

Propofol suppresses migration, invasion, and epithelial-mesenchymal transition in papillary thyroid carcinoma cells by regulating miR-122 expression

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Abstract. – **OBJECTIVE:** Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer and PTC patients with invasion and metastases features have a poor prognosis. Propofol is an intravenous anesthetic which has been reported to be involved in cancer progression. However, the roles of propofol and the exact molecular mechanisms in PTC remain largely unknown.

MATERIALS AND METHODS: Cells viability was detected using the CCK-8 (Cell Counting Kit-8) assay. The expressions of microRNA-122 (miR-122) were measured by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). Cells migration and invasion abilities were investigated by transwell. Western blot was used to demonstrate the expression of metastasis- and EMT-related proteins.

RESULTS: We found a significant inhibition of cells viability in TPC-1 and IHH-4 cells compared to Nthy-ori 3-1 cell line after exposed to propofol. The functional experiment showed propofol could suppress cells migration, invasion, and EMT in PTC. Subsequently, a decreased expression of miR-122 was detected in TPC-1 and IHH-4 cells, while a promotion of propofol on miR-122 expression was identified. Furthermore, we found miR-122 could inhibit cells migration, invasion, and EMT in PTC. Next, the rescue study indicated that miR-122 inhibitor transfection could attenuate propofol-induced suppression on TPC-1 and IHH-4 cells metastasis.

CONCLUSIONS: Propofol suppresses migration, invasion, and EMT in papillary thyroid carcinoma cells by regulating miR-122 expression. The findings may indicate significant clinical im-

plications for anesthetic agents to prevent metastasis and improve outcomes in papillary thyroid carcinoma.

Key Words:

PTC, Propofol, MiR-122, Metastasis, EMT.

Abbreviations

PTC = Papillary thyroid carcinoma; MiR-122 = microRNA-122; qRT-PCR = quantitative Real Time-Polymerase Chain Reaction; miRNAs = microRNAs; FTC = follicular thyroid carcinoma; ATC = anaplastic thyroid cancer; CCK-8 = Cell Counting Kit-8.

Introduction

Thyroid carcinoma is the most common thyroid malignancy, accounting for about 1% of systemic malignancies, including papillary, follicular, undifferentiated, and medullary cancer¹. Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for more than 80% of thyroid cancers². PTC patients usually are accompanied by lower malignancy and better prognosis. However, PTC patients with invasion and metastases features, such as proliferation and detachment of tumor cells from the primary tumor, extra-thyroidal invasion, angiogenesis, lymph node or vascular dissemination, advanced tumor-node-metastasis stage or recurrences, have a poor prognosis^{3,4}. Therefore, the identification

of the metastasis process will make us find a novel diagnosis or therapeutic intervention for PTC.

Propofol (2,6-diisopropylphenol) is a predominant intravenous hypnotic agent commonly used for induction and maintenance of anesthesia and widely administered for sedation in the ICU⁵. Propofol not only has multiple anesthetic advantages, but also exerts diverse non-anesthetic effects⁶. Propofol has an additional biologic activity of anti-inflammatory and antioxidant, can decrease the production of proinflammatory cytokines, alter the expression of nitric oxide, and inhibit neutrophil function⁷. Moreover, it has antiemetic, analgesic, and neuroprotective effects⁶⁻⁸. In addition, increasing evidence has revealed the functional roles of propofol in diverse cancer types. Chen et al⁹ identified propofol suppressed proliferation and migration of papillary thyroid cancer cells by the down-regulation of lncRNA ANRIL. Then, it will be of great value to explore the connection, as well as the molecular mechanism between propofol and PTC. MicroRNAs (miRNAs) are endogenous, single-stranded, noncoding RNAs with 18 to 25 nucleotides in size. MiRNAs are implicated in many biological and pathological processes, such as proliferation, differentiation, metastasis, and apoptosis. Furthermore, various human diseases, including cancer, are associated with the aberrant expression of miRNAs¹⁰⁻¹². MiRNAs expression is deregulated in many types of human tumors, including thyroid cancers. Also, it could be responsible for tumor initiation and progression¹², which suggests that it is a hallmark of the cancer. MicroRNA-122 (miR-122) is considered to be a novel tumor-related miRNA implicated in tumor progression via functioning as a tumor suppressor or oncogene^{13,14}. Recently, emerging studies have drawn the focus on the role of miR-122 in thyroid carcinoma. Reddi et al^{15,16} indicated that miR-122 exerted a tumor suppressor activity in follicular thyroid carcinoma (FTC) and that miR-122 up-regulation may act as a tumor growth modulator by inhibiting angiogenic pathways. Also, they showed that miR-122 acts as tumor suppressor miRNA involved in the development of anaplastic thyroid cancer (ATC). However, the roles of miR-122 and the exact molecular mechanisms in PTC remain largely unknown. In the present study, we found propofol could suppress cells migration, invasion, and EMT in PTC, while the interaction between propofol and miR-122 was identified. Propofol could exert its inhibitory effects

on PTC cells by regulating miR-122. These findings indicated significant clinical implications for propofol agents to prevent metastasis and improve outcomes in papillary thyroid carcinoma.

