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lncRNA HCG22 regulated cell growth and metastasis of papillary thyroid cancer via negatively modulating miR-425-5p

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Abstract

Introduction: Papillary thyroid cancer (PTC) is a common malignant tumour in the endocrine system with increasing incidence. LncRNA HCG22 (HCG22) was noticed to be dysregulated in PTC, but its specific function and mechanism remain unknown. The function of HCG22 and its underlying molecular mechanism was investigated to evaluate its potential as a biomarker for PTC.

Material and methods: The expression of HCG22 was detected in PTC cells (TPC-1, SNU790, GLAG-66, and BCPAP) and normal thyroid cells (Nthy-ori) using real time quantative polymerase chain reaction (RT-qPCR). HCG22 and miR-425-5p were regulated by cell transfection. The cell proliferation and metastasis were assessed by CCK8 and Transwell assay.

Results: HCG22 was upregulated in PTC cells, of which the knockdown suppressed the proliferation, migration, and invasion of PTC cells. miR-425-5p was downregulated in PTC cells, which was negatively regulated by HCG22. Silencing miR-425-5p could reverse the inhibitory effect of HCG22 knockdown on the cellular processes of PTC.

Conclusions: HCG22 served as a tumour promoter in PTC cells, which regulated cell proliferation and metastasis via negatively regulating miR-425-5p. **(Endokrynol Pol 2024; 75 (1): 20–26)**

Key words: *papillary thyroid cancer; cell growth; migration; invasion; ceRNA; miR-425-5p*

Introduction

Thyroid cancer is a common malignant tumour in the endocrine system, and the incidence in women is higher than that in men, after breast cancer, lung cancer, and colorectal cancer [1]. Although most thyroid cancers are benign, some show poor prognosis, and the therapeutic effects are always unsatisfactory [2]. Thyroid cancer has become the fastest increasing tumour, with the pathologic types of papillary thyroid carcinoma (PCT), medullary thyroid carcinoma (MTC), follicular thyroid carcinoma (FTC), and undifferentiated thyroid carcinoma (UDTC). PTC is the most common type, accounting for 80–90% of new cases [3]. In the past decades, surgical resection, radioiodine therapy, and postoperative thyroid stimulating hormone inhibition therapy have achieved great effects in most PTC patients, but a huge number of PTC patients with high malignancy are still prone to in situ recurrence and distant metastasis [4]. The unclear molecular mechanism of PTC occurrence and development is one of the potential reasons for these adverse events. Therefore, it is necessary to extensively research correlated mechanisms and identify novel and accurate biomarkers of PTC.

The pathogenesis and progression of PTC involves various processes, stages, and signalling. Previous studies have made progress in the molecular mechanism of PTC onset, including the mutation of related genes, such as RAS and BRAF, the rearrangement of RET/PTC and PAX8-PPARγ, and the involvement of non-coding RNAs (ncRNAs) [5]. Long non-coding RNAs (lncRNAs) are important members of ncRNAs, accounting for a huge percentage of the human genome. Although lncRNAs lack an obvious open reading frame and are unable to code proteins, they might be able to interact with RNAs or DNAs and therefore regulate transcription and translation, and mediate signalling transduction and the pathological processes of cancers [6, 7]. Some studies have explored several candidate lncRNAs that were dysregulated in thyroid cancer and associated with clinical prognosis, where lncRNA HCG22 (HCG22)

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was included [8]. However, there is a lack of direct evidence to demonstrate the specific function and underlying mechanisms in PTC development, which would improve the present knowledge of PTC pathogenesis and development. The proliferation and metastasis of tumour cells are critical processes in the development of cancer, which determine its malignancy. HCG22 was identified as a regulator of oral squamous cell carcinoma, and it is associated with the progression of steroid-induced ocular hypertension with abnormal expression [9–11]. Therefore, the dysregulation of HCG22 in PTC also implies its potential in regulating tumour progression, which needs to be disclosed.

