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Inhibition of long non-coding RNA TUG1 on gastric cancer cell transference and invasion through regulating and controlling the expression of miR-144/c-Met axis

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ABSTRACT

Objective: To discuss the expression of long noncoding RNA TUG1 (lncRNA-TUG1) in gastric carcinoma (GC) and its effects on the transferring and invading capacity of gastric carcinoma cells.

Methods: Forty cases of carcinoma tissue and para-carcinoma tissue were selected from GC patients who underwent surgical removal in Zhejiang Provincial Hospital of Chinese Traditional Medicine and Wenzhou Central Hospital from January, 2013 to December, 2014; the expressing level of lncRNA-TUG1 in GC and para-C tissues was detected by applying the qRT-PCR technique. The correlation between lncRNA-TUG1 expression and patients' clinical data was classified and analyzed. SGC-7901 cells were transfected using lncRNA-TUG1 specific siRNA. Changes of the transferring and invading capacity of siRNA-transfected SGC-7901 cells were scratch-tested and transwell-detected. qRT-PCR was applied to detect the expression level of microRNA-144 after lncRNA-TUG1 was silenced. Changes of c-Met mRNA and protein expressions was detected by qRT-PCR and western-blot test.

Results: The expression level of lncRNA-TUG1 in GC tissue was significant higher than that in para-C tissue ($P < 0.05$) and the high expression level of lncRNA-TUG1 in GC tissue was significantly correlated with tumor lymph nodes metastasis and advance TNM phasing ($P < 0.05$). The transferring and invading capacity of SGC-7901 cells was highly inhibited after being transfected by lncRNA-TUG1 specific siRNA ($P < 0.05$). The results of qRT-PCR and western-blot proved that the expression of microRNA-144 was significantly boosted and the expression level of c-Met mRNA and protein was inhibited after lncRNA-TUG1 was silenced ($P < 0.05$).

Conclusions: lncRNA-TUG1 shows an up-regulated expression in GC tissue and that bears a correlation with clinicopathological features of malignant tumor. lncRNA-TUG1 can promote the transferring and invading capacity of GC by inhibiting the pathway of microRNA-144/c-Met.

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1. Introduction

Gastric carcinoma is a common malignant tumor of digestive system [1]. Due to the features of concealed morbidity, rapid development and easy postoperative recurrence, gastric carcinoma has become one of the most major public health problems that jeopardize Chinese people's health [2]. Because molecular targeting treatment has significant application value in gastrointestinal tumors [3], the study of the molecular biological characteristics of gastric carcinoma cells is of great importance in finding new therapeutic target and improving the diagnosis and treatment of gastric carcinoma.

lncRNA is a type of non-decoding single stranded RNA with a length of above 200 nucleotides [4]. More and more evidence [5] shows that lncRNA, by multiple ways, can regulate a variety of pathological processes including the growth and transference of tumor and angiogenesis so as to facilitate the occurrence and development of malignant tumors. The abnormal expression of lncRNA and its biological function is one of the research highlights of gastric carcinoma molecular pathology in recent years. In a latest research, it is indicated that lncRNA-TUG1 has significant regulatory function in the developing process of cancers [6], but its clinical significance to gastric carcinoma and biological functions are still unclear. This study, by detecting the expression of lncRNA-TUG1 and its functions in regulating the transferring and invading processes of SGC-7901 cells, explores the clinical significance and functional mechanism of lncRNA-TUG1 in the development of gastric carcinoma so as to provide theoretical basis to the molecular diagnosis and targeted therapy of gastric carcinoma.

2. Materials and methods

2.1. Clinical specimens and primary reagent

Carcinoma tissue and para-carcinoma tissue (>2 cm away from the tumor) were selected as clinical specimens from forty gastric carcinoma patients with an average age of 51.2 ± 1.1 years who underwent surgical removal in Zhejiang Provincial Hospital of Chinese Traditional Medicine and Wenzhou Central Hospital from January, 2013 to December, 2014. None of the forty patients had conducted chemoradiotherapy before undergoing surgery. All the specimens were preserved in liquid nitrogen. qRT-PCR kit was purchased from Beijing Tiangen Biotechnology Limited company. Both lncRNA-TUG1 siRNA and negative control siRNA was purchased from Shanghai Jima Biotechnology Limited Company. Trizol reagent and lipofectamineTM 2000 was from American Invitrogen company; miR-144 qRT-PCR primers kits from Guangzhou Ruibo Biotechnology Limited Company; lncRNA-TUG1 primers (forward primer 5′-TAGCAGTTCCCCAATCCTTG-3′; reverse primer 5′-TAGCAGTTCCCCAATCCTTG-3′), c-Met primers (forward primer 5′-GTCGGAGTAGAGCGTCGAGA-3′; reverse primer 5′-CAGCGCGATCAGGTA GAGC-3′) and β-actin primers (forward primer 5′-CTCCATCCTGGCCTCG CTGT-3′; reverse primer 5′-GCTGTCACCTTCACCGTTCC -3′) were all synthesized by Shanghai Shenggong Biotechnology Limited Company; matrigel was from American BD company; Transwell from American Corning Company; rabbit-anti-human c-Met polyclonal antibody and mouse-anti-human β-actin monoclonal antibody from American CST company; fetal calf serum from Zhengjiang Tianhang Biotechnology Limited Company; 1×DMEM fluid nutrient medium from American HyClone Company; human gastric carcinoma cells SGC-7901 from Cell Resource Center, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences; RIPA lysate, BCA protein quantification kit and ECL kit all from Shanghai Biyuntian Biotechnology Institute.