Materials and Methods

Cell Culture and Propofol Exposure

Human PTC cell lines, including TPC-1 and IHH-4, and normal human thyroid follicular epithelial Nthy-ori 3-1 cell line, were purchased from American Type Culture Collection (ATCC; Manassas, VA, USA). Human PTC cell lines were maintained in Dulbecco's Modified Eagle's Medium (DMEM; Invitrogen, Carlsbad, CA, USA). The Nthy-ori 3-1 cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640) medium (Invitrogen, Carlsbad, CA, USA). Each medium was supplemented with 10% fetal bovine serum (FBS; Gibco, Rockville, MD, USA). All cells were incubated at 37°C in a humidified incubator with 5% CO₂. Propofol was obtained from Sigma-Aldrich (St. Louis, MO, USA). Propofol was dissolved in dimethyl sulfoxide (DMSO) following the manufacturer's instructions. After that, cells were treated with propofol from 0 to 10 µg/mL for 48 h, while the cells treated by the same volume of the vehicle were regarded as blank controls.

Cell Transfection

The miRNA mimic or inhibitor targeting miR-122 (miR-122 or anti-miR-122) and their corresponding negative controls (miR-NC or anti-miR-NC) were synthesized by the GenePharma Corporation (Shanghai, China). Cell transfection was performed by Lipofectamine 3000 reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions.

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

Total RNA was extracted from PCT cells using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. The first-strand cDNA was synthesized from total RNA by using the QuantiTect Reverse Transcription Kit (Qiagen, Hilden, Germany). Then, qRT-PCR was carried out by the SYBR Green II core kit (Qiagen, Hilden, Germany) and an ABI 7500 real-time RT-PCR system under the following procedure: 95°C for 10 min, followed by 40 cycles of 95°C for 15 s, 60°C for 20 s, and 72°C for 40 s. The expression of U6 served as an internal control. The relative ex-

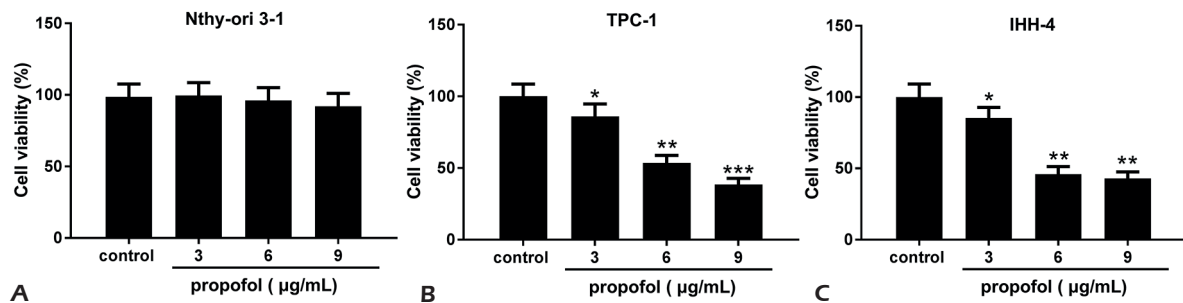


Figure 1. Propofol inhibited PTC cells viability. Cells viability was measured by CCK-8 assay in normal human thyroid follicular epithelial Nthy-ori 3-1 cell line (A) and human PTC cell lines (TPC-1 and IHH-4) (B-C) after exposed to propofol for 48 h at 3/6/9 µg/ml. * $p < 0.05$.

pressions of miR-122 were calculated by the $2^{-\Delta\Delta Ct}$ method. The primer sequences used in this study were listed as follows: miR-122 forward, 5'-AG-CGTGGAGTGTGACAATGG-3' and reverse, 5'-GTCGTATCCAGTGCAGGGTCCGAG-3'; U6 forward, 5'-CTCGCTTCGGCAGCACA-3' and reverse, 5'-AACGCTTCACGAATTTGCGT-3'.

Transwell Assay

Transwell assay was conducted to measure cell migration and invasion using a 24-well. The cells, once treated or transfected at a concentration of 1×10^5 /ml in 100 ml serum-free Dulbecco's Modified Eagle's Medium (DMEM), were seeded into the upper with or without a Matrigel chamber. The lower chamber was filled with 500 µl Dulbecco's Modified Eagle's Medium (DMEM) containing 10% fetal bovine serum (FBS). After incubation for 48 h at 37°C, the non-migrated or non-invasion cells in the upper chamber were removed with a cotton swab, and the cells in the lower chamber were fixed and stained by 0.1% crystal violet for 10 min at room temperature. Five fields randomly selected were counted using a microscope.

