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ORIGINAL RESEARCH

RETRACTED ARTICLE: miR-182 promotes tumor growth and increases chemoresistance of human anaplastic thyroid cancer by targeting tripartite motif 8

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Yao Liu
Bing Zhang
Tiefeng Shi
Huadong Qin

The Fourth Department of General Surgery, The Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, People's Republic of China

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Abstract: Chemotherapy is one of the most effective forms of cancer treatment and has been used in the treatment of various malignant tumors. We have gained significant insight into the mechanisms of chemoresistance but the details of the molecular mechanisms remain unclear. In the present study, we found that tripartite motif 8 (TRIM8) expression was downregulated in anaplastic thyroid cancer (ATC) tissues and cell lines. This downregulation of TRIM8 was significantly correlated with the upregulation of miR-182 in human ATC tissues. Bioinformatic analysis and luciferase reporter assays identified TRIM8 as a direct target of miR-182 in ATC. A functional assay using an MTT assay and colony formation showed that miR-182 induced cellular growth by repressing TRIM8 expression. Additionally, overexpressed miR-182 contributed to the chemoresistance of ATC cells by the repression of TRIM8 expression. In conclusion, these results demonstrate that miR-182/TRIM8 may be a therapeutic target for the treatment of chemoresistant human thyroid papillary cancer.

Keywords: miR-182, TRIM8, ATC, growth, chemoresistant

Introduction

Anaplastic thyroid carcinoma (ATC) is the most common aggressive histology subtype of thyroid malignancy and causes up to 14%–39% of thyroid cancer-related deaths.[1,2] Although treatment strategies for patients with ATC include surgery, radiotherapy, and chemotherapy, these therapies sometimes fail due to therapeutic resistance.[3] However, the underlying molecular mechanisms of this resistance remain incompletely understood.

MicroRNAs (miRNAs) are a class of small, endogenous, noncoding RNAs (~22 nucleotides in length) that act as negative regulators of target genes by binding to the 3′-untranslated regions (3′-UTR) of genes, resulting in gene silencing and/or translational repression. A growing number of studies have found that miRNAs function as either onco-miRNAs or tumor suppressors in different steps of human cancers and are associated with tumor initiation, development, and progression.[4–6] Some miRNAs are dysregulated in ATC, including miR-618,[7] miR-200,[8] miR-99a,[9] miR-206,[10] and miR-20a.[11] A recent study reported overexpression of miR-182 in papillary thyroid carcinoma compared to the levels in adjacent normal tissues.[12] However, the specific role of miR-182 in anaplastic thyroid cancer and the underlying mechanisms remain to be established.

In this study, we confirmed the upregulation of miR-182 and downregulation of tripartite motif 8 (TRIM8) in human ATC tissues and cells. Additionally, we found

Correspondence: Huadong Qin
The Fourth Department of General Surgery, The Second Affiliated Hospital of Harbin Medical University, 157 Baojian Road, Harbin, 150086, People's Republic of China
Email huadongqinaa@163.com

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that miR-182 induced cellular growth by directly targeting TRIM8 while increasing chemoresistance to cisplatin. Our study demonstrates that miR-182 is a novel regulator of cisplatin sensitivity in ATC and may be exploited as a potential new therapeutic target to improve the efficacy of this drug for chemotherapy.

Methods

Tumor tissue samples

A total of 30 pairs of ATC and the adjacent normal thyroid tissues were obtained from The Second Affiliated Hospital of Harbin Medical University from 2010 to 2014. Tissues were immediately stored at −80°C and histologically confirmed. Written informed consent was obtained from all patients, and the study approved by the Human Research Ethics Committee of The Second Affiliated Hospital of Harbin Medical University.

Cell culture and transfection

The human anaplastic thyroid carcinoma cell lines, SW1736 and 8305C, and human thyroid follicular epithelial cells (Nthy-ori 3-1) were cultured in Dulbecco's Modified Eagle's Medium supplemented with 10% fetal bovine serum, containing 100 U/mL penicillin and 100 mg/mL streptomycin. Cells were maintained at 37°C in a humidified atmosphere containing 5% CO_2.

miR-182 mimics, miR-182 inhibitor, and scrambled miRNA were synthesized and purified by GenePharma (Shanghai, People's Republic of China). The CDS sequence of TRIM8 was cloned into the pcDNA3.1(+) vector (Promega, WI, USA) as previously described and then directly confirmed by DNA sequencing. All transfections were carried out using Lipofectamine 2000 (Invitrogen, CA, USA) according to the manufacturer's instructions.

