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*Basic Study***MiR-30e-3p inhibits gastric cancer development by negatively regulating THO complex 2 and PI3K/AKT/mTOR signaling**

Gu XJ *et al.* MiR-30e-3p/THOC2 axis in gastric cancer

Xiao-Jing Gu, Ya-Jun Li, Fang Wang, Ting Ye

Abstract**BACKGROUND**

¹ Gastric cancer (GC) is a common type of digestive cancer with high morbidity and mortality rates worldwide. Considerable effort has been expended in understanding the mechanism of GC development and metastasis. The current study therefore explores the involvement of microRNAs in the regulation of GC progression.¹¹

AIM

To explore the expression and function of miR-30e-3p in GC development.

METHODS

MiR-30e-3p was found to be downregulated in GC, with low levels thereof predicting poor outcomes among patients with GC. Functionally, we revealed that miR-30e-3p suppressed cell growth and metastatic behaviors of GC cells. Bioinformatics analysis predicted that THO complex 2 (THOC2) ¹ was a direct target of miR-30e-3p, and the interaction between miR-30e-3p and THOC2 was further validated by a luciferase reporter assay.

RESULTS

Our findings revealed ¹ that knockdown of THOC2 inhibited the growth and metastatic behaviors of GC cells. After investigating signaling pathways involved in miR-30e-3p regulation, we found that the miR-30e-3p/THOC2 axis regulated the PI3K/AKT/mTOR pathway in GC.

CONCLUSION

Our findings suggest the novel functional axis miR-30e-3p/THOC2 is involved in GC development and progression. The miR-30e-3p/THOC2 axis could be utilized to develop new therapies against GC.

Key Words: Gastric cancer; MiR-30e-3p; THO complex2; PI3K/ AKT/ mTOR signaling

Gu X, Li Y, Wang F, Ye T. MiR-30e-3p inhibits gastric cancer development by negatively regulating THO complex 2 and PI3K/ AKT/ mTOR signaling. ¹⁰ *World J Gastrointest Oncol* 2022; In press

¹ **Core Tip:** Gastric cancer (GC) is a common digestive cancer with high morbidity and mortality rates worldwide. Considerable effort has been expended in understanding the mechanism of GC development and metastasis. Given that microRNAs ⁶ have been found to participate in the regulation of GC progression, we explored the expression and function of miR-30e-3p in GC development and revealed that knockdown of THO complex 2 (THOC2) inhibited the growth and metastatic behaviors of GC cells. After investigating signaling pathways involved in miR-30e-3p regulation were investigated, we found that the miR-30e-3p/THOC2 axis regulated the PI3K/AKT/mTOR pathway in GC.

INTRODUCTION

Gastric cancer (GC) is a common type of digestive cancer with high morbidity and mortality rates worldwide^[1]. *Helicobacter pylori* (*H. pylori*) infection has been considered the most significant risk factor for GC, especially in China^[2,3]. Nonetheless, the incidence of GC has substantially declined with improvements in the treatment of *H. pylori* infection over the past decades^[4]. Technical advances of diagnosis and therapy improve the survival of patients with GC^[5,6]. However, the prognosis remains unsatisfactory as patients with GC are mostly diagnosed at later stages and develop drug-resistance after treatment. Thus, it is essential to understand the tumorigenesis of GC and identify novel early diagnostic biomarkers and therapeutic targets for its treatment.

MicroRNAs (miRNAs) are small non-coding RNAs that participate in various biological processes^[7]. Mounting evidence has shown that miRNA regulates tumorigenesis of multiple cancers, including GC^[8,9]. MiRNAs exert their functions in GC development and metastasis by modulating tumor cell growth and malignancy^[10]. For instance, miR-181a acts as an oncogenic miRNA in GC by negatively regulating caprin-1 expression, and overexpression of miR-181a predicts poor patient survival^[11]. In contrast, microRNA profiling has identified that miR-6165 is a tumor suppressor and inhibits GC progression by regulating STRN4^[12]. Moreover, miRNAs can be utilized as biomarkers for GC diagnosis and patient prognosis^[13]. Our preliminary screening identified low miR-30e-3p expression in GC tissues. It has been reported that miR-30e-3p suppressed clear cell renal cell carcinoma (ccRCC) development and metastasis via targeting snail 1^[14]. Nevertheless, the function of miR-30e-3p in GC has yet to be studied.

