European Review for Medical and Pharmacological Sciences 2019; 23: 6579-6587

Sevoflurane inhibits the progression of PTC by downregulating miR-155

Y. LI[1], Q.-G. ZENG[1], J.-L. QIU[2], T. PANG[3], H. WANG[4], X.-X. ZHANG[4]

[1]Department of Thyroid and Breast Surgery, the Fifth Affiliated Hospital, Sun Yat-Sen University, Zhuhai, Guangdong
[2]Department of Surgery, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong
[3]Department of Anesthesiology, the Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou, Guangdong
[4]Department of Anesthesiology, the Fifth Affiliated Hospital, Sun Yat-Sen University, Zhuhai, Guangdong

Yi Li and Qingan Zeng contributed equally to this work

Abstract. – OBJECTIVE: Surgery resection is the primary treatment for papillary thyroid carcinoma (PTC) patients with the risk of tumor cell invasion and distant metastasis. Sevoflurane is a volatile anesthetic agent widely used in clinical applications. However, the effect of sevoflurane on PTC cells and its precise mechanism remain largely unknown.

MATERIALS AND METHODS: Cell viability was assessed by MTT assay. The migrative and invasive abilities of the cells were measured by transwell assay. The protein expression level of Bax, Bcl-2, MMP 9, and MMP 2 were detected by Western blot. Cell apoptosis was analyzed by flow cytometry. The qRT-PCR analysis was used to determine miR-155 expressions.

RESULTS: Sevoflurane greatly decreased the viability of PTC cells in a dose-dependent manner. Moreover, sevoflurane significantly inhibited migration and invasion, but increased the apoptosis in PTC cells, which could be reversed by the addition of miR-155. Besides, sevoflurane evidently increased the Bax protein level and inhibited the protein level of Bcl-2, MMP9, and MPP2 in PTC cells. In addition, miR-155 was upregulated in PTC cells; however, the amount of miR-155 would be decreased in PTC cells treated with sevoflurane. Furthermore, abrogation of miR-155 promoted cell apoptosis and inhibited cell migration and invasion in PTC cells.

CONCLUSIONS: Sevoflurane inhibited migration and invasion, while enhanced cell apoptosis by downregulating miR-155 in PTC cells, suggesting important clinical implications for anesthetic agents to prevent the metastasis in PTC.

Key Words:
Sevoflurane, Migration and invasion, Apoptosis, MiR-155.

Abbreviations

TC = thyroid cancer, PTC = papillary thyroid carcinoma, miRNA = microRNA, mRNA = messenger RNA, JCRB = Japanese Collection of Research Bioresources, ECACC = European Collection of Cell Cultures, miR-155 = miR-155 mimic, miR-NC = miR-negative control, DMSO = dimethyl sulfoxide, TBST = Tris-Buffered Saline Tween 20, ECL = enhanced chemiluminescence, FITC = fluorescein isothiocynate, PI = propidium iodide, cDNA = complementary DNA, SD = standard deviation.

Introduction

Thyroid cancer (TC) is one of the most prevalent endocrine neoplasm malignancies, and its incidence rate has rapidly increased over the past few decades[1,2]. TC can be classified into four subtypes: papillary, follicular, medullary, and anaplastic thyroid cancer. Among them, papillary thyroid carcinoma (PTC) is the most frequent subtype of thyroid cancer, accounting for more than 80%[3,4]. Although the majority of the PTCs are biologically indolent and have a relatively good prognosis, PTC patients with aggressive features frequently have poor prognosis[5,6]. Therefore, the identification of new drugs or potential molecular mechanism for migration and invasion processes is important to reduce the incidence of tumors and improve prognosis in patients with PTC. The effects of anesthetics and anesthesia techniques may affect the long-term outcome in patients undergoing cancer surgery[7]. Sevoflurane is a volatile anesthetic agent and extensively used

Corresponding Author: Xuexia Zhang, MD; e-mail: zhxuex@sysu.edu.cn

in clinical applications. In recent years, increasing numbers of studies have shown that sevoflurane has anti-proliferative effects on colon cancer cells and laryngeal cancer cells[8,9]. In addition, sevoflurane could prevent the invasion and migration of non-small-cell lung cancer cells[10]. However, the effect of sevoflurane on the progression of PTC cells remains poorly understood. Sevoflurane has been reported to affect the expression of microRNA (miRNA) that controls different physiological systems via regulating messenger RNA (mRNA) expression[11]. MicroRNAs (miRNAs) are endogenous non-coding RNAs (approximately 22 nucleotides in length) that can regulate gene expression at the posttranscriptional level[12]. MiRNAs have been reported to be closely associated with a variety of biological and pathological processes, such as cell proliferation, migration, invasion, and apoptosis[13]. To date, previous documents[14-17] indicated that miR-155 is involved in immune function and cancer development, and is upregulated in several cancers, including breast cancer, liver cancer, cervical cancer, and lung cancer. In addition, miR-155 has been reported to function as an oncogene in PTC[18]. However, the sevoflurane affects miR-155 functions in the PTC process which is still largely unknown. In the present study, we first explored the effects of sevoflurane on PTC cell viability, migration, invasion, and apoptosis. We further explored whether these effects were mediated by miR-155 in PTC cells, providing potentially effective therapy for the treatment of PTC.

Materials and Methods

Cell Culture and Transfection

Human PTC cell lines (TPC-1 and IHH-4) were bought from the Type Culture Collection of the Chinese Academy of Sciences (Shanghai, China) and Japanese Collection of Research Bioresources (JCRB) Cell Bank (Osaka, Japan), respectively. The normal human thyroid cell line Nthy-ori 3-1 was obtained from the European Collection of Cell Cultures (ECACC; Porton Down, UK). All cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM; HyClone, South-Logan, UT, USA) supplemented with 10% fetal bovine serum (FBS; PAN, Adenbach, Bavaria, Germany) at 37°C in an incubator containing 5% CO_2.

