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MiR-506 suppresses papillary thyroid carcinoma cell proliferation and metastasis *via* targeting IL17RD

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Abstract. – OBJECTIVE: The aim of this study was to determine the role of microRNA-506-3p (miR-506) in papillary thyroid carcinoma (PTC), and to further explore the underlying mechanism.

PATIENTS AND METHODS: The expression level of miR-506 in clinical cases was detected by Real Time-fluorescence quantitative Polymerase Chain Reaction (RT-qPCR). Meanwhile, RT-qPCR was performed to determine miR-506 expression in different PTC cell lines. Bioinformatics software was used to predict the possible target genes of miR-506. Dual-Luciferase reporter gene assay together with Western blot (WB) assay were used to verify the prediction results. Finally, cellular functions such as proliferation and metastasis capacities were detected *in vitro*.

RESULTS: RT-qPCR was used to measure the expression level of miR-506 in 80 paired PTC cases. The results showed that the expression level of miR-506 in PTC tissues was significantly decreased. *In vitro*, miR-506 expression was also markedly suppressed in four PTC cell lines. TPC-1 cells expressed the lowest level of miR-506. Subsequently, the target gene of miR-506 was predicted by TargetScan, miRBase and miRanda. The prediction results indicated that IL17RD was an alternative target gene of miR-506. Furthermore, miR-506 was found to remarkably inhibit the Luciferase activity of wild-type IL17RD. However, it had no effect on mutant-type. Besides, the protein expression level of IL17RD was significantly reduced in miR-506-overexpressing TPC-1 cells. More importantly, the restored expression of IL17RD could alleviate the blocking effects of miR-506 on cell proliferation, migration and invasion.

CONCLUSIONS: In this study, we found that miR-506 could inhibit the proliferation and metastasis of PTC cells. Meanwhile, IL17RD might be a downstream target of the biological process. Our findings provided a new therapeutic direction for the treatment of PTC.

Key Words
Papillary thyroid carcinoma (PTC), MicroRNA-506-3p (miR-506), Interleukin-17 receptor D (IL17RD), Epithelial-Mesenchymal Transition (EMT).

Introduction

Thyroid carcinoma (TC) is the most common malignant tumor of the endocrine system[1]. It is known that TC usually has 4 different pathological types. Papillary TC (PTC) accounts for more than 90% of all malignant thyroid tumors, which is also the most common type of malignant thyroid tumors. PTC is usually characterized by slow progression and good prognosis. However, due to high morbidity and recurrence rates (about 20-40%), the mortality rate of PTC accounts for approximately more than 50% of total TC[2]. Therefore, studying the specific molecular mechanisms of PTC occurrence and development has become a work direction for contemporary clinicians and researchers. In addition, it is of important significance to increase the early diagnosis and survival rates of patients, as well as to improve its prognosis.

Micro-ribonucleic acid (miRNA) is an endogenous single-stranded non-coding RNA composed of about 18-22 nucleotides. MiRNA regulates the translation and stability of target genes through complete and incomplete binding to their 3'-untranslated region (UTR)[3]. A large number of studies have demonstrated that miRNAs have different expressions in various malignant tumors, thereby playing important roles in the occurrence and development of malignancies. Existing studies have confirmed that miRNAs are also abnormally expressed in PTC tissues.

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About 38% of known miRNAs are down-regulated, while about 32% of them are up-regulated[4,5]. Therefore, the unique expression features of miRNA may serve as the basis for the preoperative clinical diagnosis of PTC.

The miR-506 precursor coding gene is located on the X chromosome Xq27.3. MiR-506-3p is the 3' end of its stem-loop structure[6]. According to previous studies, miR-506 is involved in the regulation of signal transduction related to the occurrence or development of various tumors[7-10]. However, the exact function of miR-506 in PTC remains unclear. Therefore, we detected miR-506 expression in large-sample PTC tissues in this study. Furthermore, we explored the correlation between miR-506 expression and PTC invasion and metastasis.