Cell Viability

Cell viability was detected using the Cell Counting Kit-8 (CCK-8) assay after treated with different concentration propofol. Briefly, cells were seeded at a concentration of 5000 per well into 96-well plates and cultured at 37°C overnight. Then, 10 µl CCK-8 solution was added to each well and incubated for another 4 h at 37°C. The absorbance was read at 450 nm using a microplate reader.

Western Blot

Protein was isolated by using radioimmuno-precipitation assay (RIPA) lysis buffer (Beyotime, Shanghai, China) from all PTC cells after

treatment and was calculated by enhanced chemiluminescence (ECL) bicinchoninic acid (BCA) Protein Assay Kit (Beyotime, Shanghai, China). 50 µg proteins were separated into 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). Then, proteins were blocked with 5% non-fat milk for 1 h at room temperature. Subsequently, the membranes were incubated with primary antibodies against MMP2, MMP9, E-cadherin, N-cadherin, Vimentin or β -actin overnight at 4°C. After the membranes were washed, they were incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies for another 2 h at room temperature. Finally, the protein blots were visualized by using an enhanced chemiluminescence (ECL) Western blotting detection kit (Amersham Biosciences, Little Chalfont, UK).

Statistical Analysis

All statistical analysis was performed by GraphPad Prism 7 (GraphPad Inc., La Jolla, CA, USA). The data were expressed as the mean $\pm$ SD from three independent experiments. Statistical analysis was calculated using the one-way analysis of variance (ANOVA) followed by Tukey's post hoc test or Student's *t*-test. $p < 0.05$ was considered as a statistically significant difference.

Results

Propofol Inhibits PTC Cells Viability

Human PTC cell lines (TPC-1 and IHH-4), and normal human thyroid follicular epithelial Nthy-ori 3-1 cell line were exposed to propofol for 48 h at 3/6/9 µg/ml. Then, cells viability was

measured, and we found a significant inhibition of cells viability in TPC-1 and IHH-4 cells, while there was no change in the Nthy-ori 3-1 cell line (Figure 1A-C). Since the viability was nearly reduced to 50% by 6 $\mu\text{g/mL}$ of propofol, 6 $\mu\text{g/mL}$ was selected as a propofol-treating condition for further investigations.

Propofol Suppresses Cells Migration, Invasion, and EMT in PTC

To explore the effects of propofol on PTC cells metastasis, cells migration, invasion, and EMT abilities were examined by transwell or Western blot, respectively. Next, the data showed propofol inhibited migration and invasion in TPC-1 and IHH-4 cells (Figure 2A-D). Moreover, Western blot results indicated the expression of MMP2 and MMP9 protein was down-regulated after treated with propofol in TPC-1 and IHH-4 cells (Figure 2 E-F). In addition, the promotion of E-cadherin, as well as the suppression of N-cadherin and Vimentin were investigated in TPC-1 and IHH-4 cells after exposed to propofol (Figure 3 A-B). All the results suggested propofol could inhibit cells migration, invasion, and EMT in PTC.

Propofol Promotes the Expression of MiR-122

The expression of miR-122 was measured using qRT-PCR, and the data showed the expression of miR-122 was notably decreased in TPC-1 and IHH-4 cell lines compared to the Nthy-ori 3-1 cell line (Figure 4A). However, once exposed to propofol for 48 h at 3/6/9 $\mu\text{g/mL}$, a significant increase of miR-122 expression was determined in TPC-1 and IHH-4 cells compared with untreated group (Figure 4 B-C). Therefore, we found that propofol enhanced the expression of miR-122.

MiR-122 Inhibits Cells Migration, Invasion, and EMT in PTC

To elucidate the effects of miR-122 on PTC, cells were transfected with miR-122 mimic and a significantly increased expression of miR-122 was measured in TPC-1 and IHH-4 cells after transfection (Figure 5 A-B). Then, cells migration, invasion, and EMT abilities were examined by transwell or Western blot, respectively. The results indicated overexpressed miR-122 inhibited migration and invasion in TPC-1 and IHH-4 cells (Figure 5C-F). In the meantime, Western blot results showed the expression of MMP2, while MMP9 protein was down-regulated in TPC-1 and IHH-4 cells (Figure 5 G-H). In addition, the promotion of E-cadherin

but the suppression of N-cadherin and Vimentin were investigated both in TPC-1 and IHH-4 cells after transfected with miR-122 mimic (Figure 6A, B). All the results suggested miR-122 could inhibit cells migration, invasion, and EMT in PTC.

Propofol Suppresses Migration, Invasion, and EMT in PTC Cells by Regulating MiR-122 Expression

Based on the previous results, we know that propofol suppressed cells migration, invasion, and EMT in PTC and promoted the miR-122 expression. Therefore, to investigate the interaction between propofol and miR-122, TPC-1 and IHH-4 cells were transfected with anti-miR-NC or anti-miR-122 after exposed to propofol. Then, cells migration, invasion abilities, and EMT in PTC were detected. We found miR-122 inhibitor transfection could attenuate propofol-induced inhibitory effects on TPC-1 cells migration, invasion, and EMT, as well as in IHH-4 cells (Figure 7 A-F). These data indicated that propofol could suppress migration, invasion, and EMT in PTC cells by regulating the miR-122 expression.

