**Original Article**

**LncRNA TMPO-AS1 serves as a sponge for miR-4731-5p modulating breast cancer progression through FOXM1**

Ying Wang$^{1,2}$, Jun Ma$^3$, Ruiqing Li$^2$, Xiaokang Gao$^2$, Hongli Wang$^2$, Guoqin Jiang$^1$

$^1$Department of Surgery, The Second Affiliated Hospital of Soochow University, Suzhou 215004, Jiangsu Province, China; $^2$Department of General Surgery, The Affiliated Hospital of Yangzhou University, Yangzhou 225012, Jiangsu Province, China; $^3$Department of Surgery Oncology, The Anqing Municipal Hospital, Anqing 246003, Anhui Province, China

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**Abstract:** Objective: To investigate the function of IncRNA-TMPO-AS1 in breast cancer (BC) and to further explore its molecular mechanism. Methods: TMPO-AS1, miR-4731-5p and FOXM1 were quantitatively determined using qRT-PCR. CCK-8 assays, plate cloning experiments, wound healing and Transwell assays, and flow cytometry were used to assess the biological behaviors of BC cells. Dual-luciferase reporter assays were used to assess the interactions between TMPO-AS1 and its downstream targets. The apoptosis and cell cycle-related proteins were quantitatively determined using Western blot. Results: In the BC tissues and cells, TMPO-AS1 was significantly increased ($P<0.05$). Functional studies suggest that the knockdown of TMPO-AS1 tremendously restrains tumor cell growth and migration ($P<0.05$). Mechanically, TMPO-AS1 negatively regulates miR-4731-5p and influences the progression of BC through the miR-4731-5p/FOXM1 axis. Conclusion: LncRNA TMPO-AS1 sponges miR-4731-5p to modulate BC progression through FOXM1.

**Keywords:** Long noncoding RNAs, TMPO-AS1, breast cancer, miR-4731-5p, FOXM1

**Introduction**

Breast cancer (BC) is an uncontrolled proliferative malignant cancer occurring in the epithelia or ductal epithelia of the breast. The female cancer incidence rate is 24.2%, making it the world’s most common cancer, among which 52.9% occurs in developing countries [1]. In China, approximately 300,000 women are diagnosed with BC each year. The etiology of breast cancer is complex and not fully understood, so it may be related to family history and genes related to breast cancer, as well as environmental factors such as sex hormones, nutrition, and diet [2, 3]. With the advances in science and technology, the medical community has made great progress in the treatment of BC; however, the clinical effectiveness of BC is still unsatisfactory. Therefore, the exploration of new strategies and new targets for the treatment of BC is a problem that needs to be focused on.

Long non-coding RNA (lncRNA) is a non-coding RNA with a length of more than 200 nucleotides [4, 5]. It has rich biological functions and is widely involved in various important physiological processes of organisms. Its detailed molecular regulatory mechanisms have been widely revealed in biological processes such as genomic imprinting, target mimicry, and functional protein transport [6-11]. TMPO antisense RNA 1 (TMPO-AS1) has been confirmed to take part in the progression of many cancers [12]. Huaan et al. proved that LncRNA TMPO-AS1 accelerates osteosarcoma occurrence by targeting miR-199a-5P/WNT7B [13]. Huang et al. expounded that in prostate cancer, TMPO-AS1 negatively regulates miR-4731-5p and influences the progression of BC through the miR-4731-5p/FOX1 axis. Conclusion: LncRNA TMPO-AS1 sponges miR-4731-5p to modulate BC progression through FOXM1.
The function and molecular mechanism of IncRNA-TMPO-AS1 in BC

observed in cancer samples. Therefore, in our study, we continued to select TMPO-AS1 for functional research and to further explore its possible molecular mechanism in BC.

Materials and methods

Samples

The 22 BC and healthy normal tissues obtained from our hospital were used for this study. The design was in line with the Ethics Committee of our hospital (2015-YKL06-018-02). Each patient signed the informed consent.