Quantitative real-time PCR

Total RNA from tissues and cell lines was extracted with TRIzol (Invitrogen) according to the manufacturer's instructions. The RNAs were reverse transcribed to cDNA using the PrimeScript™ real-time-polymerase chain reaction (PCR) Kit (Takara, Shiga, Japan). And then quantitative PCR was performed on iQ5 real-time PCR detection system (Bio-Rad Laboratories Inc., Hercules CA, USA) with SYBR Premix EX Taq (Takara). U6 and β-actin were used as endogenous controls for detection of miRNA and messenger RNA (mRNA), respectively. All measurements were carried out in triplicate. The fold changes in gene expression were calculated using the $2^{-\Delta\Delta Ct}$ method. The primer sequences were used as follows: TRIM8 forward: 5′CGTGGAGATCCGAAGGAATGA3′; reverse: 5′CAGGCGCTTGTCTGACTCG3′; GAPDH forward: 5′GGGAAACTGTGGCGTGAT-3′; reverse: 5′GGGTGTC GCTGTTGAAGT3′.

Dual-luciferase reporter assay

The TRIM8 3′-UTR containing the miR-182 targeting sequence was cloned into the pGL3 basic plasmid as described previously.[13] In dual-luciferase reporter assays, cells were cultured to ~80% confluence in a six-well plate, and then co-transfected either pGL3-WT-TRIM8-3′-UTR (wild-type) or pGL3-Mut-TRIM8-3′-UTR (mutant) vector with the miR-182 mimic for 48 hours. Luciferase activities were measured using the Dual-Luciferase Reporter Assay system (Promega) and normalized to firefly luciferase activity.

MTT assay

Cells transfected with RNA oligonucleotides or plasmids for different time periods were seeded in 96-well plates (5×10^3/well). The cells were treated with various concentrations of cisplatin for various times, and untreated cells served as a control. Subsequently, 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (Sigma-Aldrich Co., St Louis, MO, USA) was used and OD value detected at 490 nm on a Bio-Tek Universal Microplate Spectrophotometer (Bio-Tek Instruments, Winooski, VT, USA).

Western blot

Cell lysed using RIPA buffer containing protease inhibitors and the total protein was extracted from the lysate, followed by centrifugation at 12,000× *g* for 10 minutes. A total of 30 μg of protein were resolved by SDS–polyacrylamide gel electrophoresis and transferred to PVDF membranes (Bio-Rad Laboratories Inc.). The membranes were incubated with the primary antibodies anti-TRIM8 (all from Abcam, Cambridge, MA, USA) at 4°C overnight, followed by incubation with horseradish peroxidase-conjugated secondary antibodies (Santa Cruz, CA, USA) for 2 hours. The protein band was detected by chemiluminescence with Pierce ECL kits (Thermo Fisher Scientific, Waltham, MA, USA). GAPDH was used as an internal control.

Colony formation assay

After the transfection of RNA oligonucleotides or plasmids for 24 hours, the cells were harvested and resuspended in complete medium containing 10% fetal bovine serum. Subsequently, 500 cells were seeded into one well of a six-well plate. These cells were cultured under standard

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culture conditions for 14 days. The colonies were fixed with methanol for 15 minutes and stained with crystal violet for 20 minutes. A light microscope was used to count the number of colonies as previous described.[14]

Statistical analysis

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis. The data are presented as the mean ± standard deviation of at least three independent experiments. Two groups were compared with Student's *t*-test. *P*-values <0.05 were considered to indicate significant differences.