Discussion

Propofol is a widely used intravenous anesthetic. Recently, numerous researches have focused on the diverse non-anesthetic effects of propofol, especially the effects on the progression of various tumors. Propofol induces apoptosis of breast cancer cells by the down-regulation of miR-24 signal pathway¹⁷. Propofol inhibits lung cancer cell viability and induces cell apoptosis by up-regulating microRNA-486 expression¹⁸. Also, it inhibits proliferation, migration, and invasion of gastric cancer cells by up-regulating microRNA-195¹⁹. However, only Chen et al⁹ have illustrated that propofol inhibited cells proliferation and migration, significantly inducing apoptosis through down-regulating the expression of ANRIL, thus blocking Wnt/ β -catenin. Therefore, based on the anti-tumor characteristics of propofol, exploring novel mechanism between propofol and PTC is necessary. In the present study, we found that propofol suppressed TPC-1 and IHH-4 cells viability, migration, and invasion. Cell metastasis-related proteins, MMP-9, and MMP-2, were all decreased by propofol treatment. Epithelial-mesenchymal transition (EMT) is involved in many essential cancer cell functions, including tissue reorganization, tumorigenesis, cancer me-

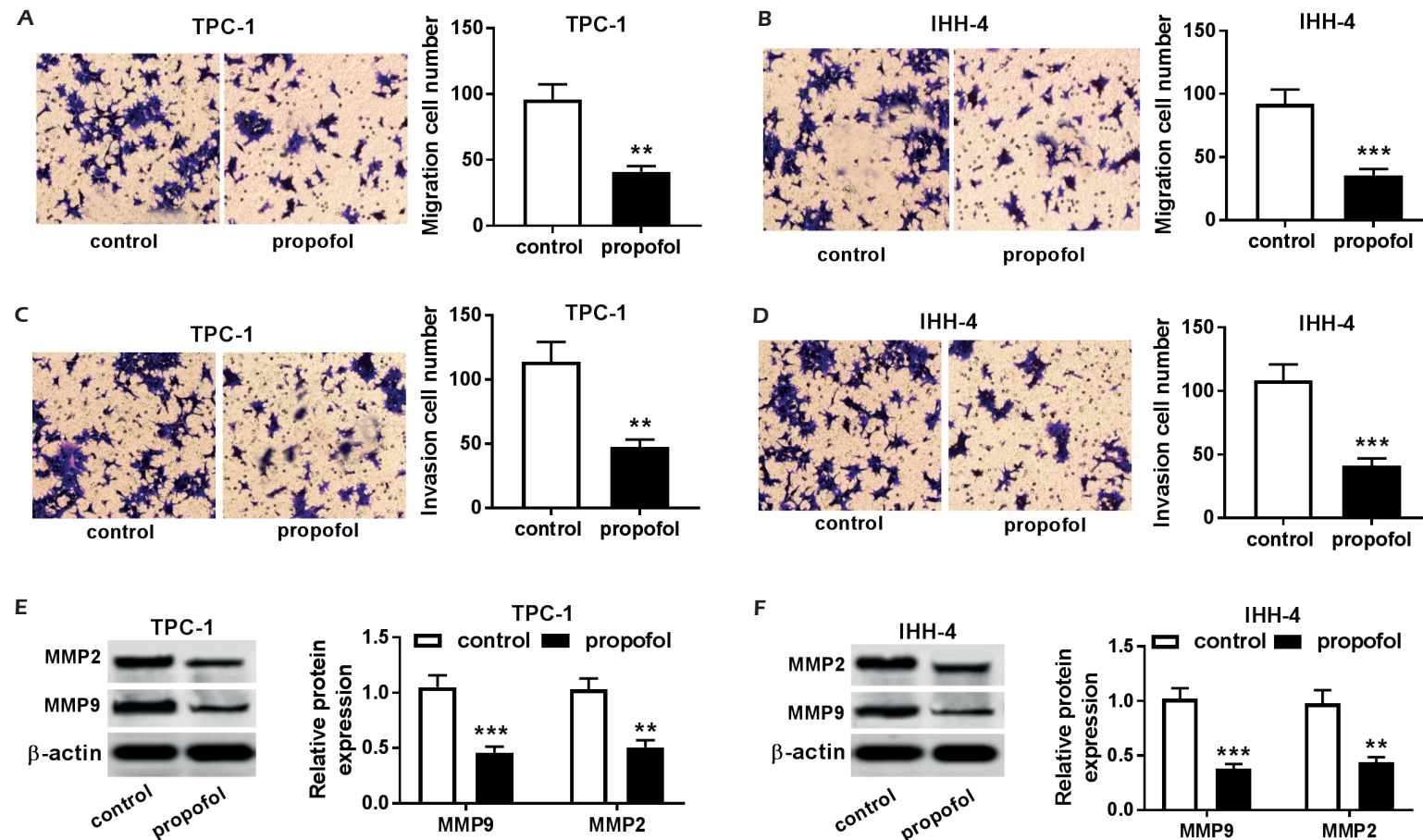


Figure 2. Propofol suppressed cells migration and invasion in PTC. **A-D**, Abilities of migration and invasion were detected using transwell assay in TPC-1 and IHH-4 cells (magnification 100 $\times$). **E-F**, Western blot was used to determine the expression of MMP2 and MMP9 protein in TPC-1 and IHH-4 cells. * $p < 0.05$.