Although the competitive endogenous RNA (ceRNA) theory is controversial, it is still considered a major path for lncRNAs to display their functional roles [12–14]. According to the prediction in an online database, miR-425-5p could bind with HCG22, and miR-425-5p has also been reported to play roles in regulating cell growth and metastasis of various human cancers, such as ovarian cancer, prostate cancer, and pancreatic cancer. Its function during the function of HCG22 in PTC was also estimated.

Material and methods

Cell culture

PTC cell lines (TPC-1, SNU790, GLAG-66, and BCPAP) and normal thyroid cells (Nthy-ori) were obtained from ATCC and cultured in RPMI-1640 culture medium (Invitrogen, USA) with 10% foetal bovine serum (FBS) at 37°C. After reaching confluence of 80–90%, the cells were used for the following experiments.

Cell transfection

Cells were transfected with siRNA of HCG22 (si-HCG22, 5′-GUCUCAUUUUAAAUCAUAUAC-3′, RiboBio Co., China) or negative controls for the knockdown of HCG22 in PTC cells. The regulation of miR-425-5p was performed by the transfection of miR-425-5p mimic (5′-AAUGACACGAUCACUCCCGUUGA-3′) or inhibitor (5′-UCAACGGGAGUGAUCGUGUCAUU-3′), and negative controls (5′-CAGUACUUUUGUGUAGUACAA-3′) were also carried out. Cell transfection was performed at room temperature with Lipofectamine 3000 (Invitrogen, USA) and assessed according to the changes in corresponding expression levels.

Real-time quantitative polymerase chain reaction (qPCR)

Cells were lysed with Trizol reagent (Invitrogen, USA) after washing with phosphate-buffered saline (PBS) twice, and they where then transferred into an Eppendorf (EP) tube without RNA enzymes. After stewing for 30 min, 200 μL chloroform was added and shaken. Then, the mixture was centrifuged at 12,000 rpm for 15 min at 4°C, and the supernatant was mixed with isopropyl alcohol at the ratio of 1:1 (v/v). After centrifugation at 7500 rpm for 5 min, total RNA was obtained as the precipitate and evaluated by the value of OD260/280.

cDNA was synthesized with isolated total RNA and miRNA First-strand cDNA kit (Tiangen, China) for miR-425-5p and the QuantiTect Reverse Transcription kit (Qiagen, USA) for HCG22. The 7500 PCR system was employed to detect the expression of miR-425-5p and HCG22 with SYBR Premix Ex TaqTM (Takara, China). The reaction conditions were as follows: 50°C for 2 min and 95°C for 15 min, and then, 40 cycles of 95°C for 30 s, 60°C for 30 s, and 72°C for 30 s. U6 and GAPDH were employed as an internal reference for miR-425-5p and HCG22, respectively. The primer sequences used in the PCR assay were as follows: HCG22 F 5′-ACAGCAGTGAAACCCACCA-3′, R 5′-GAAGCCCAATCCAACAAAGAGC-3′; miR-425-5p F 5′-GGGGAGTTAGGATTAGGTC-3′, R 5′-TGCGRGRCGRGGAGTC-3′; U6 F 5′-CTCGCTTCGGCAGCACA-3′, R 5′-AACGCTTCACGAATTTGCGT-3′; GAPDH F 5′-GACTGAGATTGGCCCGATG-3′, R 5′-GACTGAGATTGGCCCGATG-3′.

Cell proliferation assay

Cells were collected after transfection and resuspended in a completed culture medium to prepare the single-cell suspension. The suspension was seeded into 96-well plates with 6 wells of each group, and the cell number of each well was 2×10^4 per well. The plates were incubated for 24, 48, 72, and 96 h followed by the addition of 10 μL CCK8 per well (Dojindo, Japan). After incubating for another 2 h, OD450 of each well was measured with a microplate reader, and the growth curve of cells was plotted.

Cell metastasis assay

Cell suspensions were seeded into the upper chamber of transwell plates, and both the upper and lower chambers were filled with culture medium, but only the medium in the lower chamber was supplemented with 10% FBS. The plates were incubated for 24 h, and the upper chamber was washed with PBS 3 times. The washed chambers were fixed with 4% paraformaldehyde for 15 min and stained with 0.1% crystal violet for 15 min. After washing 3 times with PBS, the chamber was wiped with a cotton swab and observed under a microscope with 5 random fields of each group. The upper chamber was pre-coated with Matrigel (BD Bioscience, USA) before evaluation of cell invasion.