Results

The expression levels of miR-182 and TRIM8 in ATC tissues and cell lines

Increased levels of miR-182 were previously reported in papillary thyroid carcinoma.[12] However, its expression in anaplastic thyroid cancer had not been investigated. Here, we measured miR-182 expression in 30 human ATC tissues and adjacent normal tissues using a quantitative real-time-PCR assay. As shown in Figure 1A, miR-182 expression was obviously upregulated in ATC tissues compared with the expression in the corresponding adjacent normal tissues. Similarly, we found that the expression level of miR-182 was evidently upregulated in ATC cell lines (SW1736 and 8305C) compared with miR-182 levels in human thyroid follicular epithelial cells (Nthy-ori 3-1; Figure 1B). Next, we measured TRIM8 expression in ATC tissues and cell lines. As shown in Figure 1C and D, TRIM8 expression was significantly lower in ATC tissues and cell lines. Collectively, our findings suggest that upregulated miR-182 may function as an oncogene and the decreased levels of TRIM8 may function as a tumor suppressor and be involved in the tumorigenesis of ATC.

miR-182 acts as a negative regulator of TRIM8 in ATC

As miRNAs inhibit by binding to the 3′-UTR of their target mRNAs, we use the miRNA target prediction website www.microRNA.org and TargetScan 6.2 and found that TRIM8 is a potential target of miR-182 (Figure 2A). To test this, a dual-luciferase reporter system was used with co-transfection of miR-182 mimic or inhibitor and a luciferase reporter plasmid containing a wild-type or mutant 3′-UTR of human TRIM8. As shown in Figure 2B and C, the results from the dual-luciferase reporter assay revealed that

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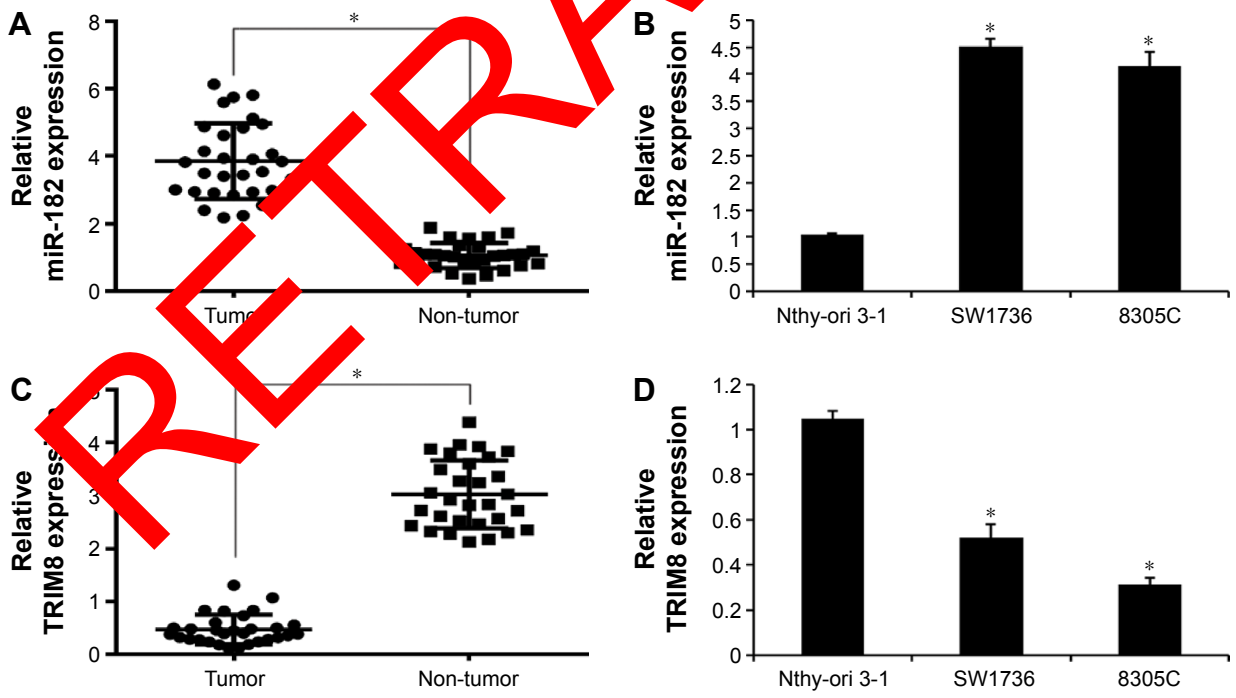

Figure 1 The expression levels of miR-182 and TRIM8 in ATC tissues and cell lines.