Cell culture

The BC cells (Hs-578T, MCF7, ZR-75-30 and HCC1937) and one line of breast cells (MCF-10A) were all purchased from the American Type Culture Collection (ATCC, USA). After resuscitation, they were inoculated in RPMI-1640 medium (Beijing Baierdi Biotechnology Co., Ltd., China) containing 10% FBS in a humidified environment at 37°C with 5% CO₂ (Sigma-Aldrich Co. LLC., USA).

qRT-PCR

Total RNA was extracted using Trizol reagent, and PrimeScript RT Master Mix kits were used for the reverse transcription. After the RNA was isolated and prepared, the expressions were measured SYBR green (Invitrogen, USA) (Shanghai Zheyan Biotech Co., Ltd., China). The relative quantities of mRNA were calculated using the 2⁻ΔΔCq method and normalized to the housekeeping gene, GAPDH. The thermocycling conditions were as follows: 96°C for 4 min; 32 cycles of 96°C for 20 sec, 57°C for 30 sec and an extension at 72°C for 1 min. The PCR primer sequences are presented in Table 2.

Cell transfection

sh-NC, sh-TMPO-AS1, sh-FOXM1, an NC mimic, an miR-4731-5p-mimic, an NC inhibitor, and an miR-4731-5p inhibitor were constructed by the Ribobio Corporation (Guangzhou, China). The plasmids were transfected into MCF7 and ZR-75-30 cells using Lipofectamine 2000 kits (Invitrogen, USA) for 48 h. The sequences of the transfections are shown in Table 1.

Table 1. The transfection sequences

<table>
<thead>
<tr>
<th>Transfection</th>
<th>Sequence (5’-3’)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sh-NC</td>
<td>ACCGGCTTAAGTTAAGTCGCCCTCGTGAAGCGAGGGCGACTTAACCTAGGTTTTTGAATTC</td>
</tr>
<tr>
<td>sh-TMPO-AS1</td>
<td>GAGCCGACUCAGAACCAATT</td>
</tr>
<tr>
<td>shRNA-FOXM1</td>
<td>TGTCTGGAATGCTTGTGAT</td>
</tr>
<tr>
<td>NC mimic</td>
<td>UUCUCGGAACGUGUCAGUTT</td>
</tr>
<tr>
<td>miR-4731-5p-mimic</td>
<td>GUGUGAGUACACGGGGGUGU</td>
</tr>
<tr>
<td>NC inhibitor</td>
<td>GUGUGAGUACACGGGGGUGU</td>
</tr>
<tr>
<td>miR-4731-5p inhibitor</td>
<td>UGCUGGGGGCCACACUGAGUGUG</td>
</tr>
</tbody>
</table>

Table 2. The primer sequences

<table>
<thead>
<tr>
<th>Primer</th>
<th>Sequence (5’-3’)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMPO-AS1 Forward</td>
<td>AGACGCCGATAAGGGACAG</td>
</tr>
<tr>
<td>TMPO-AS1 Reverse</td>
<td>AGCAGAAGCTCTCACA</td>
</tr>
<tr>
<td>miR-4731-5p Forward</td>
<td>GGCACAGCATGCTGCCCC</td>
</tr>
<tr>
<td>miR-4731-5p Reverse</td>
<td>CCAGTGCAGGGTCCAGGTGA</td>
</tr>
<tr>
<td>U6 Forward</td>
<td>GTCTCGTCTCGGAGCAGCATATAC</td>
</tr>
<tr>
<td>U6 Reverse</td>
<td>AAAATATGGAACGCTTCACGAGTTTG</td>
</tr>
<tr>
<td>FOXM1 Forward</td>
<td>ACCGCTACTTGACATGGAC</td>
</tr>
<tr>
<td>FOXM1 Reverse</td>
<td>GGGAGTTCGCTTGTGTC</td>
</tr>
<tr>
<td>GAPDH Forward</td>
<td>CTACCACGATGGACACCATATG</td>
</tr>
<tr>
<td>GAPDH Reverse</td>
<td>CGCGTTGCTCACAATGTTCAT</td>
</tr>
</tbody>
</table>

Cell Counting Kit-8

MCF7 and ZR-75-30 cells adjusted to appropriate concentration (5×10^5 cells) were inoculated on 96-well plates (Sigma-Aldrich Co. LLC., USA) and treated accordingly. Then CCK-8 solution was added to each well, and the wells were incubated for 2 hours in the dark. The optical density (OD) values were determined by measuring the absorbance at 450 nm on a microplate reader (Molecular Devices, San Jose, USA).
The function and molecular mechanism of IncRNA-TMPO-AS1 in BC

Plate cloning experiment

The same densities of the MCF7 and ZR-75-30 cells in each group were collected and incubated in 6-well plates (Sigma-Aldrich Co. LLC., USA), and cultured continuously for two weeks. After the cells were washed, MCF7 and ZR-75-30 were fixed with methanol (Shanghai Bojing Chemical Co., Ltd., China) and stained with crystal violet (Hubei Jusheng Technology Co., Ltd., China). Finally, the effective clones were calculated.