Dual-luciferase reporter assay

The binding sites between HCG22 and miR-425-5p were predicted from an online database (https://rnasysu.com/encori/index.php). Wild-type and mutant-type HCG22 luciferase reporter vectors were established with binding sites and mutant sites, respectively. The constructed vectors were transfected into cells with miR-425-5p mimic, inhibitor, or negative controls with the help of Lipofectamine 2000 (Invitrogen, USA). The luciferase activity of HCG22 was detected by a chemiluminescence detector normalized to Rinella.

Statistical analysis

All data were expressed as mean ± standard deviation (SD) (n = 3). Difference comparison was carried out with one-way ANOVA followed by Duncan's post-hoc test using SPSS 26.0 software (IBM, USA, $p < 0.05$).

Results

Expression of HCG22 in PTC cell lines

In TPC1, SNU790, GLAG-66, and BCPAP cells, HCG22 was significantly upregulated relative to the normal cell Nthy-ori (Fig. 1A). Although the difference between PTC cells was insignificant, TPC1 and SNU790 showed greater sensitivity to the upregulation of HCG22; therefore, they were selected for the following experiments. The transfection of siRNA-HCG22 (si-HCG22) dramatically suppressed its expression in both TPC1 and SNU790 cells (Fig. 1B).

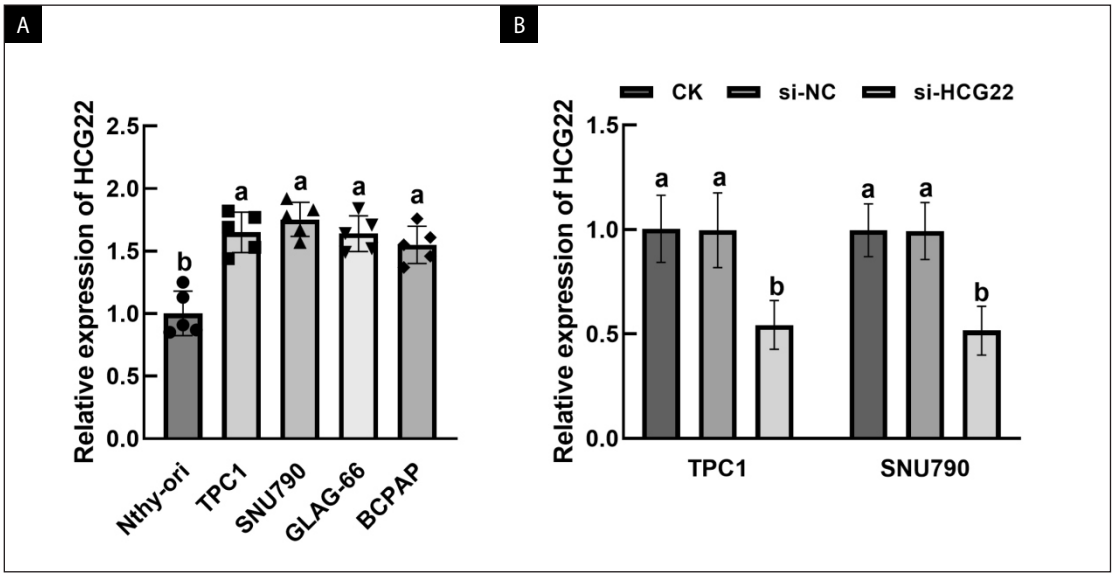

Figure 1. *HCG22 was upregulated in papillary thyroid cancer (PTC) cells compared with normal cells (***A***), which were suppressed by the transfection of si-HCG22 in TPC1 and SNU790 cells (***B***). The different letters indicate statistical significance*

HCG22 regulates cell growth and metastasis of PTC

The cell counting kit 8 (CCK8) assay revealed that the knockdown of HCG22 in TPC1 and SNU790 cells significantly inhibited cell proliferation compared with non-transfected cells (Fig. 2A). Moreover, the silenced HCG22 was also found to suppress the migration (Fig. 2B) and invasion (Fig. 2C) of TPC1 and SNU790 cells by Transwell assay. These results indicated the tumour promoter role of HCG22 in TPC cells.