Notes: (**A**) qRT-PCR assay detected the expression of miR-182 in ATC tissue and adjacent normal tissue. (**B**) qRT-PCR assay detected the expression of miR-182 in ATC cell lines (SW1736 and 8305C) and human thyroid follicular epithelial cells (Nthy-ori 3-1). (**C**) qRT-PCR assay detected the expression of TRIM8 in ATC tissue and adjacent normal tissue. (**D**) qRT-PCR assay detected the expression of TRIM8 in ATC cell lines (SW1736 and 8305C) compared with that of human thyroid follicular epithelial cells (Nthy-ori 3-1). *$P<0.01$ versus Nthy-ori 3-1 group.

Abbreviations: ATC, anaplastic thyroid cancer; qRT-PCR, quantitative real-time-polymerase chain reaction; TRIM8, tripartite motif 8.

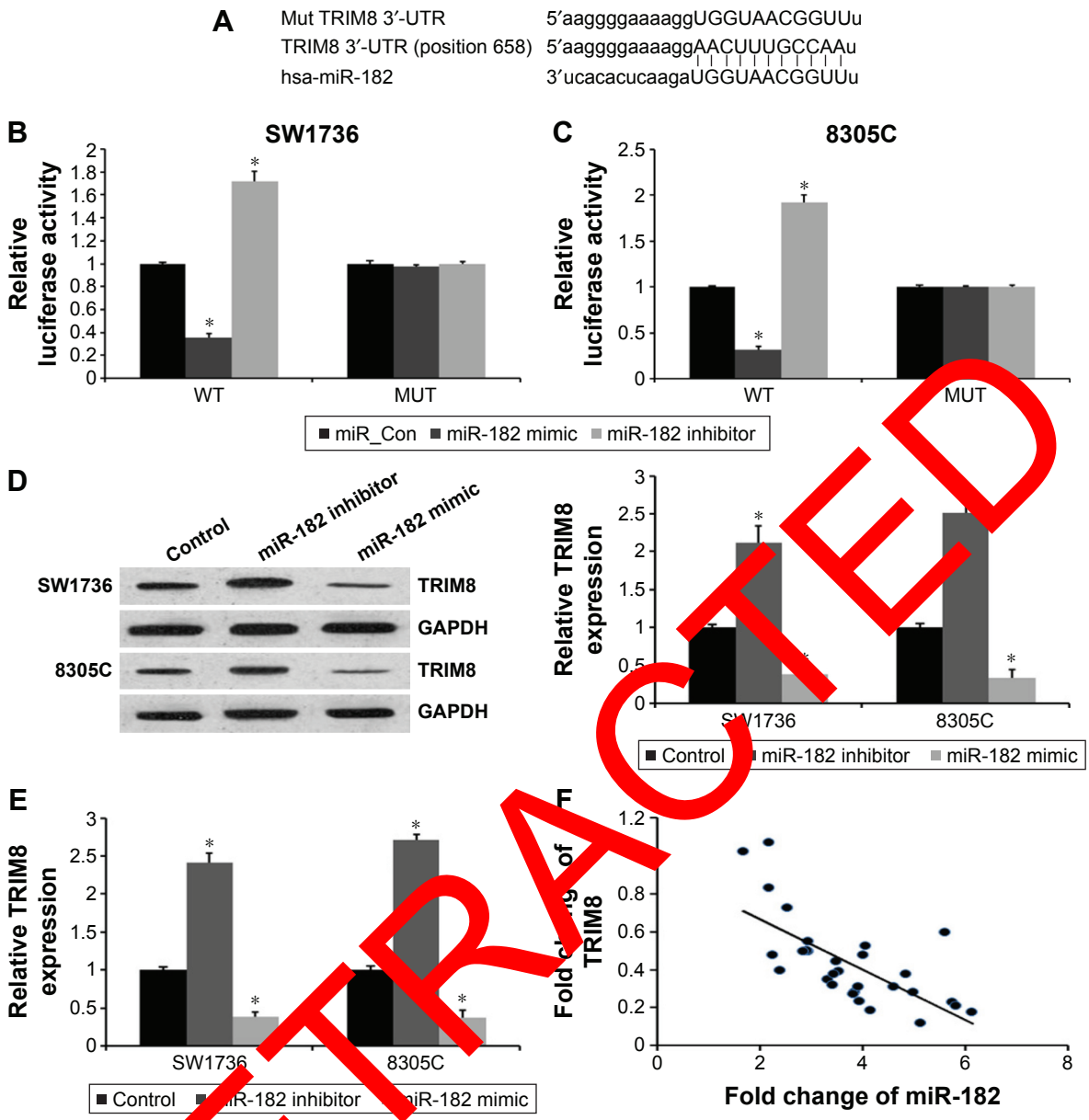

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Figure 2 miR-182 directly targets TRIM8 in ATC cells.