Patients and Methods

Tissue Samples and Cell Lines

From July 2015 to April 2017, 80 patients diagnosed with PTC after surgery in the Taizhou Municipal Hospital were enrolled in this study. Meanwhile, carcinoma tissues and para-carcinoma normal tissues were surgically resected. Human PTC cell lines (FTC-133, IHH-4, TPC-1 and K1) and normal thyroid gland cell line (Nthy-ori3-) were purchased from the Shanghai University of Chinese Academy of Sciences Library (Shanghai, China). All cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Grand Island, NY, USA) containing 10% fetal bovine serum (FBS; Gibco, Grand Island, NY, USA) and 1% penicillin-streptomycin. The cells in the logarithmic phase were collected for subsequent experiments. This study was approved by the Ethics Committee of Taizhou Municipal Hospital. Signed informed consents were obtained from all participants before the study.

Cell Transfection

MiR-506 mimics, negative control (miR-NC) and LV-IL17RD were transiently transfected into TPC-1 cells according to the instructions of Lipofectamine™ 2000 (Invitrogen, Carlsbad, CA, USA). Transfected TPC-1 cells were cultured in an incubator with 5% CO_2 at 37°C. 48 h after transfection, cells were collected for subsequent experiments.

Three groups were established *in vitro*: the miR-NC group (negative control), the Mimics group (TPC-1 cells transfected with miR-506 mimics) and the Mimics + IL17RD group (TPC-1 cell co-transfected with miR-506 mimics and LV-IL17RD).

Target Prediction and Dual Luciferase Reporter Gene Assay

The possible target genes of miR-506 were predicted using target gene prediction software miRBase (http://www.mirbase.org/), TargetScan (http://www.targetscan.org/) and PicTar (http://pictar.mdc-berlin.de/).

According to the prediction results, IL17RD was found a possible target gene of miR-506. Stable PTC-1 cells were inoculated into 96-well plates (4×10^6/well) with a total volume of 100 μL per well. Then the cells were incubated in a 5% CO_2, 37°C incubator for 24 h. Subsequently, cell transfection was performed according to the instructions of Lipofectamine™ 2000 reagent. 4 groups were established, including the miR-506/IL17RD-Wt-3'UTR group, the NC/IL17RD-Wt-3'UTR group, the miR-506/IL17RD-Mut-3'UTR group and the NC/IL17RD-Mut-3'UTR group. 48 h after transfection, the medium was discarded. The fluorescence value was determined in strict accordance with the Dual-Luciferase assay kit (Promega; Madison, WI, USA).

Real Time Fluorescence-Quantitative Polymerase Chain Reaction (RT-qPCR) Analysis

Total RNA in tissues and cells was extracted using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Complementary deoxyribose nucleic acid (cDNA) was synthesized using SYBR PrimeScript miRNA Reverse Transcription-Polymerase Chain Reaction (RT-PCR) kit and PrimeScript RT Master Mix (TaKaRa, Otsu, Shiga, Japan). The expression level of miR-506 was detected *via* qPCR using SYBR Green II. U6 was used as an internal reference for miR-506. The relative expression levels of miRNA and mRNA were calculated by the $2^{-\Delta\Delta Ct}$ method. Primer sequences used in this study were as follows: miR-506, F: 5'-TTGGAACCAACTCCTTACTC-3', R: 5'-CCCGGGATGTGTCTCAAGGA-3'; U6: F: 5'-GCTTCGGCAGCACATATACTAAAAT-3', R: 5'-CGCTTCAGAATTTGCGTGTCAT-3'.