HCG22 regulates miR-425-5p

Reduced miR-425-5p was observed in PTC cells compared with normal cells (Fig. 3A). While the knockdown of HCG22 significantly improved miR-425-5p in TPC1 (Fig. 3B) and SNU790 (Fig. 3C) cells, which was suppressed by the transfection of the inhibitor. Additionally, the luciferase reporter showed that miR-425-5p could negatively regulate the luciferase activity of HCG22 with several binding sites (Fig. 3D).

HCG22 regulates PTC cellular processes via miR-425-5p

The suppressed proliferation of TPC1 and SNU790 by HCG22 knockdown was found to recover after the transfection of the miR-425-5p inhibitor (Fig. 4A). The inhibitory effects of silenced HCG22 on the migration (Fig. 4B) and invasion (Fig. 4C) of PTC cells were also reversed by the knockdown of miR-425-5p.

Discussion

Recently, numerous investigations have focused on the role of HCG22 in human diseases. In human cancers, HCG22 has been reported to possess different expressions and functions. For example, HCG22 was identified as an inhibitor in oesophageal squamous cell carcinoma and oral squamous cell carcinoma that suppressed cellular processes via regulating functional miRNAs or mRNAs [9, 10, 15]. The dysregulation of HCG22 was observed in various cancers and was also included in diagnostic and prognostic signatures, such as gastric adenocarcinoma, ocular hypertension, and bladder cancer [16–18]. HCG22 was also identified as a prognostic biomarker in PTC patients, which was significantly correlated with the overall survival in The Cancer Genome Atlas (TCGA) [19]. Herein, HCG22 was found to be upregulated in PTC cells. Tumour progression is a complex process involving cell proliferation, metastasis, and differentiation. The suppression of HCG22 inhibited the growth and metastasis of PTC cells. The uncontrolled proliferation of tumour cells induced the progression of cancers, and the increasing metastasis is the major cause of cancer malignancy [20, 21]. Therefore, the inhibition of PTC cellular processes by HCG22 knockdown suggested its tumour promoter role in the development of PTC.

The downstream miRNA has been the focus to explore the molecular mechanism underlying the function of HCG22. The ceRNA mechanism has been considered the main pathway of lncRNAs to display their function, which has attracted special attention in cancer research. miR-425-5p has been predicted as the direct target of HCG22 with several binding sites, and it has been reported to mediate the inhibitory effect of HCG22 on cellular processes of oral squamous cell