Wound healing assay

When MCF7 and ZR-75-30 were fully fused, a pipette tip was applied to create a scratch wound on the confluent cells in the center. The migration and cell movement of the entire wound area were observed with an inverted optical microscope (Oberkochen, Germany), and the images were taken after 48 h with a camera connected to the microscope (Sony-Cyber Shot, Shanghai Suoguang Visual Products Co., Ltd., China). The cell migration ability was statistically analyzed according to the cell healing.

Transwell assays

For the migration, MCF7 and ZR-75-30 (1×10⁵ cells) were inoculated into the top of a 24-well Millipore Transwell chamber (Millipore Corporation) 48 h after the transfection. A complete medium was added into the lower chamber. After 24 h, 4% paraformaldehyde (Shanghai Bojing Chemical Co., Ltd., China) was adopted for fixation and 0.1% crystal violet was used for staining, respectively. For the invasion, we coated the top of the 24-well Millipore Transwell Chamber with diluted Matrigel (BD Biosciences) for 45 min at room temperature. The remaining steps of the assay were similar to those of the migration assay.

Western blot

The extracted protein (30 µg) was separated using 10% SDS-PAGE and then transferred onto PVDF membranes (Millipore, MA, USA). Following blockage with 5% skimmed milk, the membranes were incubated with rabbit anti-human primary antibodies (Bax and Bcl-2, 1:1000, Cell Signaling Technology; Cleaved-caspase-3 and Cleaved-caspase-9, 1:1000, Proteintech Group Inc.; Cyclin D1, p21, Cox-2, MMP-2, MMP-9, FOXM1, and GAPDH, 1:1000, Sigma-Aldrich Co. LLC), and then with HRP-conjugated secondary antibody. The intensity of the protein expression was measured using ECL chemiluminescence.

Luciferase reporter assay

First, Wt-TMPO-AS1 and Wt-FOXM1 were constructed using the pmirGLO reporter (Promega). Mut-TMPO-AS1 and mut-FOXM1 were constructed using a TaKaRa MutanBEST kit (TaKaRa). Next, the MCF7 and ZR-75-30 were then co-transfected with the above vectors and the miR-4731-5p mimics or mimics-NC. After 48 h, the luciferase activities were determined.

RNA immunoprecipitation (RIP)

As described before, the cultured cells were first lysed with an RIP buffer (Shanghai Haoran Biotechnology Co., Ltd., China) [12]. The pre-cleared lysates were incubated with Magna RIP RNA-Binding Protein Immunoprecipitation Kit (Millipore). Then anti-Ago2 antibody (1:1000, Shanghai Huzhen Industrial Co., Ltd., China) was used to conduct the RIP. Finally, the RNA complex was purified by treatment with Trizol (Shanghai Yubo Biotechnology Co., Ltd., China), and the expression levels of the corresponding genes were measured.

Flow cytometry assay

After 48 h culture, the transfected cells (5×10⁵) were first incubated with Annexin V (Sigma-Aldrich Co. LLC.) in the dark for 20 min. Subsequently, PI (Sigma-Aldrich Co. LLC., USA) was also added. The apoptosis and cell cycle were determined using a flow cytometer (BD Biosciences, USA).

Nucleocytoplasmic separation

A PARIS Kit (Life Technologies, USA) was used to extract the RNAs in the cytoplasms and nuclei. qRT-RCR was conducted to quantitatively measure the total RNA in each fraction.

Statistical analysis

All the data were processed using SPSS19.0. Student’s t-tests or one-way ANOVA followed by post hoc comparisons (Dunnett’s test) were used to calculate the differences. P<0.05 indicated a significant difference between groups.
The function and molecular mechanism of IncRNA-TMPO-AS1 in BC

Results

TMPO-AS1 is highly expressed in breast cancer tissues and cells

In the tumor tissues, TMPO-AS1 was sharply increased (Figure 1A and 1B; \( P<0.01 \)). Our further survival analysis showed that high TMPO-AS1 expression is associated with lower overall survival (Figure 1C, \( P<0.01 \)). Subsequently, we selected four commonly used BC cell lines and one breast cell line MCF-10A and determined the transcription levels of TMPO-AS1 in the above cells. The results indicated that, compared with MCF-10A, TMPO-AS1 was up-regulated, especially in MCF7 and ZR-75-30 (Figure 1D; all \( P<0.01 \)).