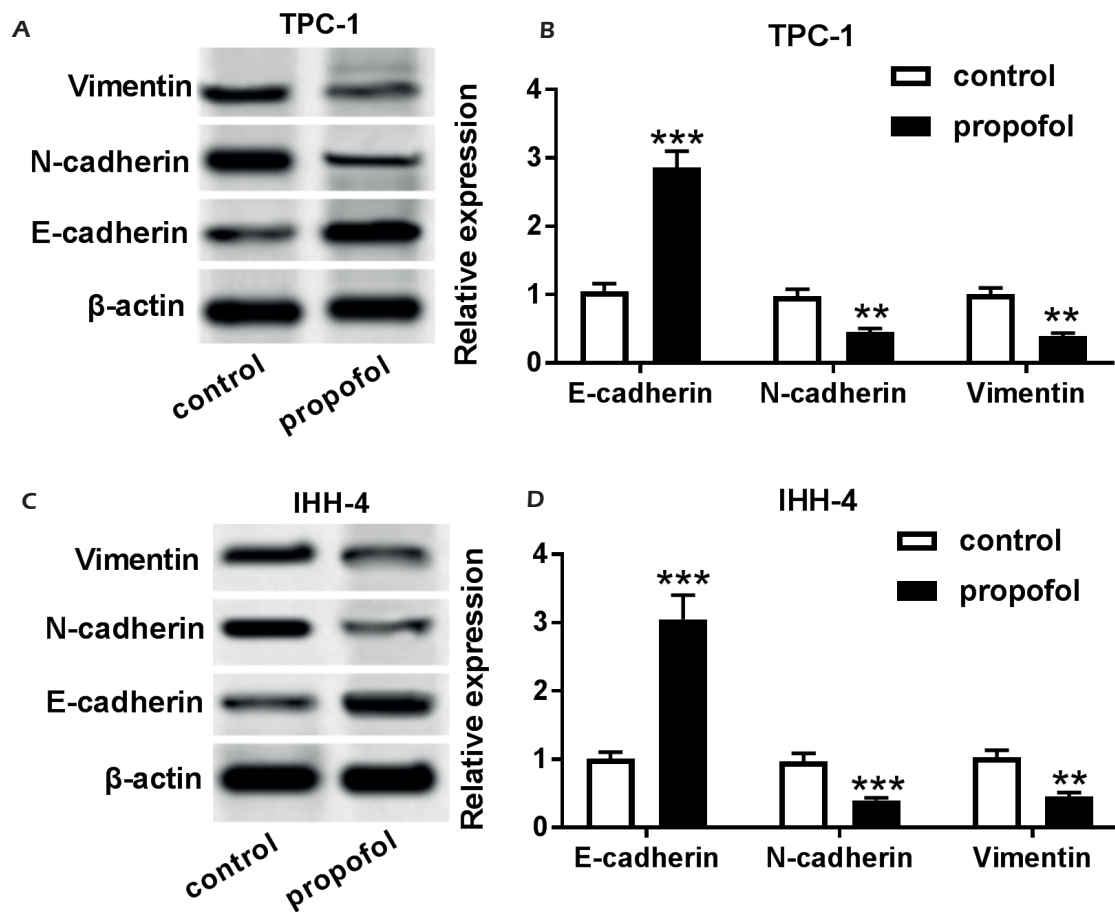


Figure 3. Propofol suppressed cells EMT in PTC. **A-B**, Protein expression of E-cadherin, N-cadherin, and Vimentin were measured via Western blot in TPC-1 and IHH-4 cells, respectively. * $p < 0.05$.

tastasis, and recurrence. EMT has become a pivotal developmental process in cancer progression and metastasis since it induces primary tumors to metastasize to other organs, allowing cancer cells to migrate, invade the surrounding tissues, and

escape into the bloodstream^{20,21}. In this work, we found that propofol treatment resulted in E-cadherin up-regulation and N-cadherin, as well as Vimentin down-regulation, indicating propofol also induced cells EMT. Therefore, we identified that