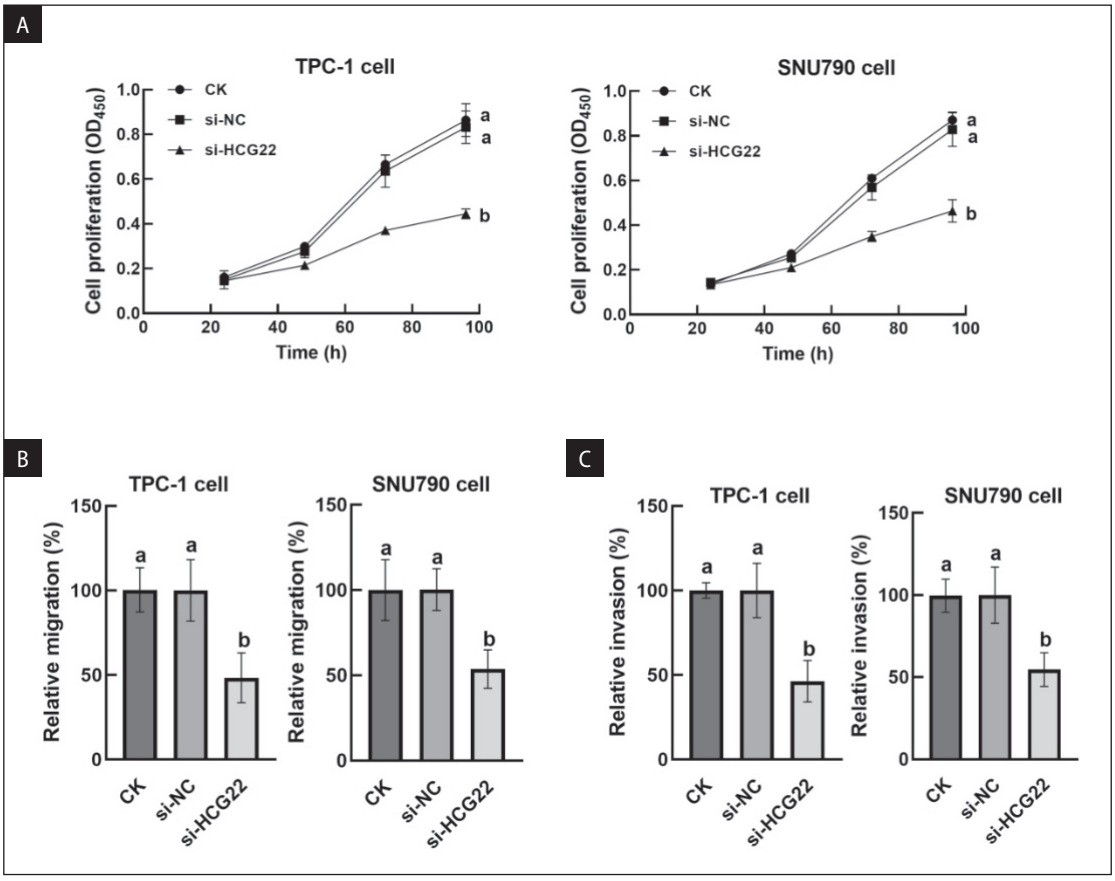

Figure 2. *Silencing HCG22 significantly suppressed the proliferation (***A***), migration (***B***), and invasion (***C***) of TPC-1 and SNU790 cells. The different letters indicate statistical significance*

carcinoma [22]. Previously, miR-425-5p was reported to play different functional roles in various diseases. For instance, miR-425-5p promoted ovarian cancer cell growth, migration, and invasion [23]. The inhibitory effect of miR-425-5p on differentiation and proliferation was revealed in porcine intramuscular preadipocytes [24]. miR-425-5p was involved in the regulation the development of various cancer by lncRNAs, such as the promoted effect of lncRNA MALAT1 on osteosarcoma, the alleviated effect of lncRNA SNHG8 on inflammation in ischaemic stroke, and the suppressor role of lncRNA LINC-PINT in laryngeal carcinoma [25–27]. In the present study, silencing miR-425-5p could reverse the inhibited growth and metastasis of PTC cells by HCG22 knockdown, indicating that the promoter role of HCG22 was mediated by miR-425-5p.

miR-425-5p was reported to target CYLD in gastric cancer mediating tumour progression and modulating AFF4 in ovarian cancer [23, 28]. However, the downstream target of miR-425-5p in PTC has not been revealed in the present study, which needs further exploration. Although there was a lack of further mechanism investigation to reveal the involved downstream genes and signalling regulated by miR-425-5p and HCG22, the present findings still demonstrate the function of lncRNAs in regulating cancer cellular processes. Additionally, the clinical trait is a common research method to explore effective biomarkers for the diagnosis and prognosis of cancers [29–32]. Future studies should collect clinical samples to assess the significance and potential of HCG22 in the clinical diagnosis and prognosis prediction of PTC. On the other hand, this study was mainly performed *in vitro*, which lacked *in vivo* validation. Establishing animal models could intuitively show the effect of lncRNAs and miRNAs on tumour progression, which should be considered in future studies.

Conclusions

Taken together, HCG22 was upregulated in PTC and served as a tumour promoter, of which the knockdown suppressed cell proliferation, migration, and invasion of PTC cells. miR-425-5p was downregulated in PTC and was negatively regulated by HCG22. Silencing miR-425-5p could attenuate the inhibitory effect of HCG22 knockdown on PTC cellular processes. Therefore, HCG22 regulates the cellular progression of PTC via modulating miR-425-5p.

