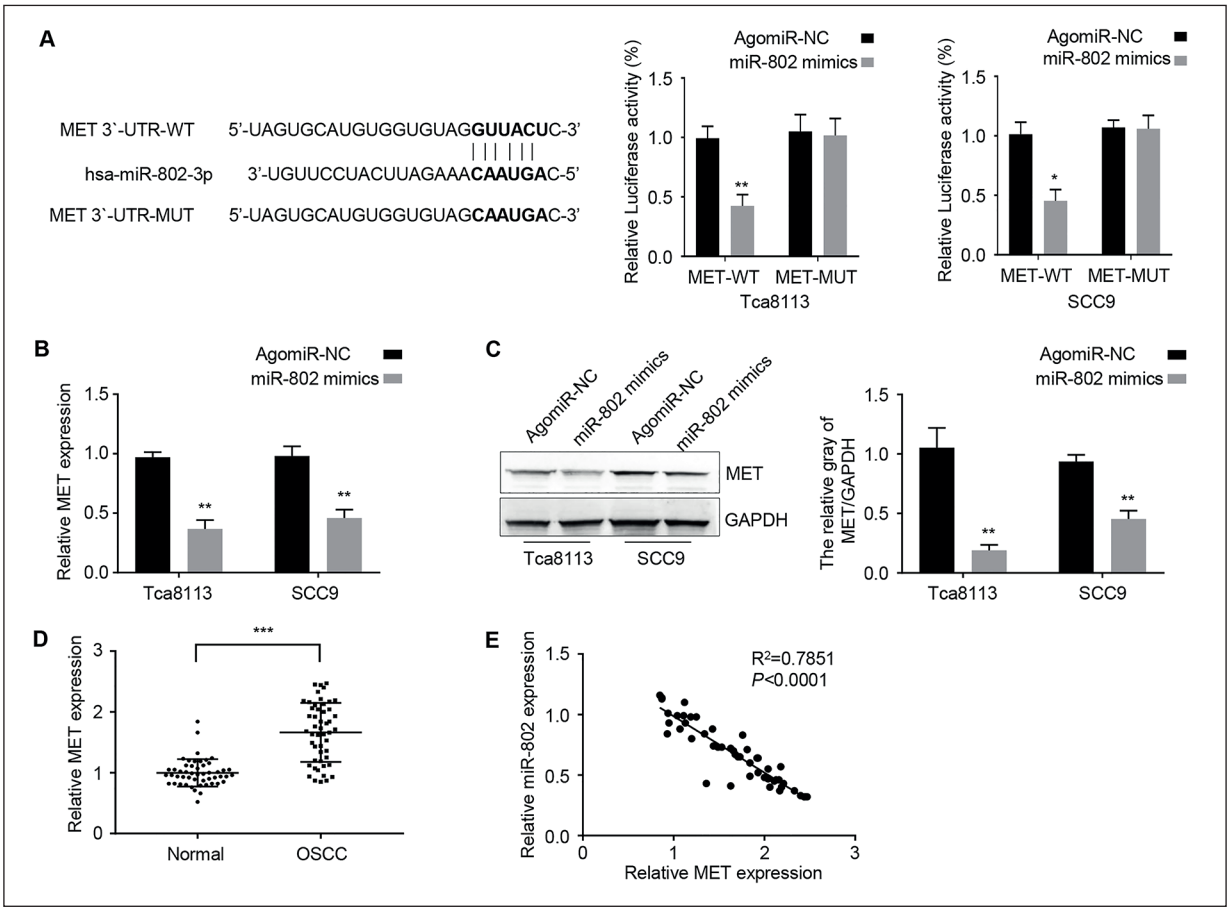

Figure 3. Inhibitory effect of miR-802 on MET expression in OSCC cells. **A**, Dual-Luciferase reporter assay showing the direct inhibitory effect of miR-802 on *MET* expression in Tca8113 and SCC9 cells. The qPCR (**B**) and Western blot (**C**) were performed to analyze the expression of endogenous MET after miR-802 mimics transfection. (**D**) qPCR showing the *MET* expression in 50 OSCC and normal tissues. **E**, The correlation between MET and miR-802 expression, determined by Pearson's correlation coefficient analysis. Significant differences were analyzed by Student's *t*-test (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

Overexpression of MET Reduced the Tumor-Suppressive Effect Caused by MiR-802 In OSCC

To ask whether miR-802 suppressed the malignant biological behavior of OSCC by targeting *MET*, we co-transfected miR-802 mimics and *MET*-overexpressing plasmids in OSCC cells. The results showed that the co-transfection of miR-802 and *MET* significantly downregulated cell viability (Figure 4A), colony formation (Figure 4B), cell migration (Figure 4C) and invasion (Figure 4D), compared with the transfection of miR-802. These data strongly suggested that miR-802 can interact with *MET* and inhibits the malignant biological behavior of OSCC.