Western Blots (WB) Analysis

Total proteins were extracted from tissues and cells using radioimmunoprecipitation assay (RIPA) lysis buffer (Beyotime, Shanghai, China). The concentration of extracted protein was quantified by the bicinchoninic acid (BCA) protein quantitative detection kit (Pierce Biotechnology, Waltham, MA, USA). Extracted protein was separated by 10% sodium dodecyl sulfate-poly-

acrylamide gel electrophoresis (SDS-PAGE) and transferred onto polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). After sealing with 5% skim milk powder at room temperature for 1 h, the membrane was washed with Tris-Buffered Saline and Tween 20 (TBST) for 10 min. Then, the hybrid membrane was cut and incubated with primary antibodies of IL17RD (1:1000, Thermo Fisher Scientific, Waltham, MA, USA) and GAPDH (1:1000, Cell Signaling Technology, Danvers, MA, USA) at 4°C overnight. On the next day, the membranes were incubated again with horseradish peroxidase (HRP)-labeled secondary antibody (1:2000). Finally, immunoreactive protein bands were detected using enhanced chemiluminescence (ECL) reagent (Thermo Fisher Scientific, Waltham, MA, USA), photographed using Alpha gel imaging and chemiluminescence system, and analyzed using Image J analysis software.

Cell Proliferation

After transfection, cells were inoculated into 96-well plates at a density of 2×10^3/200 μL (200 μL/well). 5 replicates were set in each group. After adherence to the wall, one 96-well plate was detected every 24 h. Briefly, 50 μL MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) was added, followed by incubation for another 2 h. Then the medium was discarded, and dimethyl sulfoxide (DMSO; Sigma-Aldrich, St. Louis, MO, USA) was added (100 μL/well) and vibrated for 10 min. The optical density (OD) value at the wavelength of 492 nm was detected using a microplate reader, and the average value was obtained. The cell proliferation curve was finally plotted.

Wound Healing Assay

The cells in the three groups were first seeded into 24-well plates (1×10^5 cells/well). A 200 μL sterile pipette tip was used to make a "1"-shaped scratch on the bottom of plates. 24 h later, the migration of cells in scratches was observed under an inverted microscope. Meanwhile, the relative mobility of cells was calculated (relative to the miR-NC group). Three duplicates were set in each group, and the experiment was repeated three times.

Transwell Assay

For the invasion test, Matrigel was added to the upper transwell chamber in advance, and then the chamber was placed in a 37°C incubator for 4 h. The cells in each group were diluted to 2×10^4/200 μL. After digestion, the cells were suspended in a serum-free medium. For the migration assay, the cells in each group were diluted to 2×10^4/200 μL. 200 μL cell suspension was added into the upper transwell chamber. Meanwhile, 600 μL medium containing 10% FBS was added to the lower transwell chamber, followed by incubation at 37°C for 24 h. Then, the solution in the upper chamber was discarded. Subsequently, the cells were washed with phosphate-buffered saline (PBS) 3 times, fixed with methanol for 15 min and stained with 1% crystal violet for 1 h. Cells on the upper basement membrane were wiped clean using a cotton swab. Finally, the number of cells passing through the basement membrane was observed under a microscope, followed by photography and counting.

Statistical Analysis

Student's *t*-test or *F*-test was used to compare the difference among different groups. All *p*-values were two-sided, and $p<0.05$ were considered statistically significant. Prism 6.02 software (La Jolla, CA, USA) was used for all statistical analysis.

Results

MiR-506 Expression in PTC Tissues and Cell Lines

In clinical cases, miR-506 expression was significantly down-regulated in PTC tissues (Figure 1A). Similarly, the results of RT-qPCR demonstrated that the expression of miR-506 in four PTC cell lines was markedly lower than that of normal thyroid cell line (Nthy-ori3-1). TPC-1 cells expressed the lowest level of miR-506 (Figure 1B). Therefore, TPC-1 cells were selected for subsequent cell proliferation and metastasis assays.