MiR-155 mimic (miR-155), miR-negative control (miR-NC), miR-155 inhibitor (anti-miR-155), and anti-NC were obtained from GenePharma (Shanghai, China). TPC-1 and IHH-4 cells were transfected with oligonucleotides using Lipofectamine 2000 transfection reagent (Invitrogen, Carlsbad, CA, USA) following the manufacturer's instructions before sevoflurane treatment.

Cell Exposure to Sevoflurane

The cells were treated with various concentrations (1.25%, 2.5%, and 5%) of sevoflurane (Maruishi Pharmaceutical Co., Osaka, Japan) for 12 h or 24 h. The protocol for treatment cells with sevoflurane was consistent with previous work[10]. In brief, the TPC-1 and IHH-4 cells in the exponential growth phase were sowed into plates and placed in a 37°C incubator containing 5% CO_2 overnight. Then, the cell culture plates were placed in an airtight glass chamber and sevoflurane was supplied by an anesthetic vaporizer (Sevorane; Abbott, Abbot Park, IL, USA). The concentrations of sevoflurane in the chamber were monitored through a gas monitor (Drager, Lubeck, Germany). After being treated with different concentrations of sevoflurane, the cells grew at normal conditions for 12 h and used for further study.

MTT Assay

The cell viability was tested by MTT assay. Briefly, the TPC-1 and IHH-4 cells were sowed into 96-well plates and cultured overnight. Then, TPC-1 and IHH-4 cells were treated with various concentrations (1.25%, 2.5%, and 5%) of sevoflurane for 12 h or 24 h and cultured in normal condition for an additional 12 h. Each well was added to 20 uL MTT (5 mg/mL) and incubated for another 4 h. The culture medium mixture was discarded, and the formazan crystal was dissolved with 150 mL dimethyl sulfoxide (DMSO; Thermo Fisher Scientific, Waltham, MA, USA) per well. The microplate reader (Bio-Rad, Hercules, CA, USA) was used to detect the absorbance at 570 nm.

Cell Migration and Invasion Assay

Migratory and invasive abilities of TPC-1 and IHH-4 cells were detected by transwell assay. For cell invasion assay, the inserts were pre-coated with Matrigel (BD, San Jose, CA, USA). TPC-1 and IHH-4 cells (2×104 cells/well) in 100 uL serum-free DMEM medium were placed in the upper chambers (Costar, Corning, NY, USA), and 500 µl DMEM medium supplemented with 10% fetal bovine serum (FBS) was added to the

lower chambers. After incubation at 37°C with 5% CO_2,, a cotton swab was used to carefully remove TPC-1 and IHH-4 cells on the upper surface. The invasive cells on lower surfaces were fixed with paraformaldehyde (Sigma-Aldrich, St. Louis, MO, USA) and stained with 0.5% crystal violet (Sigma-Aldrich, St. Louis, MO, USA) in darkness for 20 min. The invasive cells in five random fields were counted by a microscope (Olympus, Tokyo, Japan). Cell migration was conducted similarly with the cell invasion assay except for the membranes of the transwell chambers without Matrigel.

Western Blot

The total protein in TPC-1 and IHH-4 cells was extracted using RIPA lysis buffer (Thermo Fisher, Waltham, MA, USA) containing protease inhibitors (Roche, Basel, Switzerland) after relevant treatment or transfection, followed by centrifugation at 12,000 g for 10 min to collect the supernatant of the protein. After quantification with the BCA Protein Assay Kit (Beyotime, Shanghai, China), the proteins (40 μg/lane) were loaded and separated by 10-12% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). Next, the gels were transferred onto the 0.22 μm polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). The membranes were blocked with Tris-Buffered Saline Tween 20 (TBST) containing 5% non-fat milk at room temperature for 2 h and subsequently incubated with the indicated primary antibodies against MMP 9 (#13667), MMP 2 (#40994), Bax (#14796), Bcl-2 (#3498), and β-actin (#4970) (1:1000; Cell Signaling Technology, Danvers, MA, USA) for 12 h at 4°C, followed by incubation with horseradish peroxidase (HRP)-conjugated secondary antibodies (Sangon Biotechnology, Shanghai, China) for 2 h at room temperature. The protein blots were visualized via enhanced chemiluminescence (ECL) chromogenic substrate (GE Healthcare, Amersham, Little Chalfont, UK) and analyzed with ImageJ software.

Apoptosis Assay

Cell apoptosis was measured by flow cytometry staining with fluorescein isothiocynate (FITC)-conjugated Annexin V and propidium iodide (PI) apoptosis kit (Sigma-Aldrich, St. Louis, MO, USA). In brief, TPC-1 and IHH-4 cells were seeded in 6-well plates and treated with sevoflurane or different transfection reagents. Thereafter, the cells were collected and stained with Annexin V-FITC and PI. After incubation in the dark environment for 15 min at room temperature, the rate of apoptotic cells was determined using a flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA).

qRT-PCR

The total RNA was isolated from the TPC-1 and IHH-4 cells using the TRIzol reagent (Invitrogen, Carlsbad, CA, USA). For miRNA analysis, the complementary DNA (cDNA) was synthesized by TaqMan microRNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA) following the manufacturer's instructions. Subsequently, qPCR was performed using SYBR Green PCR Kit (Toyobo, Tokyo, Japan) with an ABI PRISM 7300 Sequence Detection System (Applied Biosystems, Foster City, CA, USA). The primers sequences were as follows: miR-155 (Forward, 5'-UUAAUGCUAAUCGUGAUAGGGGU-3'; Reverse, 5'-CCCUAUCACGAUUAGCAUUAAUU-3'), U6 (Forward, 5'-CTCGCTTCGGCAGCACA-3'; Reverse, 5'-AACGCTTCACGAATTTGCGT-3'). The relative expressions of miR-155 were calculated using the $2^{-\Delta\Delta Ct}$ method and normalized to U6.