THO complex 2 (THOC2) is an RNA-binding protein involved in mRNA export, genomic stability, and mitotic progression^[15]. THOC2 is essential for the early embryonic development of zebrafish^[16]. Zhou *et al*^[17] reported that THOC2 serves as an oncogene in melanoma and that knockdown of THOC2 inhibits the growth and

metastasis of melanoma. Nevertheless, the function and regulation of THOC2¹ in GC remain unclear.

In the current study, we showed that miR-30e-3p⁴⁴ was downregulated in GC tissues and cell lines, and low miR-30e-3p levels predicted unfavorable prognosis in patients with GC. Overexpression of miR-30e-3p³⁵ suppressed the malignant behaviors of GC cells by negatively regulating THOC2. We also confirmed that the miR-30e-3p/THOC2 axis⁴⁰ regulated the PI3K/AKT/mTOR pathway in GC. These findings indicate that miR-30e-3p/THOC2 could³⁵ serve as a novel diagnosis biomarker and therapeutic target for GC treatment.

³ **MATERIALS AND METHODS**

Patient tissues

Human GC tissues and matched adjacent tissues¹³ (20 pair) were obtained during surgery on patients with GC at General Hospital of Ningxia Medical University. The primary clinicopathological features of the patients are summarized in Supplementary Table 1. The tissues were stored in liquid nitrogen until further use. All tissue samples were validated by two independent pathologists.⁸ All patients participating in the study provided written informed consent. The Institutional Review Board and ethics committee of Ningxia Medical University reviewed and approved the protocol.

⁴² *Cell culture*

Human GC cells (MGC803, AGS, MKN45, and BGC-823) and control human GES-1⁵ cells were obtained from American Type Culture Collection (ATCC, VA, United States) and cultured following the guidelines provided by ATCC in an incubator at 37 °C and 5% CO₂.³

Quantitative real-time polymerase chain reaction

RNA from tissue specimens or cells⁵ were extracted using Trizol (Thermo Scientific, United States) and reverse-transcribed into cDNA using the TaqMan microRNA RT Kit⁵

(Thermo Scientific, United States). Quantitative real-time polymerase chain reaction (qRT-PCR) was conducted using the PowerUP SYBR Master Mix (Applied Biosystems, United States). The $2^{-\Delta\Delta CT}$ method was used to calculate the relative expression of miR-30e-3p or THOC2. The sequences of primers were as follows: miR-30e-3p: 5'-GCGTCTTTCAGTCGGATGTTTACAGC-3'; COLEC12: 5'-TCTCCTCCGTCAGTAACCGT-3', and 5'-CAGGCTTGATTGACACTGGC-3'; CNPY2: 5'-GGCCACTCCTATTCTACGGC-3', and 5'-CATCCAAAGCCAGAGTGAGC-3'; YTHDF3: 5'-CGAGAAGCAGAGAGCGAGAG-3', and 5'-TACTGCTAATGCCAGGCACC-3'; SLC25A33: 5'-TGTGCCTCCTGCATTGCTTA-3', and 5'-TCTGCAGTTCTAGGGCAGGT-3'; NPY2R: 5'-CGAGGTCCAGGTCAGTTGTA-3', and 5'-TACTGTGCGCATGCTCTTGA-3'; CDKN1B: 5'-AGTGTCTAACGGGAGCCCTA-3', and 5'-AAGAATCGTCGGTTGCAGGT-3'; C20orf202: 5'-GTGCTCTAGTGCTCTGGCAA-3', and 5'-CATCTGTTGTGTGGCCCTCT-3'; THOC2: 5'-TATGGGCTACTCTGGGCAGT-3', and 5'-TAAGTCCGGTGGCACTTCAC-3'.

Transfection

MiR-30e-3p mimics (5'-CUUUCAGUCGGAUGUUUACAGC-3'), miR-30e-3p inhibitors (5'-CTGTAAACATCCGACTGAAA-3'), and the relative negative controls (5'-UCACAACCUCCUAGAAAGAGUAGA-3') were purchased from GenePharma (Shanghai, China). SiRNA targeting THOC2 (siRNA1: CGAAUUUUUGCAUUUAUGUCG-3', siRNA1: 5'-CAUGAUAGUUCAACAUACAGA-3') and scramble negative control (5'-UUCUCCGAACGUGUCACGUTT-3') were obtained from GeneCopoeia (Shanghai, China). Transfection was conducted using FuGene HD (Roche, Switzerland).

Cell growth assays

Cell growth was assessed using a colony formation assay and CCK-8 assay as previously described^[18].

Transwell assay

Transwell assay was conducted using a transwell 24-well plate (Corning, United States) with or without matrigel precoating (BD Bioscience, United States). Cells were suspended in medium without serum and added into the upper chamber. The bottom chamber was filled with 500 μ L complete medium. After 48 h, the migration or invasive cells were fixed, stained with crystal violet, and then calculated.