Discussion

OSCC is the most frequent malignancy of oral cancers in the world, but there are no effective treatments. Here, we found that miR-802 can function as a tumor suppressor of OSCC by targeting the proto-oncogene *MET*. Although the interaction between miRNAs and *MET* in OSCC has been investigated, it is the first time to test the relationship between miR-802 and *MET* in OSCC tissues and cell lines. Our data suggest that miR-802 is a promising candidate that could be used as a molecular target to treat OSCC.

MiRNAs are the critical regulator for cell proliferation, migration, and invasion of OSCC.

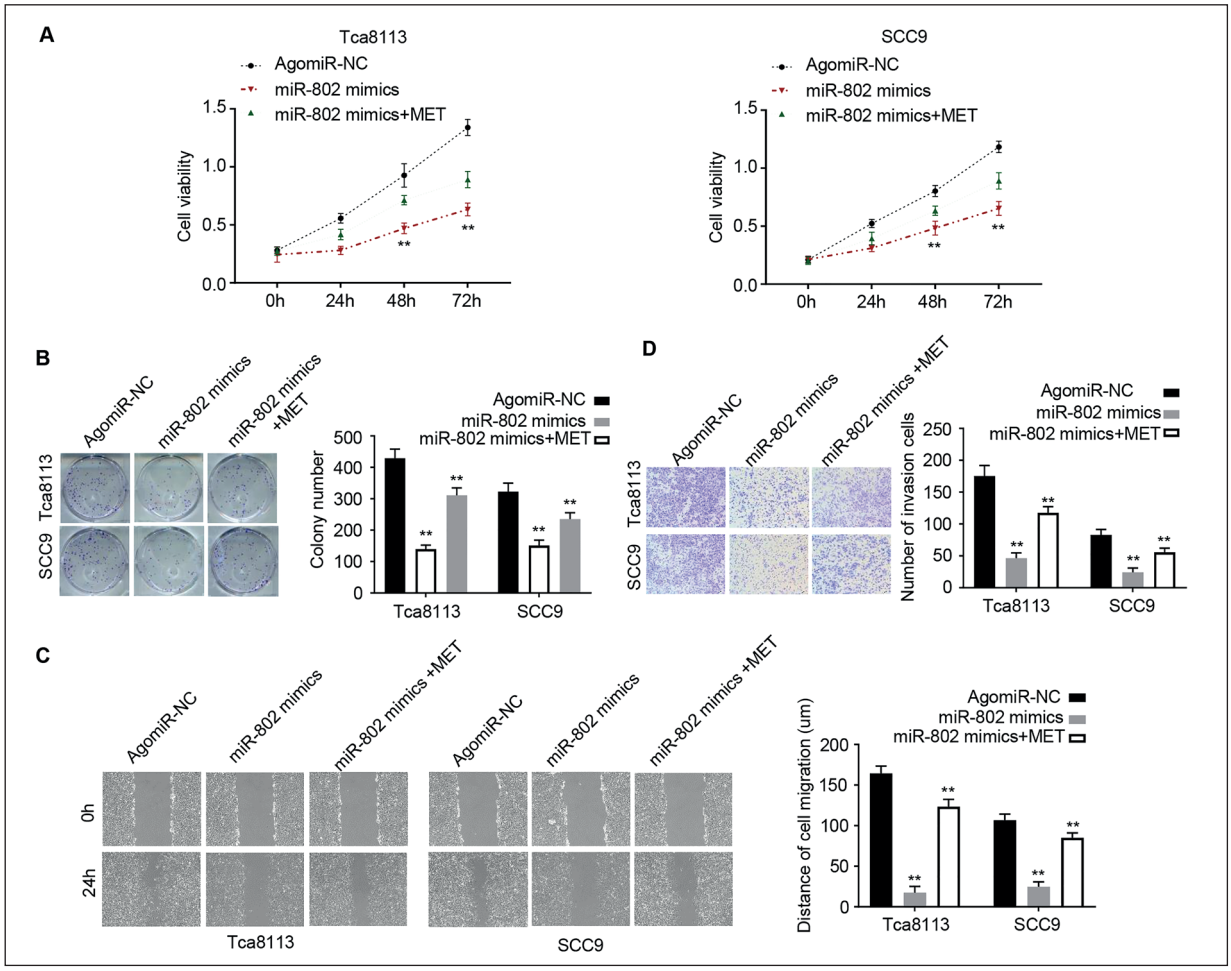

Figure 4. MiR-802 directly targeted MET to inhibit the malignant biological behavior of OSCC. After the co-transfection of miR-802 and MET-overexpressing plasmid in Tca8113 and SCC9 cells. **A**, Cell viability was analyzed by CCK-8 assay. **B**, Colony formation after the co-transfection of miR-802 and MET-overexpressing plasmid in Tca8113 and SCC9 cells (magnification, ×20). **C**, Cell migration test after the co-transfection of miR-802 and MET-overexpressing plasmid, determined by wound healing assay (magnification, ×10). **D**, Cell invasion was analyzed after the co-transfection of miR-802 and MET-overexpressing plasmid, determined by transwell assay (magnification, ×20). Significant differences were analyzed by Student's *t*-test (** $p < 0.01$).