Notes: (**A**) Sequence alignment of miR-182 and 3′-UTR of TRIM8. Luciferase reporter assay. SW1736 (**B**) and 8305C (**C**) cells were transiently co-transfected with miR-182 mimics or miR-182 inhibitor and WT or MUT 3′-UTR of TRIM8 with miRNAs as indicated. (**D**) Western blot assay revealed the effects of miR-182 on the expression levels of TRIM8 in SW1736 and 8305C cells. (**E**) qRT-PCR assay revealed the effects of miR-182 inhibitor and miR-182 mimic on the expression levels of TRIM8 in SW1736 and 8305C cells. (**F**) Correlation of miR-182 levels with TRIM8 mRNA levels was examined by qRT-PCR in 30 cases of ATC tissues. Data are presented as mean±SD from three independent experiments. *$P<0.05$ versus control group.

Abbreviations: ATC, anaplastic thyroid cancer; SD, standard deviation; UTR, untranslated regions; TRIM8, tripartite motif 8; mRNA, messenger RNA; SD, standard deviation; WT/MUT, wild-type/mutant.

the miR-182 mimic significantly inhibited luciferase activity and the miR-182 inhibitor increased luciferase activity when co-transfected with the wild-type TRIM8 3′-UTR. The miR-182 mimic and inhibitor failed to affect the expression of luciferase constructs with mutated target sites, suggesting that miR-182 directly targets the 3′-UTR of TRIM8. Additionally, mRNA and protein expression levels of TRIM8 after miR-182 overexpression or inhibition were measured by quantitative real-time-PCR and Western blotting in both SW1736 and 8305C cells (Figure 2D and E), confirming that miR-182 negatively regulates TRIM8 expression by directly targeting the 3′-UTR. Additionally, we analyzed the relationship between TRIM8 and miR-182 expression in the same ATC tissues. As shown in Figure 2F, the mRNA levels of miR-182 and TRIM8 were inversely correlated as determined by Spearman's correlation analysis (R=–0.695, $P<0.01$). Taken together, these data strongly supported the model that TRIM8 is a direct target of miR-182 in ATC.

miR-182 promotes cellular growth by repressing TRIM8 expression

To elucidate the role of miR-182 in the development and progression of ATC, two ATC lines (SW1736 and 8305C) were transfected using Lipofectamine 2000 transduction with miR-182 mimics, inhibitors, or a negative control. The MTT assay showed that overexpressed miR-182 dramatically induced the proliferation of ATC in both SW1736 and 8305C cells. In contrast, miR-182 inhibitors inhibited cell proliferation in SW1736 and 8305C (Figure 3A and B). The colony formation assay indicated that miR-182 upregulation significantly promoted the proliferation rate of SW1736 and 8305C cells compared to the control, but when cells were transfected by the miR-182 inhibitor, there was miR-182 suppression and decreased proliferation (Figure 3C). Interestingly, the increased MTT OD value and colony formation induced by miR-182 mimic could be reversed by TRIM8 in ATC (Figure 3B and C). Collectively, we conclude that miR-182 induces cell proliferation through TRIM8 in ATC cells.

miR-182 enhances the cisplatin resistance of ATC cells

Previous studies found that miRNAs may play a role in the chemosensitivity or chemoresistance of several cancers.[14–16] We next investigated the role of miR-182 on the chemoresistance of ATC cells to cisplatin. ATC cells were transfected with a miR-182 mimic or miR-182 inhibitor or co-transfected with miR-182 and TRIM8, and th[illegible]re tested for their sensitivity to cisplatin. As sh[illegible]wn in Fig[illegible]e 4, the MTT assay was used to evaluate the [illegible]oliferation [illegible] SW1736 and 8305C in response to 2[illegible]nM cisp[illegible]tin trea[illegible]ent for different amounts of time (24, 48, [illegible]d 72 [illegible]s). Next, an MTT assay was used to e[illegible]uate [illegible]e proliferation of SW1736 and 8305C in re[illegible]onse to [illegible] hours [illegible] varying concentrations