Luciferase reporter assay

The putative WT or mutated 3'-UTR of THOC2 was cloned into the pGL3 plasmid (Promega, United States). The luciferase reporter vector and control Renilla vector were co-transfected into AGS or BGC-823 cells with miR-30e-3p mimics or control. The relative luciferase activity was assessed 48 h later using the Dual-Glo kit (Promega, United States).

Western blot

Protein lysate preparation, SDS-PAGE, and Western blot were performed following the standard protocol. The following primary antibodies were used: THOC2 (ab129485) from Abcam, United States and mTOR (#2983), Akt (#4685), and PI3K (#17366) from Cell Signaling Technology, United States. E-cadherin (20874-1-AP), N-cadherin (22018-1-AP), vimentin (10366-1-AP), CNPY2 (14635-1-AP), YTHDF3 (25537-1-AP), SLC25A33 (17794-1-AP), CDKN1B (25614-1-AP), and β -actin (81115-1-RR) were purchased from Proteintech; COLEC12 (SAB1403383) was purchased from Sigma; and was purchased from NPY2R (PA5-102110) from Invitrogen.

Tumor implantation in vivo

Four-week-old male BALB/c nude mice were obtained from Jiangsu Aniphe Biolaboratory Inc. The guidelines for the animal studies were approved by the Animal Care Committee of Ningxia Medical University Hospital. BGC-823 cells were selected

for tumor implantation. Around 48 h after transfection of miR-30e-3p mimic, approximately 1×10^7 BGC-823 cells were harvested and implanted subcutaneously into the nude mice.

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Statistical analysis

All results were presented as mean \pm SD. Statistical analysis was conducted using GraphPad Prism V6.0 (GraphPad, United States). Student t -test or one-way ANOVA was used as necessary. A $P < 0.05$ indicated statistical significance.

RESULTS

MiR-30e-3p expression is downregulated in patients with GC and low expression of miR-30e-3p predicts poor outcome

We first examined the miR-30e-3p expression in several GC cell lines. As detailed in Figure 1A, miR-30e-3p levels were lower in GC cells (MGC803, AGS, MKN45, and BGC-823) than in control GES-1 cells. Additionally, we demonstrated that miR-30e-3p expression was much lower in GC tissues than in matched adjacent non-tumor tissues (Figure 1B). Kaplan-Meier survival analysis suggested that patients with low miR-30e-3p expression had worse overall survival rate compared to those with high miR-30e-3p expression (Figure 1C). Thus, miR-30e-3p might function as a tumor suppressor in GC.

Overexpression of miR-30e-3p suppresses the malignant behaviors of GC cells

To explore miR-30e-3p function in GC, we transfected miR-30e-3p mimics into AGS or BGC-823 cells, after which the overexpression of miR-30e-3p was validated using qRT-PCR (Figure 2A). Functionally, we found that miR-30e-3p overexpression suppressed cell proliferation and colony formation of AGS or BGC-823 (Figure 2B and C). Furthermore, transfection of miR-30e-3p mimics resulted in decreased metastatic abilities of GC cells, with lesser cell migration or invasion (Figure 2D and E). In addition, transfection of miR-30e-3p mimics increased E-cadherin expression but decreased the expression of N-cadherin and vimentin (Figure 2F). These findings

suggest that overexpression of miR-30e-3p suppresses the growth and metastatic behaviors of GC cells.

Inhibition of miR-30e-3p promotes the malignant behaviors of GC cells

Conversely, we utilized miR-30e-3p inhibitors to suppress miR-30e-ep expression in GC cells (Figure 3A). MiR-30e-3p inhibitors also dampened the cell proliferation of GC cells (Figure 3B). Inhibition of miR-30e-3p promoted a higher colony number in AGC or SGC-823 cells compared with the control or negative control group (Figure 3C). Consistently, inhibition of miR-30e-3p enhanced GC cell migration and invasion (Figure 3D and E). In addition, transfection of miR-30e-3p inhibitors suppressed E-cadherin expression but promoted N-cadherin and Vimentin expression (Figure 3F). Taken together, both the overexpression and knockdown experiments demonstrated that miR-30e-3p negatively regulated GC cell growth and metastasis.