The expressions of lots of miRNAs were found altered in OSCC[19], suggesting the progression of OSCC is epigenetically regulated by miRNAs. Expressions of miR-12b and miR-9 were down-regulated in OSCC, and overexpressing them inhibited cell proliferation[20,21]. Several miRNAs, such as miR-124, miR-491-5p, miR-17/20a, and miR-26a/b, were low expressed in OSCC, but their function was mainly related to the inhibitory effects on cell migration and invasion. In this work, we found that the low expressed miR-802 in OSCC not only plays roles in cell viability, but also regulates cell colony formation, migration and invasion *in vitro*, and even the tumor growth *in vivo*. This finding suggests that miR-802 has a more critical role in the progression of OSCC.

We further dissected the mechanisms of the inhibition effect of miR-802 on OSCC and found that *MET* is the target of miR-802. We validated the direct interaction between *MET* and miR-802 by the Luciferase reporter assay. The negative correlation between *MET* and miR-802 expression confirmed miR-802 could directly regulate *MET* expression *in vivo*. Moreover, overexpressing *MET* in OSCC cells reduced the anti-tumor activity of miR-802. Therefore, miR-802 suppresses OSCC by targeting *MET*. It has been found that *MET* is highly expressed in OSCC patients. Therefore, *MET* is considered a possible prognostic factor and a useful molecular marker to monitor the progression of OSCC[17,22,23]. Notably, two independent studies[14,15] also demonstrated that *MET* is the target of miRNAs in OSCC. Combined with our investigation, we speculate that *MET*-regulated the malignant biological behavior of OSCC can be controlled by multiple miRNAs. In the future, we may try to intervene in the expression of miRNAs and *MET* to treat OSCC.