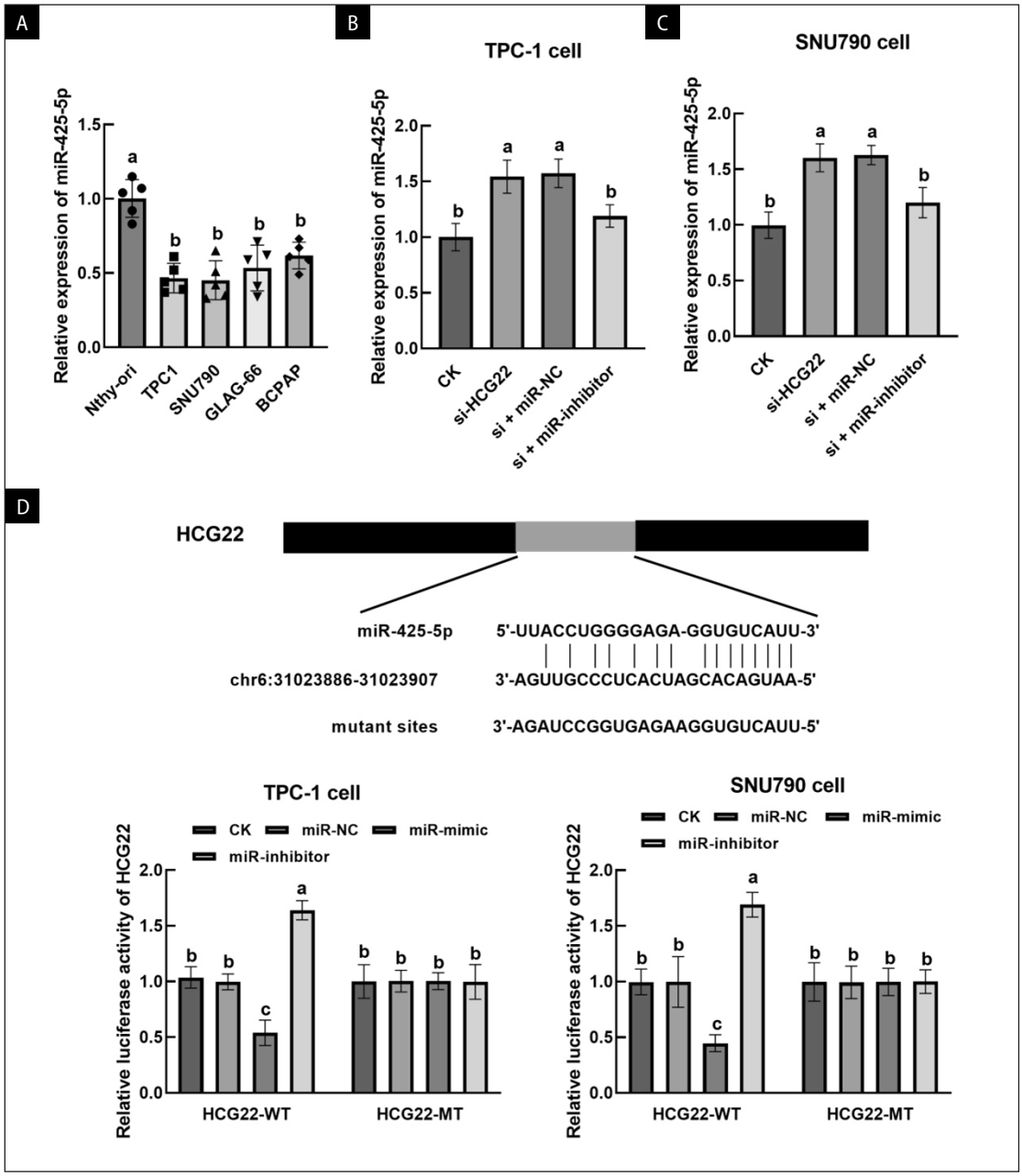

Figure 3. *miR-425-5p was downregulated in papillary thyroid cancer (PTC) cells compared with the normal cells (***A***).* **BC.** *The knockdown of HCG22 significantly enhanced the expression of miR-425-5p, which was reversed by the transfection of miR-425-5p inhibitor in TPC1 (***B***) and SNU790 cells (***C***);* **D.** *miR-425-5p could negatively regulate the luciferase activity of HCG22 in TPC1 and SNU790 cells. The different letters indicated statistical significance.*

Data availability statement

The corresponding author can provide relevant data for this study.