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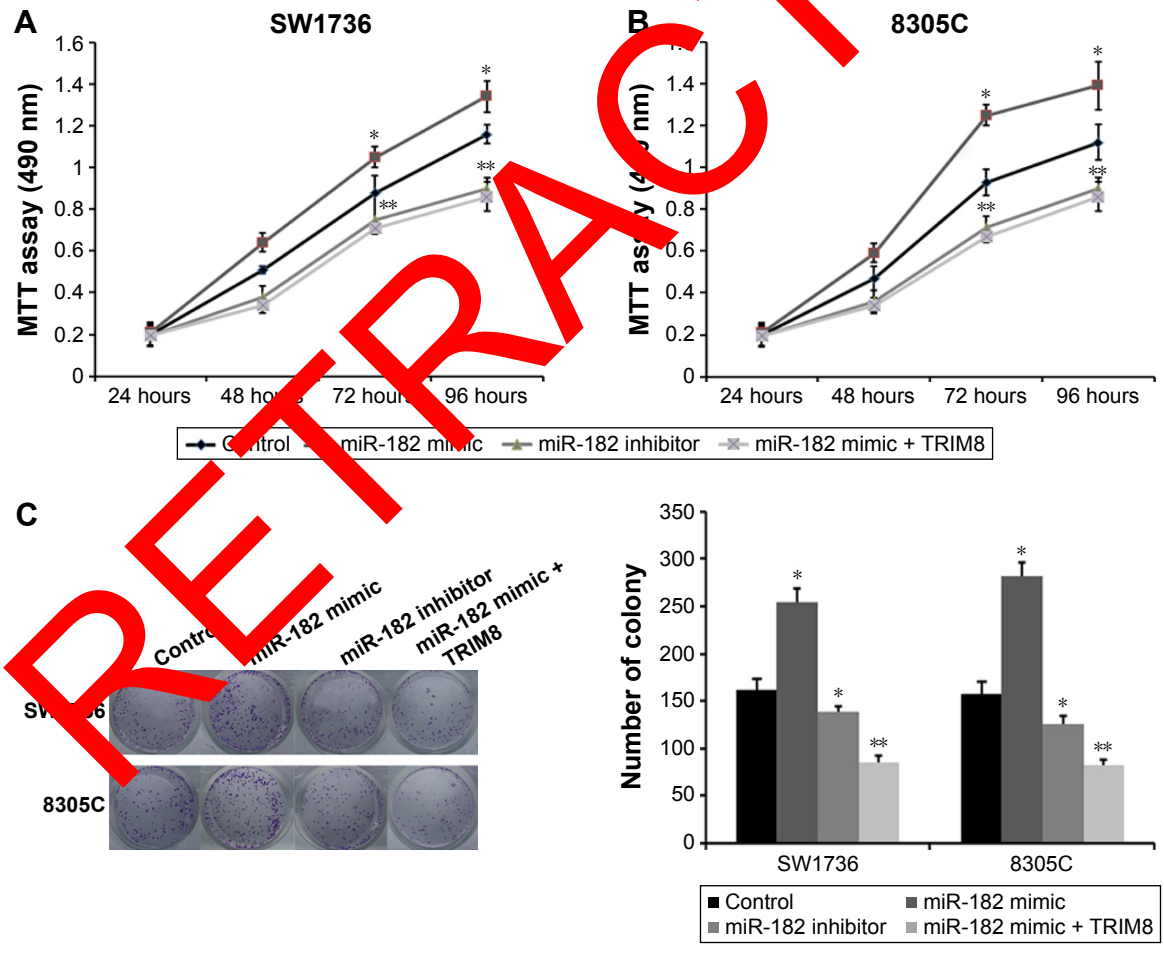

Figure 3 miR-182 affects ATC cell proliferation and colony formation.