Statistical Analysis

All results were performed as the mean ± standard deviation (SD) from more than three independent replicates. The statistical differences between the two groups were analyzed by the Student's *t*-test. GraphPad Prism version 6.0 software (GraphPad Software, San Diego CA, USA) was conducted to statistical analysis. In all figures, $p < 0.05$ was considered a significant difference.

Results

Sevoflurane Inhibited the Viability of PTC Cells

To explore the roles of sevoflurane on PTC cell viability, the cells were treated with different concentrations of sevoflurane for 12 h or 24 h. Compared with the untreated group, the addition of sevoflurane greatly reduced the viability of TPC-1 and IHH-4 cells in a dose-dependent manner; however the effect was smaller with respect to Nthy-ori 3-1 group (Figures 1A-1C). Taken together, these data indicated that sevoflurane significantly suppressed the viability of PTC cells.

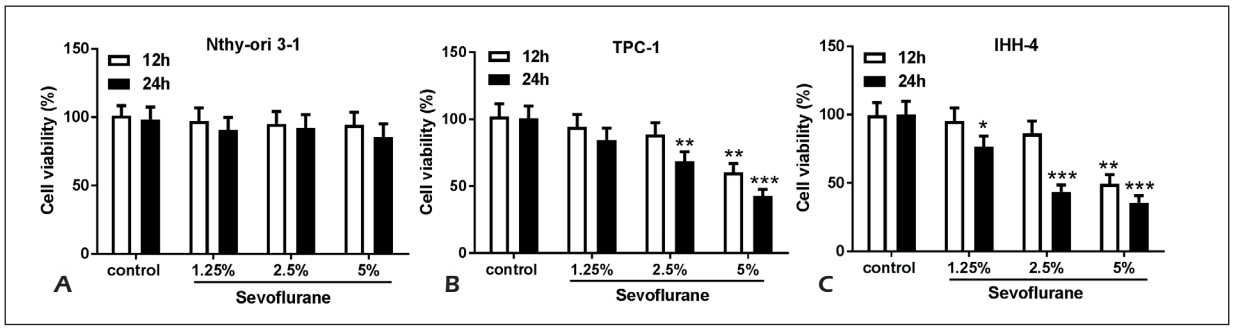

Figure 1. Effect of sevoflurane on the viability of PTC cells. The cells were treated with different concentrations of sevoflurane for 12 h or 24 h. **A-C**, MTT assay determined the effect of sevoflurane on the viability of PTC cells and Nthy-ori 3-1 cells. *p<0.05, **p<0.01, ***p<0.001.

Sevoflurane Decreased the Migrative and Invasive Abilities of PTC Cells

To investigate the effects of sevoflurane on PTC cell migration and invasion, the TPC-1 and IHH-4 cells were exposed to sevoflurane (2.5%) for 12 h. The results showed that the TPC-1 and IHH-4 cells treated with sevoflurane remarkably inhibited the migrative and invasive abilities when compared with the untreated group (Figures 2A-2D). Besides, matrix metalloproteinases proteins were analyzed in TPC-1 and IHH-4 cells by Western blot. The results displayed that the levels of MMP 9 and MMP 2 expression were markedly decreased in TPC-1 and IHH-4 cells treated with sevoflurane (Figures 2E and 2F). All these findings suggested that sevoflurane could inhibit the migrative and invasive capacities of PTC cells.