THOC2 is a direct target of miR-30e-3p in GC cells

Bioinformatics analysis identified THOC2 as a top candidate of miR-30e-3p (Figure 4A and Supplementary Table 2). Overexpression of miR-30e-3p inhibitor significantly promoted CNPY2, YTHDF3, SLC25A33, C20orf202, and THOC2 expression, among which THOC2 demonstrated the greatest upregulation (Figure 4B). After also detecting the protein levels of these potential target genes, we found that the results were consistent with the mRNA expression level of these genes (Figure 4C and D). Moreover, suppression of miR-30e-3p also upregulated THOC2 expression in GES-1 cells (Figure 4E), suggesting that miR-30e-3p could bind to the 3'-URT of THOC2 (Figure 4F). Luciferase reporter assay further confirmed the binding between miR-30e-3p and the wild-type 3'-UTR of THOC2 (Figure 4F). We found that THOC2 expression was significantly higher in GC cells than in GES-1 cells (Figure 4G). Furthermore, both THOC2 mRNA and protein levels were markedly enhanced in GC tissues (Figure 4H-J). THOC2 expression was negatively associated with miR-30e-3p expression in GC tissues (Figure 4J). Hence, THOC2 is a direct target of miR-30e-3p in GC cells.

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Knockdown of THOC2 suppresses the malignant behaviors of GC cells

To evaluate the function of THOC2 in GC, we silenced THOC2 expression in AGS or BGC-823 cells using siRNA targeting THOC2 (Figure 5A). THOC2 knockdown significantly dampened colony formation and cell viability of GC cells (Figure 5B and 5C). The CCK-8 assay showed that knockdown of THOC2 significantly inhibited GC cells proliferation (Figure 5D). Furthermore, the metastasis behaviors of GC cells transfected with siTHOC2 were drastically inhibited (Figure 5E-H). In addition, silencing THOC2 significantly increase E-cadherin expression but decreased the expression of N-cadherin and Vimentin in AGS and BGC-823 cells (Figure 5I). In summary, the provided data indicated that knockdown of THOC2 suppresses the malignant behaviors of GC cells.

MiR-30e-3p/THOC2 axis regulates the PI3K/AKT/mTOR pathway in GC cells

A previous study has demonstrated that the THO complex participates in the modulation of the p53 and PI3K/AKT pathways^[19]. As such, we examined the PI3K/AKT/mTOR pathway in GC and analyzed the functional role of miR-30e-3p/THOC2. As shown in Figure 6A and B, inhibition of miR-30e-3p enhanced PI3K/AKT/mTOR expression, whereas overexpression of miR-30e-3p using miR-30e-3p mimics significantly decreased the expression of PI3K/AKT/mTOR in AGS or BGC-823 cells. Additionally, we demonstrated that THOC2 knockdown inhibited the expression of PI3K/AKT/mTOR (Figure 6C and D). Moreover, a restoration assay designed by our group showed that inhibition of miR-30e-3p interfered with THOC2 siRNA and that miR-30e-3p played a regulatory role by directly targeting THOC2 to regulate PI3K/AKT/mTOR signaling pathway in gastric cancer (Figure 6E and F). Thus, miR-30e-3p/THOC2 might regulate GC cell growth and metastasis by modulating the PI3K/AKT/mTOR signaling pathway.

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MiR-30e-3p inhibits GC cells growth in vivo

To investigate the function of miR-30e-3p on GC cell growth *in vivo*, BGC-823 cells transfected with miR-30e-3p mimics after 48 h were injected subcutaneously into BALB/c nude mice. After 16 d, the growth status of the tumor was analyzed. The tumor diameter of the miR-30e-3p mimic group was significantly smaller than that of the control group (Figure 7A). The tumor volume and weight of the miRNA mimic group were smaller than that of the control group (Figure 7B and C). In addition, we also detected the protein expression of THOC2, the target gene of miR-30e-3p, and genes associated with the PI3K/AKT/mTOR signaling pathway (Figure 7D). Accordingly, we found that the protein expression of these genes was consistent with that *in vitro*. Taken together, the presented data showed that miR-30e-3p inhibits GC cells growth *in vivo*.

DISCUSSION

Accumulating evidence has revealed that miRNAs play important regulatory roles in GC development and metastasis^[20]. MiRNAs can also serve as non-invasive diagnostic biomarkers for GC^[21]. In line with this, the current study sought to further investigate the expression and function of miR-30e-3p. Notably, we found that miRNA-30e-3p functioned as a tumor suppressor in GC and that miR-30e-3p overexpression inhibited GC cell growth and invasion. Additionally, we identified that THOC2 was a target of miR-30e-3p and that knockdown of THOC2 suppressed the malignant behaviors of GC cells. Taken together, our results demonstrated that miR-30e-3p/THOC2 could be utilized to develop new diagnostic biomarker and therapeutic target for GC treatment.