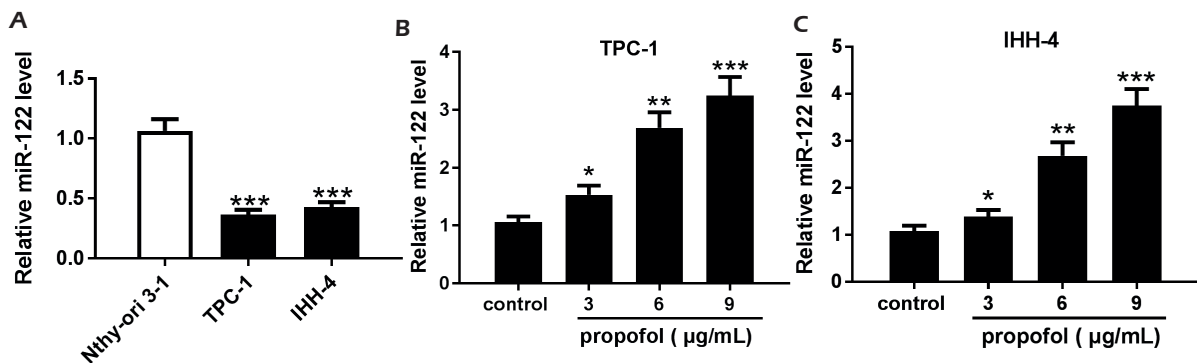


Figure 4. Propofol promoted the expression of miR-122. **A**, Level of miR-122 was examined by qRT-PCR in Nthy-ori 3-1, TPC-1, and IHH-4 cell lines. **B-C**, After exposed to propofol for 48 h at 3/6/9 $\mu\text{g/ml}$, miR-122 expression was determined in TPC-1 and IHH-4 cells using qRT-PCR, respectively. * $p < 0.05$.

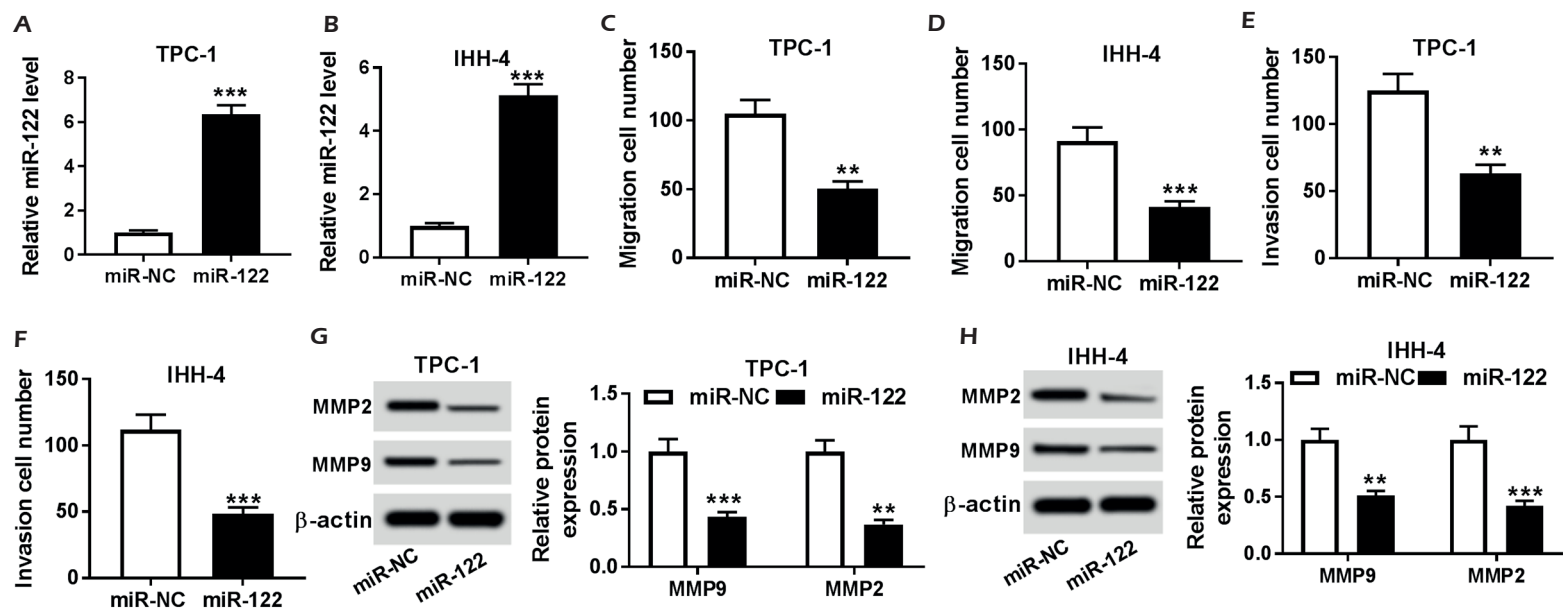


Figure 5. MiR-122 suppressed cells migration and invasion in PTC. **A-B**, Expression of miR-122 was detected in TPC-1 and IHH-4 cell lines after transfected with miR-122 mimic and miR-NC. **C-F**, Abilities of migration and invasion were detected using transwell assay in TPC-1 and IHH-4 cells. **G-H**, Western blot was used to determine the expression of MMP2 and MMP9 protein in TPC-1 and IHH-4 cells. * $p < 0.05$.