Conclusions

Taken together, these sudies revealed that miR-802 expression was suppressed in OSCC tissues and cells. The upregulation of miR-802 directly repressed proto-oncogene *MET* and then restrained the malignant biological behavior of OSCC. Therefore, miR-802 is a promising target for treating OSCC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Mignogna MD, Fedele S, Lo Russo L. The World Cancer Report and the burden of oral cancer. Eur J Cancer Prev 2004; 13: 139-142.
2) Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. Nat Rev Cancer 2011; 11: 9-22.
3) Choi S, Myers JN. Molecular pathogenesis of oral squamous cell carcinoma: implications for therapy. J Dent Res 2008; 87: 14-32.
4) Comoglio PM, Trusolino L, Boccaccio C. Known and novel roles of the MET oncogene in cancer: a coherent approach to targeted therapy. Nat Rev Cancer 2018; 18: 341-358.
5) Lo Muzio L, Farina A, Rubini C, Coccia E, Capogreco M, Colella G, Leonardi R, Campisi G, Carinci F. Effect of c-Met expression on survival in head and neck squamous cell carcinoma. Tumour Biol 2006; 27: 115-121.
6) Sun Z, Liu Q, Ye D, Ye K, Yang Z, Li D. Role of c-Met in the progression of human oral squamous cell carcinoma and its potential as a therapeutic target. Oncol Rep 2018; 39: 209-216.
7) Knopf A, Lempart J, Bas M, Slotta-Huspenina J, Mansour N, Fritsche MK. Oncogenes and tumor suppressor genes in squamous cell carcinoma of the tongue in young patients. Oncotarget 2015; 6: 3443-3451.
8) Ambros V. The functions of animal microRNAs. Nature 2004; 431: 350-355.
9) Frixa T, Donzelli S, Blandino G. Oncogenic microRNAs: key players in malignant transformation. Cancers (Basel) 2015; 7: 2466-2485.
10) Ren W, Li C, Duan W, Du S, Yang F, Zhou J, Xing J. MicroRNA-613 represses prostate cancer cell proliferation and invasion through targeting Frizzled7. Biochem Biophys Res Commun 2016; 469: 633-638.
11) Hunt S, Jones AV, Hinsley EE, Whawell SA, Lambert DW. MicroRNA-124 suppresses oral squamous cell carcinoma motility by targeting ITGB1. FEBS Lett 2011; 585: 187-192.
12) Wu X, Gong Z, Sun L, Ma L, Wang Q. Micro RNA-802 plays a tumour suppressive role in tongue squamous cell carcinoma through directly targeting MAP 2K4. Cell Prolif 2017; 50: e12336.
13) Shin K-H, Bae SD, Hong HS, Kim RH, Kang MK, Park N-H. MiR-181a shows tumor suppressive effect against oral squamous cell carcinoma cells by downregulating K-ras. Biochem Biophys Res Commun 2011; 404: 896-902.
14) Fukumoto I, Koshizuka K, Hanazawa T, Kikkawa N, Matsushita R, Kurozumi A, Kato M, Okato A, Okamoto Y, Seki N. The tumor-suppressive microRNA-23b/27b cluster regulates the MET oncogene in oral squamous cell carcinoma. Int J Oncol 2016; 49: 1119-1129.
15) Li M, Li Z, Wang X, Wang Y, Zhao C, Wang L. Function of miR-152 as tumor suppressor in oral squa-

mous cell carcinoma cells by targeting c-MET. Oncol Rep 2018; 39: 1173-1180.

16) Zhang X, Hu F, Liu L, Xu B. Effect of silencing of mediator of DNA damage checkpoint protein the on the growth of oral squamous cell carcinoma in vitro and *in vivo*. Eur J Oral Sci 2019; 127: 494-499.

17) Chen YS, Wang JT, Chang YF, Liu BY, Wang YP, Sun A, Chiang CP. Expression of hepatocyte growth factor and c-met protein is significantly associated with the progression of oral squamous cell carcinoma in Taiwan. J Oral Pathol Med 2004; 33: 209-217.

18) Freudlsperger C, Alexander D, Reinert S, Hoffmann J. Prognostic value of c-Met expression in oral squamous cell carcinoma. Exp Ther Med 2010; 1: 69-72.

19) Wiklund ED, Gao S, Hulf T, Sibbritt T, Nair S, Costea DE, Villadsen SB, Bakholdt V, Bramsen JB, Sørensen JA. MicroRNA alterations and associated aberrant DNA methylation patterns across multiple sample types in oral squamous cell carcinoma. PLoS One 2011; 6: e27840.

20) Shiiba M, Shinozuka K, Saito K, Fushimi K, Kasamatsu A, Ogawara K, Uzawa K, Ito H, Takiguchi Y, Tanzawa H. MicroRNA-125b regulates proliferation and radioresistance of oral squamous cell carcinoma. Br J Cancer 2013; 108: 1817-1821.

21) Yu T, Liu K, Wu Y, Fan J, Chen J, Li C, Yang Q, Wang Z. MicroRNA-9 inhibits the proliferation of oral squamous cell carcinoma cells by suppressing expression of CXCR4 via the Wnt/β-catenin signaling pathway. Oncogene 2014; 33: 5017-5027.

22) Marshall DD, Rornberg LJ. Overexpression of scatter factor and its receptor (c-met) in oral squamous cell carcinoma. Laryngoscope 1998; 108: 1413-1417.

23) Muzio LL, Leonardi R, Mignogna M, Pannone G, Rubini C, Pieramici T, Trevisiol L, Ferrari F, Serpico R, Testa N. Scatter factor receptor (c-Met) as possible prognostic factor in patients with oral squamous cell carcinoma. Anticancer Res 2004; 24: 1063-1070.