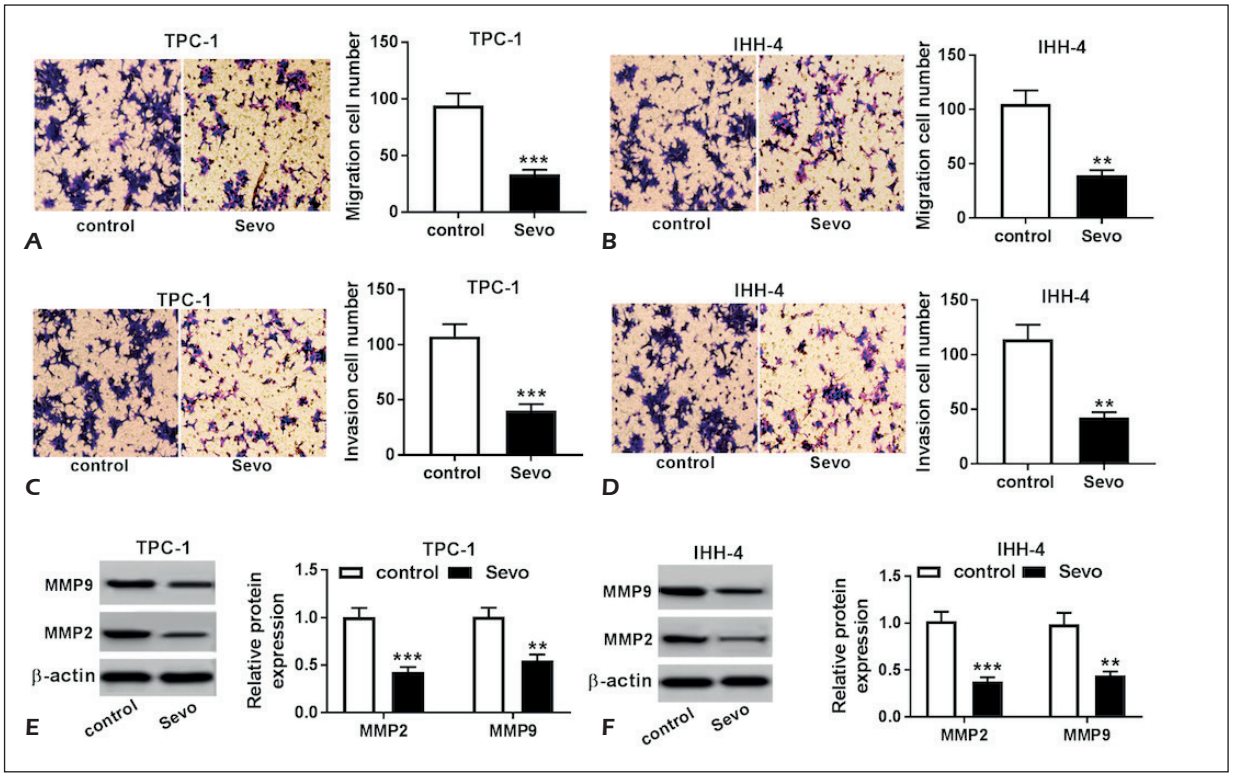

Figure 2. Effects of sevoflurane on PTC cell migration and invasion. The cells were treated without (control) or with sevoflurane (2.5%) for 12 h. **A**, and **B**, Cell migration was investigated in TPC-1 and IHH-4 cells by transwell assay. **C**, and **D**, The effect of sevoflurane on cell invasion was evaluated in TPC-1 and IHH-4 cells. E, and F, The expressions of MMP 9 and MMP 2 protein were measured in TPC-1 and IHH-4 cells by Western blot. **p<0.01, ***p<0.001.

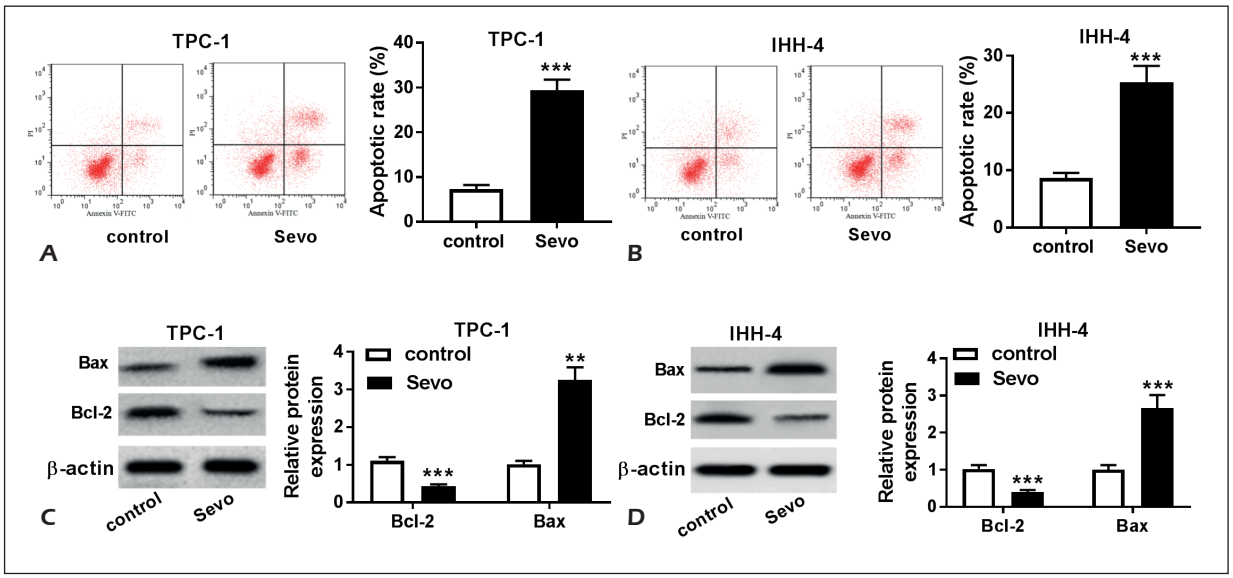

Figure 3. Effect of sevoflurane on PTC cell apoptosis. The cells were treated without (control) or with sevoflurane (2.5%) for 24 h. **A**, and **B**, Cell apoptosis was detected in TPC-1 and IHH-4 cells by flow cytometry. **C**, and **D**, The levels of Bax and Bcl-2 protein were analyzed in TPC-1 and IHH-4 cells by Western blot. **$p<0.01$, ***$p<0.001$.

Sevoflurane Promoted Apoptosis of PTC Cells

Furthermore, we analyzed the role of sevoflurane in PTC cell apoptosis. The results of the apoptosis assay demonstrated that the apoptotic rate was remarkably increased in TPC-1 and IHH-4 cells exposed to sevoflurane compared with that in the untreated group (Figures 3A and 3B). Moreover, the protein of Bax (pro-apoptotic) expression was prominently upregulated and the Bcl-2 (anti-apoptotic) expression was downregulated in TPC-1 and IHH-4 cells exposed to sevoflurane compared with that in the untreated group (Figures 3C and 3D). Thus, sevoflurane significantly promoted the apoptosis of PTC cells.

Sevoflurane Suppressed MiR-155 Expression in PTC Cells

To determine whether sevoflurane could alter the abundance of miR-155 in PTC cells, the expression level of miR-155 was analyzed by qRT-PCR. As displayed in Figure 4A, the level of miR-155 was evidently higher in TPC-1 and IHH-4 cells treated with sevoflurane than Nthy-ori 3-1 cells. Besides, TPC-1 and IHH-4 cells treated with sevoflurane dramatically upregulated the expression of miR-155 in a dose-dependent manner as compared to those of the control group (Figures 4B and 4C). These results demonstrated that sevoflurane treatment induced a great decrease of miR-155 expression in PTC cells.