Prediction and Identification of MiR-506 Target Genes

According to the prediction results, the 3'UTR sequence of IL17RD gene might be the target of miR-506 (Figure 2A). To further verify our assumption, Dual-Luciferase reporter gene assay was performed. The transfection efficiency of mimics was first determined by RT-qPCR (Figure 2B). Dual-Luciferase reporter gene assay revealed that miR-506 significantly inhibited the Luciferase activity of IL17RD 3'UTR sequence in TPC-1 cells. However, it did not affect the Luciferase activity of IL17RD mutation se-

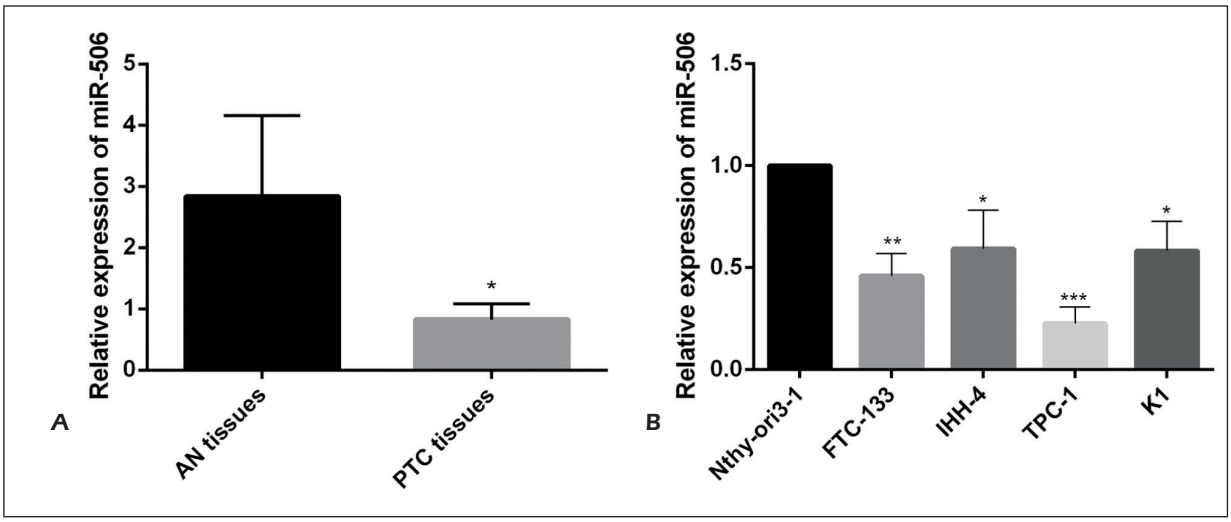

Figure 1. The expressions of miR-506 in papillary thyroid cancer (PTC) cases and cells. **A**, Difference in the expression of miR-506 between PTC tissues and adjacent normal tissues. (*p<0.05 compared with adjacent normal tissue). **B**, Difference in the expression of miR-506 between PTC cells and normal thyroid gland cells. (*p<0.05, **p<0.01, ***p<0.001 compared with Nthy-ori3-1 cells).

quence (Figure 2C). Moreover, the results of WB demonstrated that the overexpression of miR-506 significantly reduced the protein expression of IL17RD (Figure 2C). The above results indicated that miR-506 could negatively regulate the expression of IL17RD in TPC-1 cells.

Effects of MiR-506 on Cell Function

MTT results showed that a statistically significant difference in cell proliferation was found between the miR-506 mimics group and the miR-NC group (Figure 3). This confirmed the inhibitory role of miR-506 in cell proliferation.

The effects of miR-506 on the migration of TPC-1 cells were examined through wound-healing assay (Figure 4A, 4B). The results showed that the wound closure in the miR-506 mimics group was remarkably larger than that of the miR-NC group. Cell invasion ability was examined by transwell assay. As shown in Figure 4A and 4C, the number of invasion cells was significantly reduced in miR-506-mimics group.