Ethics statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of The First People's Hospital of Neijiang.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by X.P.C., C.M., Y.W. and J.Y.H. The first draft of the manuscript was written by Y.W., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors state that there is no conflict of interest in this study.

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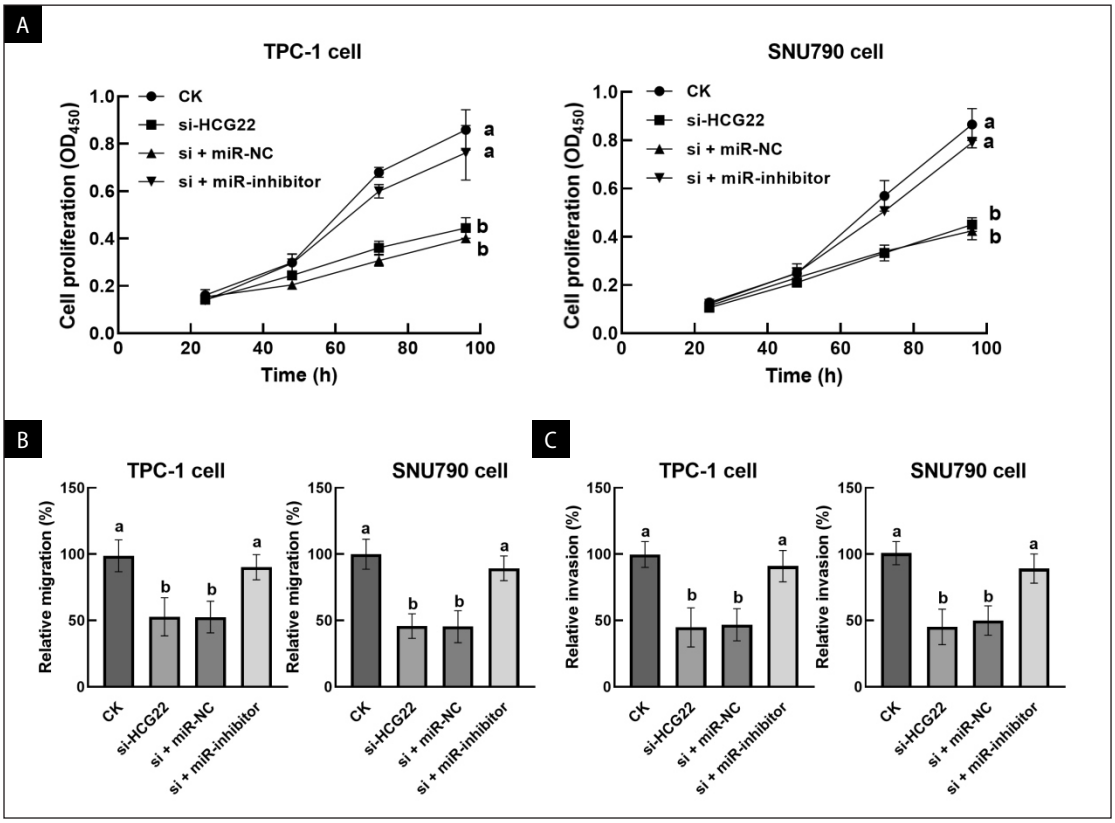

Figure 4. *Silencing miR-425-5p could alleviate the inhibitory effect of HCG22 knockdown on the proliferation (***A***), migration (***B***), and invasion (***C***) of TPC1 and SNU790 cells. The different letters indicated statistical significance*

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