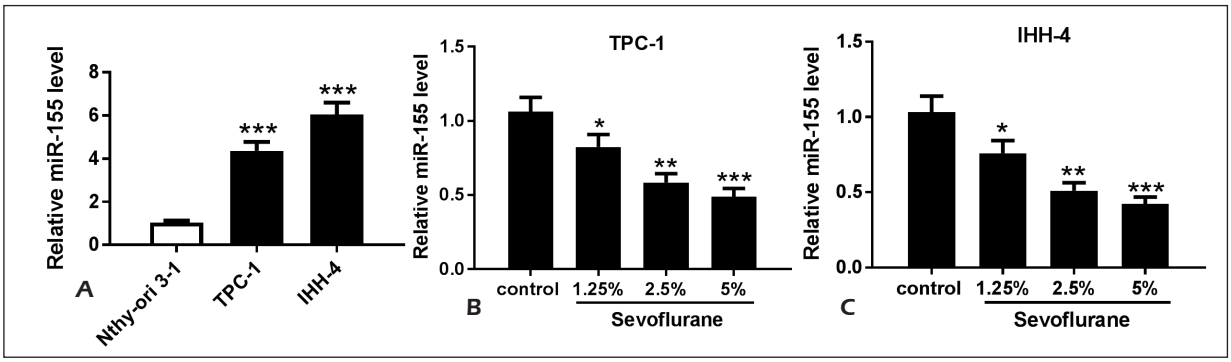

Figure 4. Effects of sevoflurane on expression of miR-155 in PTC cells. **A**, The expression level of miR-155 was analyzed in PTC cells and Nthy-ori 3-1 cells by qRT-PCR. **B**, and **C**, The abundance of miR-155 was detected in PTC cells treated without (control) or with sevoflurane (2.5%) for 24 h by qRT-PCR. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Knockdown of MiR-155 Inhibited PTC Cells Progression

To explore the effects of miR-155 on PTC progression, anti-miR-155 or anti-miR-NC were transfected into TPC-1 and IHH-4 cells. We found that the overexpression of miR-155 significantly downregulated the expression of miR-155 in TPC-1 and IHH-4 cells compared to anti-miR-NC group (Figures 5A and 5B). Moreover, the abrogation of miR-155 significantly reduced the number of migrated or invasive cells in PC-1 and IHH-4 cells (Figures 5C-5F). In addition, the knockdown of miR-155 remarkably increased cell apoptosis of TPC-1 and IHH-4 cells (Figures 5G and 5H). Furthermore, the inhibition of miR-155 conspicuously decreased the proteins of Bcl-2, MMP 9, and MMP2 expression and increased the protein level of Bax in TPC-1 and IHH-4 cells (Figures 5I and 5J). These data indicated that the knockdown of miR-155 promoted cell apoptosis and limited cell migration and invasion in TPC-1 and IHH-4 cells.

Overexpression of MiR-155 Reversed Sevoflurane Inhibition-Mediated Progression of PTC

To further confirm whether the inhibitory effects of sevoflurane on cell migration, invasion, and apoptosis were mediated by miR-155 in PTC cells, we transfected miR-155 into PC-1 and IHH-4 cells prior to exposure to sevoflurane. As shown in Figures 6A-6D, the upregulation of miR-155 abolished the inhibitory effects of sevoflurane on PC-1 and IHH-4 cell migration and invasion. In addition, the overexpression of miR-155 reversed the effects of sevoflurane on increased cell apoptosis in PC-1 and IHH-4 cells (Figures 6E and 6F). Moreover, the Western blot analysis revealed that PC-1 and IHH-4 cells transfected with miR-155 also prevented the decrease of Bcl-2 MMP 9 and MMP2 protein expression and the increase of Bax protein expression caused by sevoflurane treatment (Figures 6G and 6H). These findings indicated that the overexpression miR-155 could abolish the effects of sevoflurane on cell migration, invasion, and apoptosis in TPC-1 and IHH-4 cells.