TMPO-AS1 knockdown restrained the growth and promotes the apoptosis of breast cancer cells

To identify the function of the TMPO-AS1 in BC, we investigated whether TMPO-AS1 affected the cell proliferation and apoptosis. As presented in Figure 2A, the TMPO-AS1 level was statistically decreased after being transfected with sh-TMPO-AS1 (\( P<0.01 \)). The CCK-8 data indicated that the knockdown of TMPO-AS1 lessened the cell viability in comparison to the sh-NC group (Figure 2B; \( P<0.01 \)). Our quantitative analysis of the colonies showed that, after the 8-day incubation, the number of colonies in the TMPO-AS1 knockdown group was decreased (Figure 2C; \( P<0.01 \)). Our cell cycle analysis indicated that the knockdown of TMPO-AS1 arrested the cells at the G1 phase (Figure 2D). The cycle-associated protein detection results presented TMPO-AS1 knockdown decreased the Cyclin D1 level, while it increased the p21 level (Figure 2E; \( P<0.01 \)). Further research on apoptosis showed that the knockdown of TMPO-AS1 increased the apoptosis (Figure 2F; \( P<0.01 \)). The subsequent western blot indicated that the TMPO-AS1 knockdown reduced the Bcl-2 level and increased the Bax, and cleaved caspases-3 and -9 levels (Figure 2G; all \( P<0.05 \)).

TMPO-AS1 knockdown inhibited breast cancer cell migration and invasion

Given that the invasion phenotype of BC cells is a hallmark of the malignant process, we sought to study the role of TMPO-AS1 in migration and invasion. As depicted in Figure 3A, the migration speed was remarkably decreased after the cells were transfected with sh-TMPO-AS1 (\( P<0.01 \)). Similarly, in Figure 3B, the invasiveness of MCF7 and ZR-75-30 was sharply weakened (\( P<0.01 \)). To further verify the role of TMPO-AS1 in the above biological behavior, we measured the expression of the migration- and invasion-related proteins. As expected, the Cox-2, MMP-2, and MMP-9 protein levels sharply decreased after the knockdown of TMPO-AS1 (Figure 3C; all \( P<0.01 \)).
The function and molecular mechanism of IncRNA-TMPO-AS1 in BC

Figure 2. Knockdown of TMPO-AS1 inhibits the proliferation of BC cells. A: The measurement of the transfection efficiency; B: The CCK-8 assay shows cell viability in the sh-NC group and in the sh-TMPO-AS1 group; C: The functional role of TMPO-AS1 on colony formation; D: Cell cycle quantification; E: The cell cycle-related protein expressions were measured; F: The cell apoptosis analysis was determined; G: The cell apoptosis-related proteins were analyzed via western blot. Compared with the sh-NC group, **P<0.01. TMPO-AS1: TMPO antisense RNA 1; BC: breast cancer. Each experiment was repeated three times.
The function and molecular mechanism of IncRNA-TMPO-AS1 in BC

**Figure 3.** TMPO-AS1 knockdown inhibits BC cell migration and invasion. A: After being transfected with sh-TMPO-AS1, the cell migration was analyzed using wound healing; Magnification, ×200; Scale bar, 300 μm. B: The migration and invasion of the cells were analyzed using Transwell assays; Magnification, ×100; Scale bar, 200 μm; C: The protein expression levels of the migration-and invasion-related proteins. Compared with the sh-NC group, **P<0.01. TMPO-AS1: TMPO antisense RNA 1. Each experiment was repeated three times.

**TMPO-AS1 acts as a molecular sponge for miR-4731-5p**

After the cytoplasmic separation, the TMPO-AS1 in the cytoplasms and nuclei were quantified, and it was found that almost 80% were expressed in the cytoplasms (Figure 4A; P<0.01). To elucidate the regulatory mode of TMPO-AS1 in the progression of BC, StarBase was used to predict the target of TMPO-AS1, and it predicted that miR-4731-5p was the target (Figure 4B). To test this prediction, we conducted a luciferase reporter assay. The result showed that the relative luciferase activity in TMPO-AS1-WT was decreased (P<0.01), but there was no change in the TMPO-AS1-Mut (Figure 4B). In addition, we examined the miR-4731-5p expression levels in the BC tissues and cells and found decreased expressions in all the above samples (Figure 4D and 4E; P<0.01). Consistently, the RIP data showed that TMPO-AS1 was dramatically enriched for Ago2 in comparison with miR-4731-5p in the MCF7 and ZR-75-30 cells (Figure 4F; P<0.01). A further analysis of the correlation between the two demonstrated that the sh-TMPO-AS1 greatly enhanced the miR-4731-5p level (P<0.01), and there is a negative correlation between the two (Figure 4G and 4H).