The current study found that GC tissues and cells had lower miR-30e-3p levels compared to matched normal tissues and control cells. Previous studies have shown that miR-30e-3p expression decreased in hepatocellular carcinoma (HCC) and that miR-30e-3p regulated HCC development by modulating MDM2/TP53 signaling^[22]. Moreover, low expression of miR-30e-3p in HCC predicted drug-resistance to sorafenib treatment^[22]. Similarly, evidence has shown that miR-30e inhibited breast cancer development and progression by targeting IRS1, and low miR-30e expression mediated the chemosensitivity of paclitaxel treatment in breast cancer^[23]. We also showed that

miR-30e-3p decreased GC⁷ cell proliferation, migration, and invasion. Low levels of miR-30e-3p in patients with GC indicated poor prognosis. Thus, miR-30e-3p functions as a tumor suppressor in GC. However, further investigations are needed to determine whether miR-30e-3p exerts regulatory effects on drug sensitivity during GC treatment. One intriguing finding¹ of the current study was the regulation of miR-30e-3p expression in GC. In ovarian cancer, lncRNA MEG3 had been found to sponge miR-30e-3p and regulate LAMA4 expression^[24].

Multiple targets of miR-30e-3p have been identified, including Ubc9, P4HA1, IRS1, and ATG5^[23,25-27]. We found that THOC2⁴⁶ was directly targeted by miR-30e-3p. Studies on the function of THOC2 in patients with psychomotor retardation showed that THOC2 was involved in mRNA-Export pathway in X-linked intellectual disability^[28,29]. The dysregulated expression of THOC2 has been reported in severe neurocognitive and growth disorders^[30]. Recently, the oncogenic function of THOC2 has been revealed in malignancies such as melanoma^[17]. To the best of our knowledge, this³¹ has been the first study to demonstrate that THOC2 exhibited oncogenic function in GC development. Knockdown of THOC2 suppressed GC cell growth and metastasis. The regulatory axis of miR-30e-3p/THOC2 has been validated using the luciferase reporter assay, and Pearson analysis indicated² that miR-30e-3p expression was negatively associated with THOC2 expression. Although our data confirmed that THOC2 was regulated by miR-30e-3p, other miRNAs might regulate THOC2, which could suppress GC development and progression.

Bioinformatics analysis was conducted to study the signaling pathways involved in miR-30e-3p/THOC2 regulation in GC. One study showed that the THO complex participates in the regulation of p53 and PI3K/AKT signaling^[19]. The PI3K/AKT pathway is critical for cancer cell survival, proliferation, and apoptosis^[31,32]. Consistently, we also found¹ that the PI3K/AKT/mTOR signaling pathway was regulated by miR-30e-3p/THOC2 axis *in vitro* and *in vivo*. Thus, our findings provide a new approach in regulating the PI3K/AKT/mTOR pathway.

CONCLUSION

¹ In conclusion, our findings suggested that miR-30e-3p directly targets THOC2 and that THOC2 mediates the tumor suppression function of miR-30e-3p in GC. Low expression of miR-30e-3p or upregulation of THOC2 predicts poor prognosis of patients with GC. ² The diagnostic and therapeutic value of miR-30e-3p/THOC2 in GC should be further investigated in future studies.

⁶ ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is a common type of digestive cancer with high morbidity and mortality rates worldwide.

Research motivation

Considerable effort has been expended in understanding the mechanism of GC development and metastasis.

Research objectives

¹ We explored the expression and function of miR-30e-3p in GC development.

Research methods

We conducted ³⁷ quantitative real-time polymerase chain reaction, transfection, cell growth assays, transwell assay, luciferase reporter assay, western blot assays to explore the expression and function of miR-30e-3p.

Research results

Our findings revealed that knockdown of THO complex 2 (THOC2) inhibited the growth and metastatic behaviors of GC cells. After investigating signaling pathways involved in miR-30e-3p regulation, we found that the miR-30e-3p/THOC2 axis regulated the ¹¹ PI3K/AKT/mTOR pathway in GC.

Research conclusions

Our findings suggested that miR-30e-3p directly targets THOC2 and that THOC2 mediates the tumor suppression function of miR-30e-3p in GC. Low expression of miR-30e-3p or upregulation of THOC2 predicts poor prognosis of patients with GC. The diagnostic and therapeutic value of miR-30e-3p/THOC2 in GC should be further investigated in future studies.

Research perspectives

Considerable effort has been expended in understanding the mechanism of GC development and metastasis. Given that microRNAs have been found to participate in the regulation of GC progression.

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