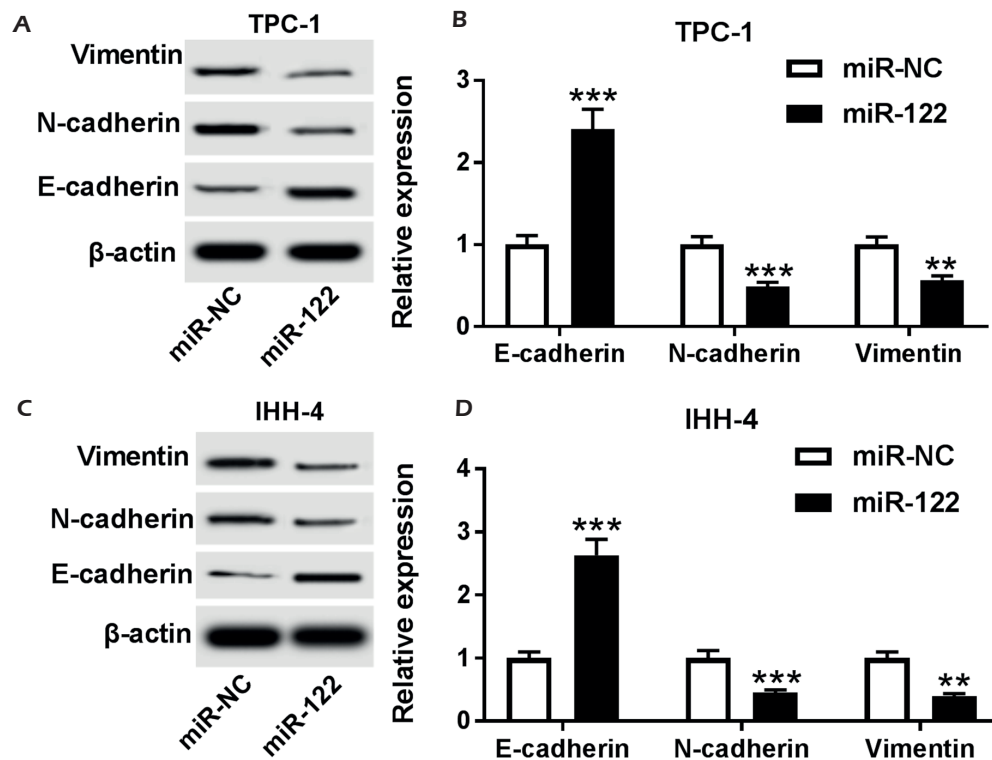


Figure 6. MiR-122 suppressed cells EMT in PTC. A-B, Protein expression of E-cadherin, N-cadherin, and Vimentin were measured using Western blot in TPC-1 and IHH-4 cells, respectively. * $p < 0.05$.

propofol could inhibit cells migration, invasion, and EMT in PTC. Various miRNAs have been revealed to be involved in the growth, proliferation, migration, and invasion of PTC and may act as a potential diagnostic and prognostic biomarkers for PTC. Liu et al²² showed that the down-regulation of miR-199a-3p in thyroid tissues was linked to the invasion and metastasis of PTC and might be a potential target for therapeutic intervention. Yin et al²³ indicated that miR-195 inhibited tumor growth and metastasis in PTC cell lines by targeting CCND1 and FGF2. Also, that miR-214²⁴ decreased cell proliferation, promoted cell apoptosis and cell cycle arrest, and decreased cell migration, invasion, and EMT in PTC. In addition, Sondermann et al²⁵ revealed that miR-9 and miR-21 could act as prognostic biomarkers for recurrence in PTC and Li et al²⁶ found miR-25-3p and miR-451a might be potential biomarkers for the diagnosis of PTC. All the data suggest that miRNAs are involved in the development of PTC. MiR-122 has been identified as a possible tumor inhibitor in FTC. In the present study, a decreased expression of miR-122 was detected in TPC-1 and IHH-4 cells. Then, miR-122 also functioned as a tumor suppressor in PTC by inhibiting cells

migration, invasion, and EMT. Chen et al⁹ illustrated that propofol suppresses proliferation and migration of PTC cells by the down-regulation of lncRNA ANRIL. Meanwhile, a negative correlation between ANRIL and miR-122-5p expression in HCC tissues was investigated, and ANRIL was demonstrated to directly bind to miR-122-5p and inhibit its expression²⁷. Therefore, we hypothesized propofol could exert the inhibitory effects by regulating the expression of miR-122 in PTC. Subsequently, the findings of the current report indicated that propofol promoted the expression of miR-122 in PTC. Next, a rescued study indicated that miR-122 inhibitor transfection could attenuate propofol-induced suppression on TPC-1 and IHH-4 cells metastasis. Taken together we investigated propofol could suppress migration, invasion, and EMT in PTC cells by regulating the miR-122 expression.