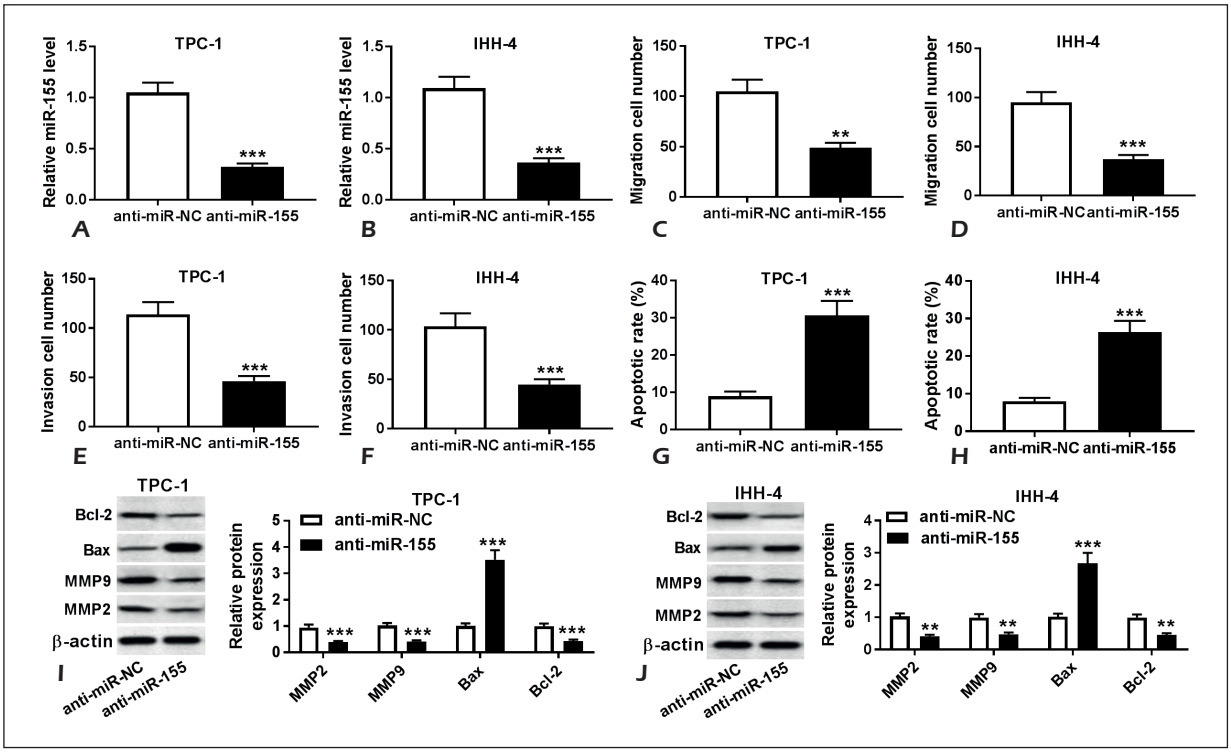

Figure 5. Effects of miR 155 inhibitor on PTC cells progression. The PTC cells were transfected with anti-miR-155 or anti-miR-NC. **A**, and **B**, The expression level of miR-155 was analyzed in TPC-1 and IHH-4 cells by qRT-PCR. **C**-**F**, Cell migration and invasion were evaluated in TPC-1 and IHH-4 cells by transwell assay. **G**, and **H**, Cell apoptosis was measured in TPC-1 and IHH-4 cells by flow cytometry. **I**, and **J**, The expressions of MMP 9, MMP 2, Bax, and Bcl-2 protein were detected in TPC-1 and IHH-4 cells by Western blot. $^{**}p<0.01$, $^{***}p<0.001$.

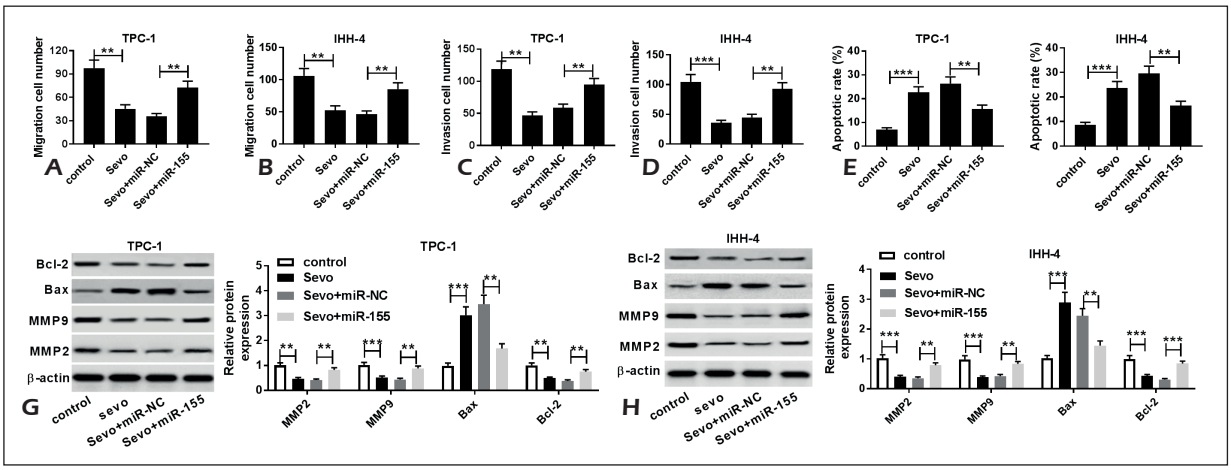

Figure 6. Abrogation of miR-155 weakened the sevoflurane inhibition-mediated progression of PTC. The PTC cells were transfected with miR-155 and then treated with sevoflurane. **A**-**D**, The effect of miR-155 inhibition on cell migration and invasion were detected in sevoflurane-treated TPC-1 and IHH-4 cells. **E**, and **F**, Cell apoptosis was examined in TPC-1 and IHH-4 cells by flow cytometry. **G**, and **H**, The levels of MMP 9, MMP 2, Bax, and Bcl-2 protein were measured in TPC-1 and IHH-4 cells by Western blot. **p<0.01, ***p<0.001.

Discussion

Previous studies[5-19] have proved that some PTC patients commonly suffer from tumor cell invasion, distant metastasis, and relapses after surgery. Hence, it is urgent to understand the molecular mechanism of PTC progression and develop effective therapeutic agents to improve the prognosis of PTC.

Sevoflurane is an inhaled anesthetic that is widely used in many cancers surgery to maintain anesthesia. Recent emerging evidenced suggested that sevoflurane could inhibit the progression of many cancer cells, including proliferation, migration, and invasion[20,21]. For instance, Liang et al[22] demonstrated that sevoflurane limited the migration and invasion of A549 cells via inactivating the p38 MAPK signaling pathway. In addition, Yi et al[23] suggested that sevoflurane could remarkably inhibit the invasion and migration of glioma cells through the upregulation miR-637. However, there is no evidence in support of the effects of sevoflurane in PTC. Thus, the purpose of this study was to explore the effects of sevoflurane on viability, migration, invasion, and apoptosis of PTC cells. Here we first demonstrated that sevoflurane greatly decreased the viability of TPC-1 and IHH-4 cells in a dose-dependent manner. Moreover, we found that sevoflurane significantly limited the migratory and invasive abilities of TPC-1 and IHH-4 cells. Thus, these findings indicated that sevoflurane remarkably inhibited TPC-1 and IHH-4 cell viability, migration, and invasion.

Some investigations[24,25] have demonstrated that MMPs play a key role in cancer cell migration, proliferation, inflammation, etc. Among these, of particular importance there are MMP 2 and MMP 9, known as a marker for malignant progression of tumors, including PTC progression[26,27]. For example, Yu et al[28] revealed that PTC patients with high expressions of MMP-2 and MMP-9 had a poorer prognosis than those with low abundance of MMP-2 and MMP-9. Emerging evidence suggested that MMP-2 and MMP-9 were involved in the metastasis of PTC[26-29]. In our study, the results showed that the levels of MMP 9 and MMP 2 were markedly decreased in TPC-1 and IHH-4 cells treated with sevoflurane. These data indicated that sevoflurane might inhibit PTC metastasis via downregulation of MMP 9 and MMP 2 expression.