Notes: An MTT assay was performed to detect the viability of SW1736 (**A**) and 8305C (**B**) cells 24, 48, 72, and 96 hours after being transfected with miR-182 mimics, miR-182 inhibitor, or co-transfected with miR-182 mimics + TRIM8. (**C**) A colony formation assay was performed to detect the effect of miR-182 on the growth of SW1736 and 8305C cells. The colonies were stained with crystal violet and then counted. Data are expressed as the mean ± SD of at least three independent experiments (*$P<0.01$ vs control group, **$P<0.01$ vs miR-182 group).

Abbreviations: ATC, anaplastic thyroid cancer; SD, standard deviation; TRIM8, tripartite motif 8.

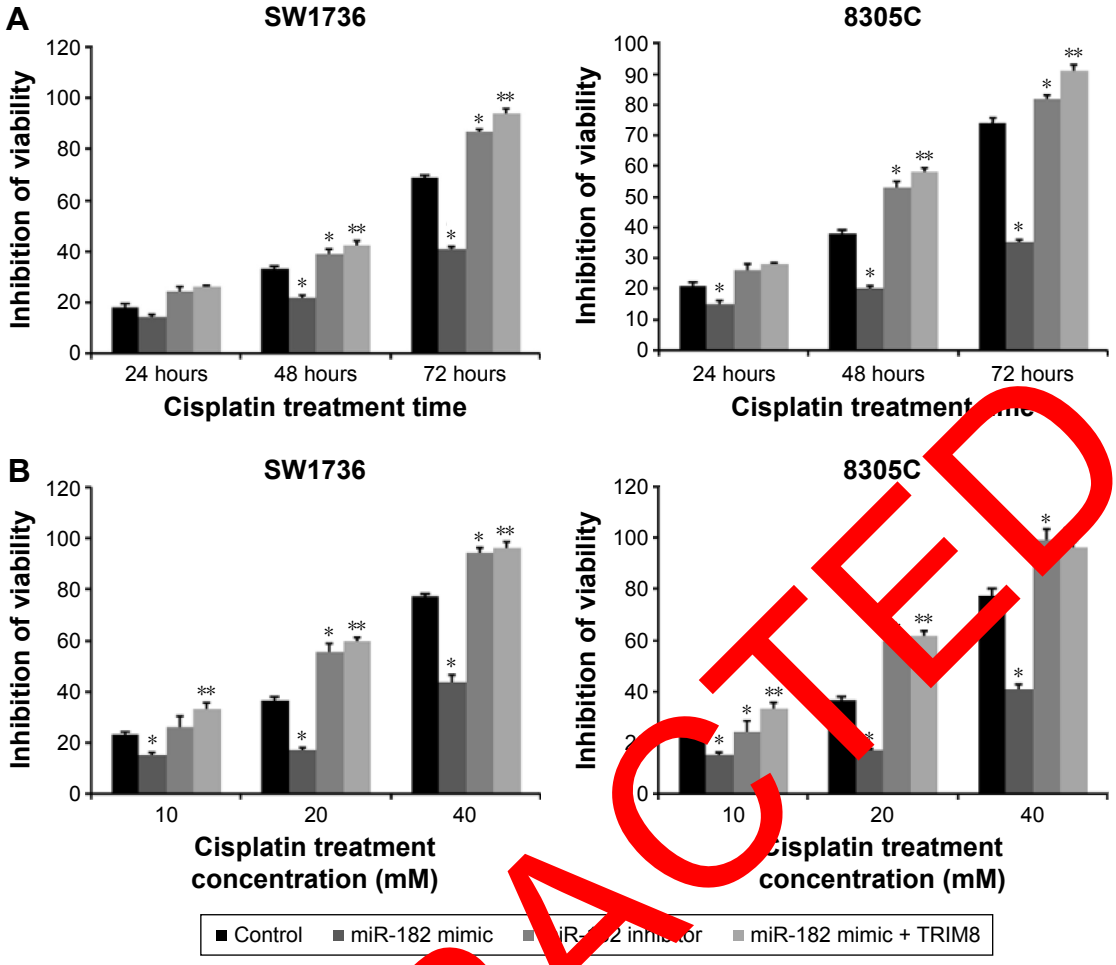

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Figure 4 miR-182 attenuates ATC cells sensitivity to cisplatin.
Notes: An MTT assay was performed to detect the viability of SW1736 (**A**) and 8305C (**B**) cells 24, 48, 72, and 96 hours after being transfected with miR-182 mimics, miR-182 inhibitor, or co-transfected with miR-182 mimics + TRIM8. (**B**) MTT assay was performed to assess the inhibition of ATC cells viability. The cells were treated with cisplatin at different concentrations (10, 20, and 40 mM) for 48 hours. Data are expressed as the mean ± SD of at least three independent experiments (*$P<0.05$ vs control group, **$P<0.01$ vs miR-182 mimic group).
Abbreviations: ATC, anaplastic thyroid cancer; SD, standard deviation; TRIM8, tripartite motif 8.