Epithelial-mesenchymal transition (EMT) plays an important role in the metastasis process of tumor cells[11,12]. In our study, we found that the protein expression of epithelial marker E-cad-

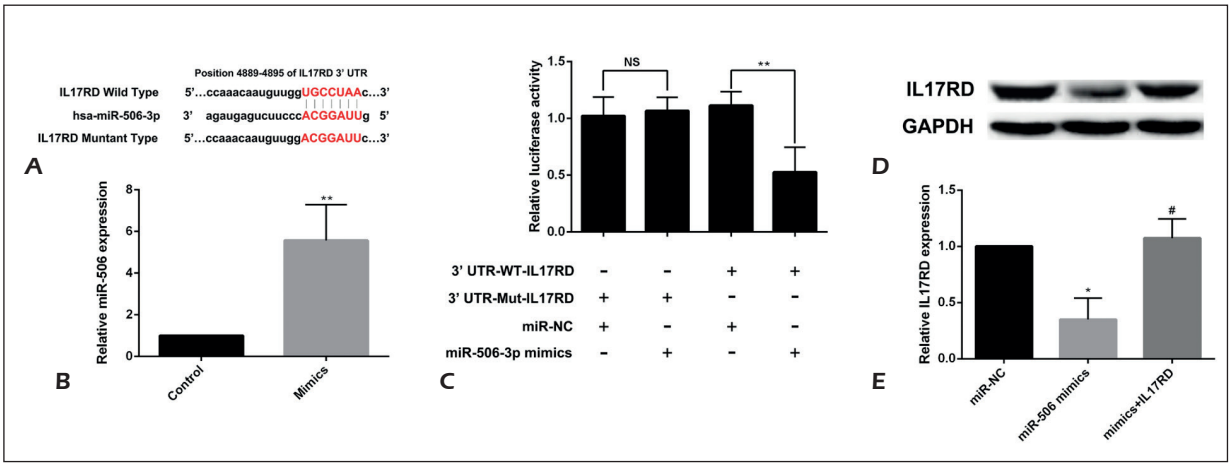

Figure 2. IL17RD was a direct and functional target of miR-506. TPC-1 cells were transfected with miR-506 mimics and inhibitor. **A**, Diagram of putative miR-506 binding sites of IL17RD. **B**, Transfection efficiency detected by RT-qPCR. (**p<0.01). **C**, Relative activities of Luciferase reporters. D-E, Protein expressions of IL17RD in TPC-1 cells. Data were presented as means ± standard deviations. (*p<0.05 vs. NC group; #p<0.05 vs. Mimics group).

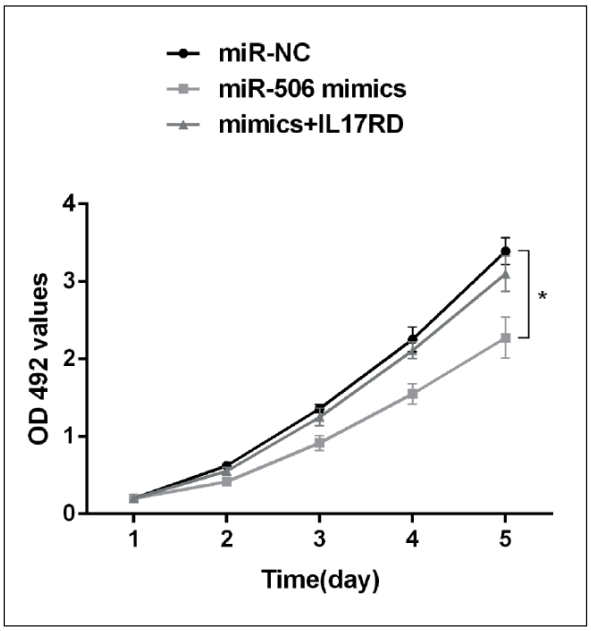

Figure 3. MiR-506 decreased cell proliferation (*p<0.05 vs. NC group).

herin increased significantly after overexpression in TPC-1 cells. However, mesenchymal marker N-cadherin was remarkably inhibited (Figure 4D-4F).