**The over-expression of miR-4731-5p inhibits BC growth, migration, and invasion**

The expression level of miR-4731-5p was significantly increased by the overexpression of miR-4731-5p as compared to that treated with...
The function and molecular mechanism of IncRNA-TMPO-AS1 in BC

The NC mimic (Figure 5A; P<0.01). The proliferation analysis results showed that overexpressed miR-4731-5p suppressed the growth of ZR-75-30 and MCF7 cells (Figure 5B and 5C; all P<0.01). The apoptosis analysis results showed that the cell apoptotic rate was tremendously increased in BC cells transfected with the miR-4731-5p mimic (Figure 5D; P<0.01). Conversely, the migration and invasion data showed that the overexpression of miR-4731-5p inhibited the ZR-75-30 and MCF7 metastasis, including both the migration and invasion (Figure 5E; P<0.01).

FOXM1 is the target of miR-4731-5p

StarBase showed a putative miR-4731-5p binding site existed for FOXM1 (Figure 6A). To confirm this hypothesis, a dual-luciferase reporter assay was done, and we found that in the wild-type FOXM1, the luciferase activity was reduced significantly after being transfected with the miR-4731-5p mimic (P<0.01). However, there was no change in the mutant FOXM1 (Figure 6B). Additionally, the FOXM1 in the tumor tissues and cells were significantly up-regulated (Figure 6C and 6D; all P<0.01). Further research found that the miR-4731-5p mimics reduced the transcription and protein translation of FOXM1 (Figure 6E and 6F; all P<0.01). Moreover, a correlation analysis found that there was a negative correlation between the two (Figure 6G).

LncRNA TMPO-AS1 accelerates the deterioration of breast cancer by targeting miR-4731-5p/FOXM1

To further study whether TMPO-AS1 executed its function in BC via the miR-4731-5p/FOXM1 axis, rescue assays were performed. MiR-4731-5p and FOXM1 were statistically reduced after the co-transfection with the sh-TMPO-AS1 (Figure 7A; P<0.05). A
The function and molecular mechanism of IncRNA-TMPO-AS1 in BC

Figure 5. The overexpression of miR-4731-5p inhibits BC cell behavior. A: After being transfected with the miR-4731-5p mimic, the transfection efficiency was determined, compared with the NC mimic, **P<0.01; B and C: The cell growth capacity was measured using CCK-8 and colony formation assays, compared with the NC mimic, **P<0.01; D: The cell apoptosis was analyzed using flow cytometry, compared with the NC mimic, **P<0.01; E: Transwell assays were conducted to measure the migration and invasion of the BC cells, compared with the NC mimic, **P<0.01. Magnification, ×100; Scale bar, 200 μm; BC: breast cancer. Each experiment was repeated three times.
The function and molecular mechanism of IncRNA-TMPO-AS1 in BC

proliferation assay showed that co-transfection with the miR-4731-5p inhibitor + sh-TMPO-AS1 reduced the growth of the TMPO-AS1-knockdown cells compared with cells transfected with the miR-4731-5p inhibitor (Figure 7B and 7C; P<0.05). We further observed that the transfection with the miR-4731-5p inhibitor decreased the apoptosis of the TMPO-AS1-knockdown cells (Figure 7D; P<0.05). Moreover, the migration and invasiveness abilities of the MCF7 and ZR-75-30 cells was significantly inhibited by the co-transfection with the miR-4731-5p inhibitor + sh-TMPO-AS1 (Figure 7E; P<0.05).