Activation of the apoptotic pathway is an important mechanism for agents to kill tumor cells[30]. Many drugs also exert their functions by inducing apoptosis in the treatment of PTC[31,32]. Bax (pro-apoptotic) and Bcl-2 (anti-apoptotic) are members of the Bcl family, and they play vital roles in the process of apoptosis. Zhang et al[33] indicated that curcumin treatment resulted in a significant increase level of Bax and decreased the level of Bcl-2 in PTC cells. Similarly, we found that the apoptotic rate was remarkably increased in TPC-1 and IHH-4 cells treated with sevoflurane. Moreover, TPC-1 and IHH-4 cells treated with sevoflurane prominently elevated the amounts of Bax, whereas reduced the quantities of bcl-2. The results indicated that sevoflurane

significantly promoted apoptosis of TPC-1 and IHH-4 cells.

Mounting evidence[23-34] suggested that sevoflurane may regulate the multiple miRNAs expression to influence the progression of cancers. Moreover, aberrant expression of miRNAs is associated with the pathogenesis of many types of cancer, including PTC[35]. MiR-155 as an oncogenic miRNA, has been shown to be involved in tumorigenesis and progression[36]. Gao et al[37] demonstrated that the abundance of miR-155 was effectively upregulated in colonic cancer tissues and cell lines. Moreover, Zhang et al[18] revealed that miR-155 functions as an oncogene in PTC via targeting adenomatous polyposis coli and activating Wnt/β-catenin signaling pathway. In addition, Lee et al[38] also proved that the mean expression of miR-155 was significantly reduced in the PTC group compared with the benign group. In this study, consistent with the previous observation, the expression of miR-155 was significantly upregulated in TPC-1 and IHH-4 cells. However, TPC-1 and IHH-4 cells treated with sevoflurane dramatically reduced the amount of miR-155 in a dose-dependent manner. Besides, the knockdown of miR-155 promoted cell apoptosis and suppressed cell migration and invasion in TPC-1 and IHH-4 cells. Furthermore, the overexpression miR-155 weakened the sevoflurane-mediated inhibition of migration and invasion and promoted the apoptosis in TPC-1 and IHH-4 cells. Hence, these findings clearly suggested that sevoflurane enhanced the apoptosis and inhibited cell migration and invasion by downregulating miR-155 in PTC cells.

Conclusions

We demonstrated that sevoflurane remarkably inhibited the viability of PTC cells. Moreover, our report presented the first evidence that sevoflurane significantly inhibited migration and invasion, but increased apoptosis in PTC cells, which was reversed by the addition of miR-155. MiR-155 was upregulated in PTC cells. However, the amount of miR-155 was decreased in PTC cells treated with sevoflurane. Besides, the knockdown of miR-155 promoted cell apoptosis and suppressed cell migration and invasion. Collectively, sevoflurane inhibited the progression of PTC by downregulating miR-155. This study might provide a better choice for anesthesiologists to choose the volatile anesthetics for the surgical resection of PTC to prevent metastasis and improve patient outcomes.

Conflict of Interests

The authors declare that they have no conflict of interests.

References

1) Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.
2) Liebner DA, Shah MH. Thyroid cancer: pathogenesis and targeted therapy. Ther Adv Endocrinol Metab 2011; 2: 173-195.
3) Bokhari A, Tiscornia-Wasserman PG. Cytology diagnosis of metastatic clear cell renal cell carcinoma, synchronous to pancreas, and metachronous to thyroid and contralateral adrenal: report of a case and literature review. Diagn Cytopathol 2017; 45: 161-167.
4) Cabanillas ME, Mcfadden DG, Durante C. Thyroid cancer. Lancet 2016; 388: 2783-2795.
5) Shi X, Liu R, Basolo F, Giannini R, Shen X, Teng D, Guan H, Shan Z, Teng W, Musholt TJ, Al-Kuraya K, Fugazzola L, Colombo C, Kebebew E, Jarzab B, Czarniecka A, Bendlova B, Sykorova V, Sobrinho-Simões M, Soares P, Shong YK, Kim TY, Cheng S, Asa SL, Viola D, Elisei R, Yip L, Mian C, Vianello F, Wang Y, Zhao S, Oler G, Cerutti JM, Puxeddu E, Qu S, Wei Q, Xu H, O'Neill CJ, Sywak MS, Clifton-Bligh R, Lam AK, Riesco-Eizaguirre G, Santisteban P, Yu H, Tallini G, Holt EH, Vasko V, Xing M. Differential clinicopathological risk and prognosis of major papillary thyroid cancer variants. J Clin Endocrinol Metab 2016; 101: 264-274.
6) Voutilainen PE, Multanen MM, Leppäniemi AK, Haglund CH, Haapiainen RK, Franssila KO. Prognosis after lymph node recurrence in papillary thyroid carcinoma depends on age. Thyroid 2001; 11: 953-957.
7) Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth 2010; 105: 106-115.
8) Kvolik S, Glavas-Obrovac L, Bares V, Karner I. Effects of inhalation anesthetics halothane, sevoflurane, and isoflurane on human cell lines. Life Sci 2005; 77: 2369-2383.
9) Kvolik S, Dobrosevic B, Marczi S, Prlic L, Glavas-Obrovac L. Different apoptosis ratios and gene expressions in two human cell lines after sevoflurane anaesthesia. Acta Anaesthesiol Scand 2009; 53: 1192-1199.
10) Liang H, Gu M, Yang C, Wang H, Wen X, Zhou Q. Sevoflurane inhibits invasion and migration of lung cancer cells by inactivating the p38 MAPK signaling pathway. J Anesth 2012; 26: 381-392.
11) Otsuki T, Ishikawa M, Hori Y, Goto G, Sakamoto A. Volatile anesthetic sevoflurane ameliorates endotoxin-induced acute lung injury via microRNA modulation in rats. Biomed Rep 2015; 3: 408-412.