However, compared with the Mimics + IL-17RD group, the behavior of miR-506 was significantly weakened after the recovery of the IL17RD expression in TPC-1 cells (Figure 4).

Discussion

PTC is the most common malignant endocrine tumor. Studies have proved that genetic and epigenetic changes are involved in the occurrence and development of PTC. MiRNAs, as small non-coding RNAs, can serve as oncogenes or tumor suppressor genes. Previously by scholars[13-17] have indicated that they play important roles in the occurrence and development of various malignancies, including PTC. Targeting miRNA may be used as a novel strategy for the diagnosis and treatment of malignant tumors. In this work, 80 fresh pathological tissue specimens of PTC were collected. RT-qPCR results found that miR-506 was lowly expressed in PTC tissues and cell lines. This indicated that miR-506 had the potential to be a biomarker for evaluating PTC prognosis.

Numerous and complicated regulatory networks of miRNAs can regulate the expression of multiple genes in a targeted manner. Meanwhile,

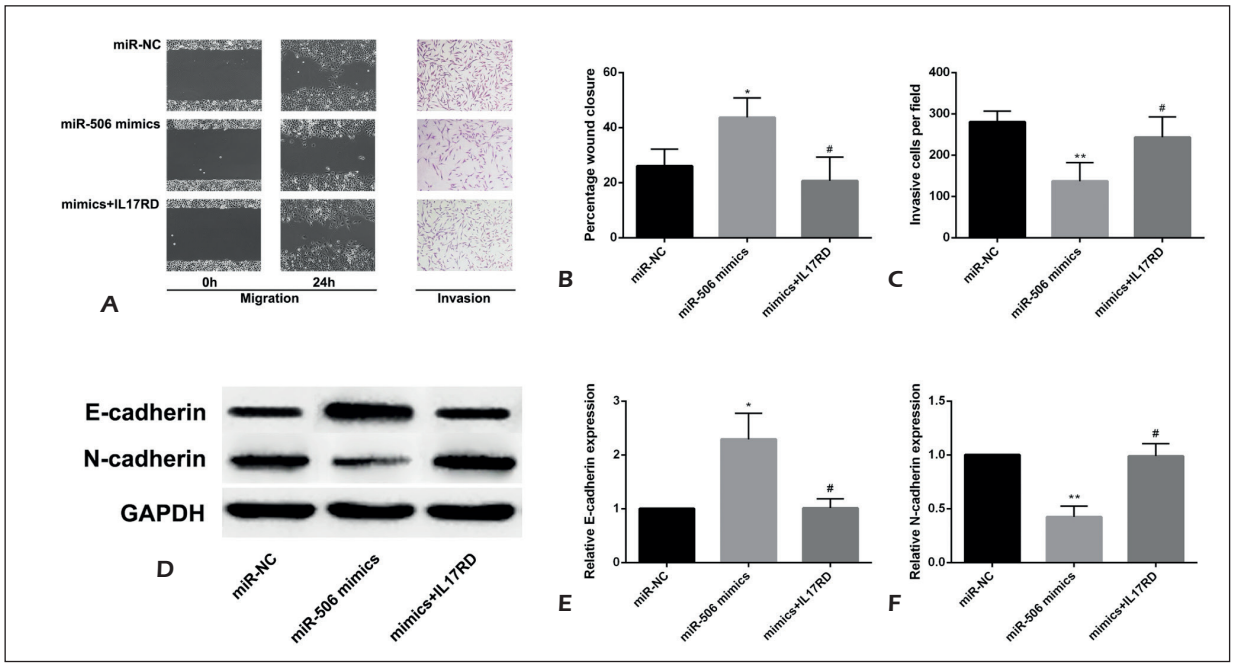

Figure 4. MiR-506/IL17RD axis inhibited the invasion and migration of PTC cells. **A-C**, The migration and invasion abilities were detected by wound-healing and transwell assays, respectively. **D-F**, Epithelial-mesenchymal transition (EMT) of TPC-1 cells. EMT markers post-transfection were detected by Western blot. Data were presented as means ± standard deviations. (*p<0.05, **p<0.01 vs. NC group; #p<0.05 vs. Mimics group).