Discussion

In recent years, various IncRNAs have been shown to regulate various cellular processes [15]. TMPO-AS1 has been shown to be a kind of IncRNA, and it has attracted much attention because of its involvement in the occurrence of various cancers. Yang et al. showed that TMPO-AS1 accelerates the growth and migration of cervical cancer cells and promotes apoptosis by regulating miR-577 [16]. Zhao et al. verified that TMPO-AS1 regulates the cell behavior of CRC cells through miR-143-3p [17]. Consistently, we represented an elevated expression of TMPO-AS1 in BC tissues and cells in our study. Importantly, the elevated expression of TMPO-AS1 was positively correlated with tumor stage and survival rate. Functional studies have indicated that silencing TMPO-AS1 greatly restrains the growth, migration, and invasion and induces the apoptosis of BC cells. Therefore, all the above data indicate that TMPO-AS1 participates in the occurrence of BC and has an important influence on the progression of BC.

miRNAs are ncRNAs that are approximately 20 nucleotides in length [18, 19]. In cells, IncRNAs act as sponge miRNAs, thereby relieving the inhibition of miRNAs on their target genes and increasing the target genes' expression levels. Previously, it was found that miR-4731-5p can regulate melanosome, and the overexpression of miR-4731-5p can reduce melanoma cell cloning by inhibiting the expression of the pro-
The function and molecular mechanism of IncRNA-TMPO-AS1 in BC

A

B

C

D

E

Am J Transl Res 2021;13(10):11094-11106
The function and molecular mechanism of IncRNA-TMPO-AS1 in BC

Figure 7. LncRNA TMPO-AS1 accelerates the deterioration of breast cancer by targeting miR-4731-5p/FOXM1. A: qRT-PCR was implemented to certify the transfection efficiency for the miR-4731-5p inhibitor and sh-FOXM1, compared with the NC mimic or sh-NC, **P<0.01; B-E: The roles of the TMPO-AS1/miR-4731-5p/FOX1 axis in BC cell proliferation, apoptosis, migration and invasion were estimated using CCK-8 and colony formation assays, flow cytometry, and Transwell assays (Magnification, ×100; Scale bar, 200 μm), compared with NC inhibitor. **P<0.01; compared with the miR-4731-5p inhibitor, *P<0.5, #P<0.01. TMPO-AS1: TMPO antisense RNA 1. BC: breast cancer. Each experiment was repeated three times.

Figure 8. A schematic diagram showing the mechanism of LncRNA TMPO-AS1 in breast cancer.

tein SSX4 [20, 21]. In the study of Yan et al., they proved that miR-4731-5p can delay the progression of glioma by inhibiting the expression of E2F2 [22]. However, the role of miR-4731-5p in BC has rarely been elucidated, let alone its molecular mechanism. In this study, we used StarBase to predict that miR-4731-5p is the downstream target of TMPO-AS1 and showed that TMPO-AS1 is negatively regulated with miR-4731-5p. Meanwhile, miR-4731-5p is low-expressed in BC and acts as a tumor suppressor to inhibit cancer.

FOXM1 is a pre-oncogene transcription factor, which belongs to the Forkhead box protein family [23, 24]. It is reported that FOXM1 takes part in the development of a variety of tumors. In gliomas, FOXM1 is overexpressed and contributes to the tumorigenicity of gliomas [25]. In basal cell carcinomas, the up-regulated expression of FOXM1 promotes the progression of this tumor [26]. Similarly, FOXM1 has been shown to be essential for proliferation and expansion during the development of liver cancer [27]. In this study, an up-regulated expression of FOXM1 was observed in the BC tissues and cells. Further we showed that FOXM1 is the target of miR-4731-5p, and there is a negative correlation between the two above. Our quantitative measurements showed that over-expressed miR-4731-5p sharply lessens the expression of FOXM1, while the addition of the miR-4731-5p inhibitor reverses this effect. Moreover, the functional assays revealed that co-transfection with sh-Foxm1 offsets the inhibitory effect of miR-4731-5p on cell growth and migration to a certain extent.

In conclusion, we showed that the up-regulation of TMPO-AS1 in BC and the silencing of TMPO-AS1 inhibits the cancer progression. Mechanistically, TMPO-AS1 counteracts miR-4731-5p-mediated FOXM1 suppression by acting as a sponge for miR-4731-5p.

A diagram of the study’s findings is shown in Figure 8. There are some limitations to this study. First, the study only conducted in vitro studies in BC cells, so we need to conduct in vivo studies; Second, the interactions between the genes need to be further verified by sequencing.

Acknowledgements

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The function and molecular mechanism of IncRNA-TMPO-AS1 in BC

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Disclosure of conflict of interest

None.

Address correspondence to: Guoqin Jiang, Department of Surgery, The Second Affiliated Hospital of Soochow University, No. 1055 Sanxiang Road, Suzhou 215004, Jiangsu Province, China. Tel: +86-0512-67784797; Fax: +86-0512-67784797; E-mail: jiang_guoqin@suda.edu.cn

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The function and molecular mechanism of IncRNA-TMPO-AS1 in BC