(10, 20, and 40 mM) of cisplatin. The results indicated that miR-182 enhanced the cisplatin chemoresistance of SW1736 and 8305C cells, as evidenced by increases in viability. Cells transfected with the miR-182 mimic exhibited a significantly lower sensitivity to cisplatin, which could be reversed by the miR-182 inhibitor or by co-transfection with TRIM8. Based on these results, we concluded that miR-182 can increase the chemoresistance of ATC cells to cisplatin by suppressing TRIM8.

Discussion

For the first time, we determined the role and mechanism of miR-182 in ATC cell growth and cellular resistance to cisplatin. We found that miR-182 expression was upregulated in ATC, and miR-182 levels were inversely correlated with TRIM8 mRNA expression in ATC tissues. In addition, miR-182 can promote cell growth and chemoresistance of ATC by directly targeting the 3′-UTR of TRIM8.

Many recent studies have demonstrated critical roles for miRNAs in the progression of various malignant tumors.[17–19] However, only a few studies have investigated potential roles for miRNAs in ATC.[20] For example, miR-206 was reported to inhibit metastasis-relevant traits by degrading MRTF-A in anaplastic thyroid cancer.[10,21] Shao et al showed that miR-4295 promotes cell proliferation and invasion in anaplastic thyroid carcinoma via CDKN1A.[22] miR-182 functions as a tumor suppressor or oncogene in various cancers.[23,24] Tang et al showed that miR-182 acts as a tumor suppressor and inhibits proliferation in gastric cancer.[25] However, Wang et al showed that miR-182 is upregulated and targets CEBPA in hepatocellular carcinoma.[26] Increased levels of miR-182 were found in tumorigenesis

of high-grade serous ovarian carcinoma.[27] Additionally, miR-182 was found to target CHL1 and control tumor growth and invasion in papillary thyroid carcinoma.[28] In this study, miR-182 expression was obviously increased in ATC tissues and cell lines. Higher levels of miR-182 promoted cellular growth in ATC cells, indicating that miR-182 functions as an oncogene in ATC.

The superfamily of TRIM-containing proteins is defined by the presence of a TRIM composed of a RING domain, one or two B-box motifs, and a coiled-coil region. These proteins participate in diverse biological processes, including important roles in immune responses by regulating various signaling pathways.[29,30] TRIM8, a member of the TRIM family, was reported to be an oncogene that is involved in the progression of various cancers.[31,32] In contrast, in glioma and renal cell carcinoma, TRIM8 was reported to act as a tumor suppressor that showed lowered expression.[13,33] However, the expression and role of TRIM8 in ATC was not previously reported. In this study, for the first time, we determined that TRIM8 is a direct target of miR-182 and that TRIM8 expression was downregulated in ATC tissues and cell lines. Overexpressed TRIM8 reversed miR-182-induced cell growth in ATC. Downstream signaling components of TRIM8 may be involved in cell migration and invasion. Further studies are needed to investigate these putative functions.

Chemoresistance has significantly limited treatment efficacy for many cancers.[34–36] Recently, miRNAs were discovered to play a role in cisplatin resistance in various cancers, including ATC.[37] However, the mechanism of this chemoresistance was poorly understood. In this study, we found that miR-182 reduced chemosensitivity to cisplatin by repressing TRIM8 expression.

In summary, we determined that miR-182 was significantly upregulated in ATC tissues and cells. Additionally, miR-182 inhibited cell proliferation and growth and mediated the chemosensitivity of ATC cells to cisplatin by targeting TRIM8. These findings may provide a novel potential biomarker for cancer diagnosis and treatment and warrant further study.

Author contributions

YL, BZ, and TS designed the study, carried out the experiments, and drafted the manuscript; TS and HQ participated in the experiments and data analysis. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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