multiple miRNAs can also jointly regulate a single target gene, thus participating in regulating various biological behaviors of tumor cells[18,19]. Currently, miRNA has become one of the research hotspots. Its specific regulatory target in diseases has been a key part of the miRNA research. In the present study, online database Targetscan predicted that there was a binding site with miR-506 in the 3'UTR of IL17RD messenger RNA (mRNA). This suggested that miR-506 might regulate IL17RD in a targeted manner. More importantly, the expression of IL17RD in PTC cells was significantly down-regulated after transfection of miR-506. Luciferase reporter gene assay verified that miR-506 could inhibit the expression of IL17RD by targeted binding to the 3'UTR of IL17RD.

IL17RD is also known as hSef. Its ligand IL-17 plays an important role in the occurrence and progression of the inflammatory response. Meanwhile, it is closely correlated with many clinical diseases, including malignant tumors[20-24]. Abnormal expression of IL17RD is considered as a common mechanism of epithelioma formation[24]. However, its regulatory role in the occurrence of the tumor remains controversial. Umstead et al[25] have found that up-regulation of IL17RD inhibits tumor cell proliferation by inhibiting fibroblast growth factor (FGF) and mitogen-activated protein kinase (MAPK) signal transduction, eventually inhibiting tumorigenesis *in vitro*. On the contrary, Ren *et al*[26] have proved that the up-regulation of IL17RD exerts a carcinogenic effect *via* enhancing epidermal growth factor (EGF). *In vitro* study has also confirmed that the IL17RD up-regulation strengthens FGF-induced migration and invasion of prostate cancer cells[27]. Therefore, IL17RD was further studied as another focus in this experiment.

It is well known that invasion and migration are major biological features of malignant tumors, which are different from benign tumors. Meanwhile, they are also the main causes of recurrence and death of PTC patients. Invasion and migration of tumor cells are a multi-stage and multi-step development processes. Tumor cells can secrete a variety of cytokines, inhibit the expression of intercellular adhesion molecules and promote cell morphology and pseudopodia formation. This may eventually enhance the motility of tumor cells, and make them shed from primary tumor lesion to free cells[28,29]. Besides, epithelial-mesenchymal transition (EMT) plays an important role in cell morphology and movement. Epithelial cells can acquire the phenotype of mesenchymal cells *via* EMT under the action of various inducers. Therefore, cell metastasis is enhanced, and cells are shed into the vascular system and escaped from anoikis, leading to metastasis to distant tissues and organs[30].

In this study, we found that the expression of IL17RD in PTC cells was significantly declined after miR-506 mimics transfection. The results of functional experiments revealed that the proliferation, invasion and migration abilities of TPC-1 cells with low expression of IL17RD were markedly decreased. Western blot assay indicated that the protein expression of E-cadherin was significantly reduced, whereas N-cadherin was increased. Correspondingly, after IL17RD was restored, the malignant function of TPC-1 cells was recovered. This indicated that the anti-tumor effect of miR-560 was closely related to IL17RD expression. The above results showed that miR-506 could inhibit the proliferation, invasion and migration capacities of PTC cells by inhibiting IL17RD expression. However, this experiment was not verified by IL17RD knock out *in vivo*, which required further experiments in the future.

Conclusions

We indicated that miR-506 could inhibit PTC cell proliferation and metastasis. Moreover, IL-17RD might be the downstream target of biological process. Our findings might provide a new therapeutic direction for the treatment of PTC.

Acknowledgements

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Conflict of Interest

The authors declare that they have no conflict of interest.

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