Conclusions

We found the inhibition effects of propofol and miR-122 on papillary thyroid carcinoma cells migration, invasion, and EMT, improving and refin-

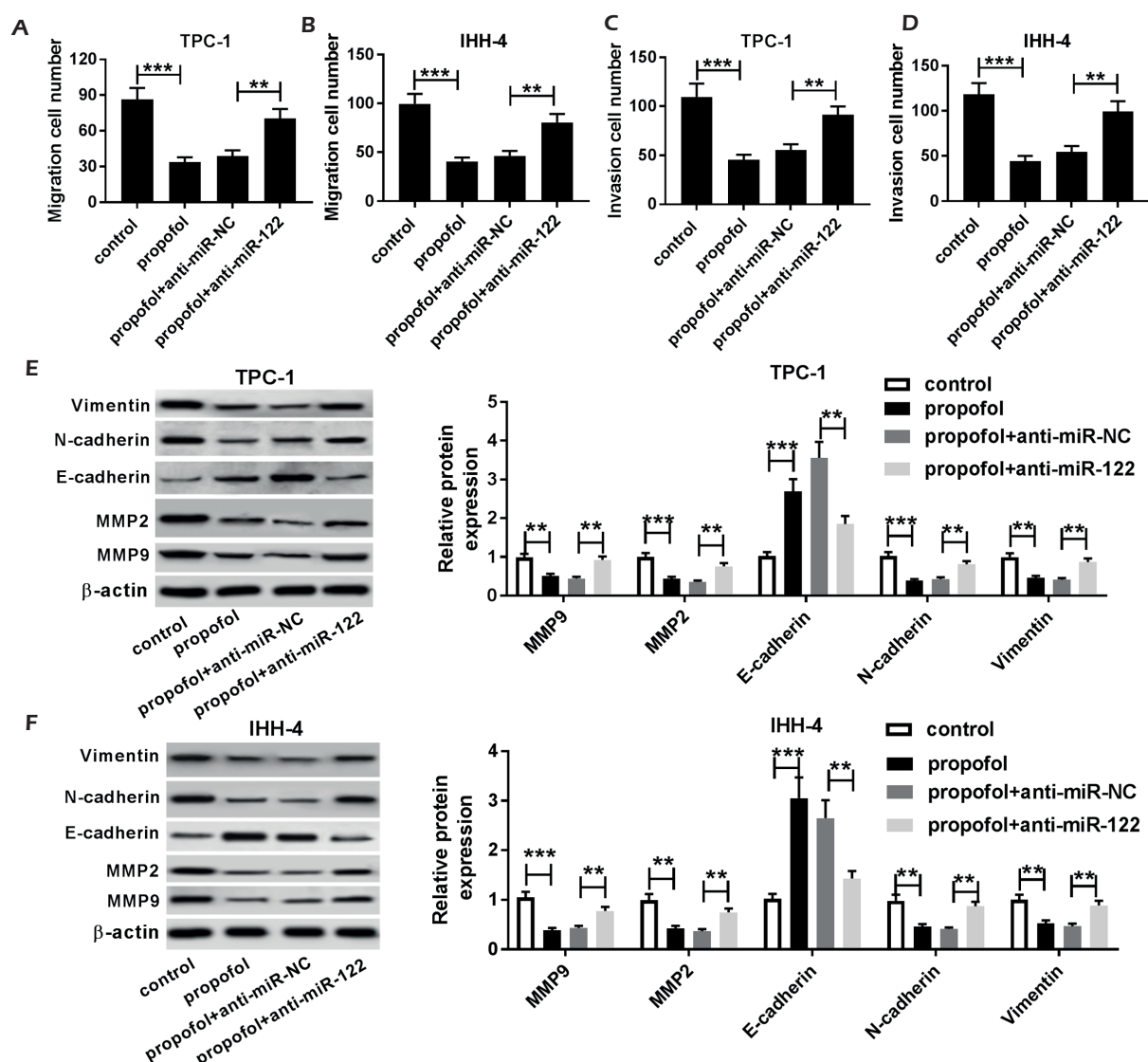


Figure 7. The interaction between propofol and miR-122 in the cells metastasis of PTC. TPC-1 and IHH-4 cells were transfected with anti-miR-NC or anti-miR-122 after treated with propofol. Subsequently, **A-D**, Abilities of migration and invasion were detected via transwell assay in TPC-1 and IHH-4 cells. **E-F**, Western blot was used to investigate the level of MMP2, MMP9, E-cadherin, N-cadherin, and Vimentin in TPC-1 and IHH-4 cells, respectively. $*p < 0.05$.

ing the research on papillary thyroid carcinoma. In the meantime, we identified the interaction between propofol and miR-122 on papillary thyroid carcinoma development, a possible mechanism involved in the anti-tumor activity in papillary thyroid carcinoma, which may offer the opportunity to prevent metastasis and develop novel therapeutics with broad clinical applicability.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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