12) Herranz H, Cohen SM. MicroRNAs and gene regulatory networks: managing the impact of noise in biological systems. Genes Dev 2010; 24: 1339-1344.
13) Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. Nat Rev Cancer 2006; 6: 259-269.
14) Mattiske S, Suetani RJ, Neilsen PM, Callen DF. The oncogenic role of miR-155 in breast cancer. Cancer Epidemiol Biomarkers Prev 2012; 21: 1236-1243.
15) Liu F, Kong X, Lv L, Gao J. MiR-155 targets TP53INP1 to regulate liver cancer stem cell acquisition and self-renewal. FEBS Lett 2015; 589: 500-506.
16) Lao G, Liu P, Wu Q, Zhang W, Liu Y, Yang L, Ma C. Mir-155 promotes cervical cancer cell proliferation through suppression of its target gene LKB1. Tumour Biol 2014; 35: 11933-11938.
17) Babar IA, Czochor J, Steinmetz A, Weidhaas JB, Glazer PM, Slack FJ. Inhibition of hypoxia-induced miR-155 radiosensitizes hypoxic lung cancer cells. Cancer Biol Ther 2011; 12: 908-914.
18) Zhang X, Li M, Zuo K, Li D, Ye M, Ding L, Cai H, Fu D, Fan Y, Lv Z. Upregulated miR-155 in papillary thyroid carcinoma promotes tumor growth by targeting APC and activating Wnt/β-catenin signaling. J Clin Endocrinol Metab 2013; 98: E1305-E1313.
19) Schneider DF, Chen H. New developments in the diagnosis and treatment of thyroid cancer. CA Cancer J Clin 2013; 63: 373-394.
20) Ecimovic P, McHugh B, Murray D, Doran P, Buggy DJ. Effects of sevoflurane on breast cancer cell function in vitro. Anticancer Res 2013; 33: 4255-4260.
21) Liang H, Yang CX, Zhang B, Wang HB, Liu HZ, Lai XH, Liao MJ, Zhang T. Sevoflurane suppresses hypoxia-induced growth and metastasis of lung cancer cells via inhibiting hypoxia-inducible factor-1α. J Anesth 2015; 29: 821-830.
22) Liang H, Gu M, Yang C, Wang H, Wen X, Zhou Q. Sevoflurane inhibits invasion and migration of lung cancer cells by inactivating the p38 MAPK signaling pathway. J Anesth 2012; 26: 381-392.
23) Yi W, Li D, Guo Y, Zhang Y, Huang B, Li X. Sevoflurane inhibits the migration and invasion of glioma cells by upregulating microRNA-637. Int J Mol Med 2016; 38: 1857-1863.
24) Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: regulators of the tumor microenvironment. Cell 2010; 141: 52-67.
25) Strongin AY. Mislocalization and unconventional functions of cellular MMPs in cancer. Cancer Metastasis Rev 2006; 25: 87-98.
26) Huang LL, Wang Z, Cao CJ, Ke ZF, Wang F, Wang R, Luo CQ, Lu X, Wang LT. AEG-1 associates with metastasis in papillary thyroid cancer through upregulation of MMP2/9. Int J Oncol 2017; 51: 812-822.
27) Roomi MW, Monterrey JC, Kalinovsky T, Rath M, Niedzwiecki A. Patterns of MMP-2 and MMP-9 expression in human cancer cell lines. Oncol Rep 2009; 21: 1323-1333.
28) Yu HZ, Li ZP, Li SG, Wu CM. [Correlations of serous levels of matrix metalloproteinases (MMP-2 and MMP-9) to invasion and metastasis of papillary thyroid carcinoma]. Ai Zheng 2005; 24: 740-742.
29) Wang N, Jiang R, Yang JY, Tang C, Yang L, Xu M, Jiang QF, Liu ZM. Expression of TGF-β1, SNAI1 and MMP-9 is associated with lymph node metastasis in papillary thyroid carcinoma. J Mol Histol 2014; 45: 391-399.
30) Debatin KM. Apoptosis pathways in cancer and cancer therapy. Cancer Immunol Immunother 2004; 53: 153-159.
31) Liu C, Yin L, Chen J, Chen J. The apoptotic effect of shikonin on human papillary thyroid carcinoma cells through mitochondrial pathway. Tumour Biol 2014; 35: 1791-1798.
32) Song F, Zhang L, Yu HX, Lu RR, Bao JD, Tan C, Sun Z. The mechanism underlying proliferation-inhibitory and apoptosis-inducing effects of curcumin on papillary thyroid cancer cells. Food Chem 2012; 132: 43-50.
33) Zhang L, Cheng X, Gao Y, Bao J, Guan H, Lu R, Yu H, Xu Q, Sun Y. Induction of ROS-independent DNA damage by curcumin leads to G2/M cell cycle arrest and apoptosis in human papillary thyroid carcinoma BCPAP cells. Food Funct 2016; 7: 315-325.
34) Tanaka S, Ishikawa M, Arai M, Genda Y, Sakamoto A. Changes in microRNA expression in rat lungs caused by sevoflurane anesthesia: a TaqMan® low-density array study. Biomed Res 2012; 33: 255-263.
35) Farazi TA, Spitzer JI, Morozov P, Tuschl T. MiRNAs in human cancer. J Pathol 2011; 223: 102-115.
36) Han S, Yang S, Cai Z, Pan D, Li Z, Huang Z, Zhang P, Zhu H, Lei L, Wang W. Anti-Warburg effect of rosmarinic acid via miR-155 in gastric cancer cells. Drug Des Devel Ther 2015; 9: 2695-2703.
37) Gao Y, Liu Z, Ding Z, Hou S, Li J, Jiang K. MicroRNA-155 increases colon cancer chemoresistance to cisplatin by targeting forkhead box O3. Oncol Lett 2018; 15: 4781-4788.
38) Lee YS, Lim YS, Lee JC, Wang SG, Park HY, Kim SY, Lee BJ. Differential expression levels of plasma-derived miR-146b and miR-155 in papillary thyroid cancer. Oral Oncol 2015; 51: 77-83.