2.2. RNA extraction and qRT-PCR

The TRIZOL instruction was followed; carcinoma and para-carcinoma tissues and total RNA of SGC-7901 were extracted. Detecting with ultraviolet spectrophotometer, only those whose OD260/OD280 ratio ranged from 1.9 to 2.1 could be classified as qualified sample. 500 ng total RNA was taken as a template and reverse transcription reaction system was prepared according to the RT-PCR kit instruction and Random 6 and Oligo-dT double-primer methods were adopted to reversely transcribe lncRNA and mRNA. After the reverse transcription, real-time PCR system was prepared with 2 uL cDNA and target genes were amplified according to real-time PCR specifications. Similarly, use miR-144 qRT-PCR kit to amplify miR-144 by following the same steps.

2.3. Cell culture

SGC-7901 cells were all inoculated in 1×DMEM medium that contained 10% fetal calf serum and were cultivated in a 37 °C incubator that contained 5% CO_2 with saturation humidity. After 2–3 stable generations, logarithmic-phased cells were taken for subsequent tests.

2.4. Cell transfection

SGC-7901 cells were inoculated in a six-well plate. Inoculum density will be subject to alignment of up to 50% after the overnight cultivation. According to the Lipofectamine® 2000 specification, transfection system was prepared with serum-free DMEM medium for each well: total volume: 2 mL, DMEM: 1 500 μL, Lipo 2000+DMEM: 5 μL + 250 μL, siRNA+DMEM: 100 pmol+250 μL. SGC-7901 cells were transfected with lncRNA-TUG1 siRNA and NC siRNA. After six hours' transfection, complete medium with 10% fetal calf serum was used.

2.5. Cell scratch healing test

24h-transfected SGC-7901 cells were taken and cultivated in six-well plate overnight till fusion reached above 90%. The original medium was absorbed and removed and then the cells were washed twice in PBS solution. 100 μL spearhead was used to make scratch and then remnant cells were washed away by PBS solution. The cells were cultivated in 1×DMEM medium with 5% serum for 48 h and the healing state of the scratched cells was observed under the inverted microscope.

2.6. Transwell

Matrigel was diluted by 1×DMEM medium. The basilar membrane of Transwell was coated with 100 μL per hole. 48h-

transfected SGC-7901 cells were collected. The cells were suspended in a serum-free medium; the cell density was adjusted into 1×10^5/mL and then inoculated in the upper well of the Transwell. 750 μL 10%-serum DMEM medium was added into each hole of the 24-well plate. After 24 h' culture in the medium, the supernatant medium was discarded and the remains were washed twice with PBS. After that, the remains were fixed with 4% paraformaldehyde and stained with crystal violet. The remnant cells were wiped off from the surface of the upper well with cotton swab and then the number of cells on the surface of lower well was counted under microscope.

2.7. Western blot

72h-transfected SGC-7901 cells were collected and cleaved by RIPA lysate and the total protein concentration was measured by adopting the BCA method. After separating the protein by vertical electrophoresis, 1:1000 diluted c-Met and β-actin primary antibodies were combined with corresponding target protein; 1:5000 diluted HRP-marked goat anti-rabbit antibody was combined with primary antibody. The relative expression of protein was detected by ECL Chemiluminescence method.

2.8. Statistical analysis

All data were analyzed by SPSS 21.0 and data were expressed as mean ± SD. Comparison among groups was conducted by *t* test or ANOVA test. $P < 0.05$ showed statistically significant difference.

3. Results

3.1. Expression difference of lncRNA-TUG1 in gastric carcinoma and para-carcinoma tissue

The expressions of lncRNA-TUG1 in 40 pairs of gastric carcinoma and para-carcinoma RNA specimens were detected by qRT-PCR. Results showed that the relative expression of lncRNA-TUG1 in gastric carcinoma tissue was (5.487 ± 0.301), while only (2.304 ± 0.027) in the corresponding para-carcinoma tissue showing significant difference between the two specimen groups ($P < 0.001$).

3.2. Correlation between the abnormal expression of lncRNA-TUG1 in gastric carcinoma tissue and patients' clinical characteristics

In order to find out whether the abnormal expression of lncRNA-TUG1 in gastric carcinoma tissue had effect on patients' clinical pathological manifestations, a dichotomy was conducted among clinical pathological characteristics and the relative expression of lncRNA-TUG1 was counted. It was discovered through statistical analyses that high expression of lncRNA-TUG1 in GC tissue had some correlations with tumor lymph nodes metastasis (>2 cm) and high TNM phasing (III+IV phase), which implies that lncRNA-TUG1 may have some biological function in the developing process of gastric carcinoma (see Table 1).

Table 1
Correlation between the expression of lncRNA-TUG1 and GC patients' clinical pathological characteristics ($n = 40$).

Item	Category	Relative expression of lncRNA-TUG1	*P*
Age	<50	5.279 ± 0.201	0.737
	≥50	5.581 ± 0.132	
Hp infected or not	Infected	5.493 ± 0.111	0.868
	Uninfected	5.334 ± 0.207	
Tumor diameter	<2 cm	5.138 ± 0.097	0.063
	≥2 cm	5.495 ± 0.114	
Tumor quantity	1	5.374 ± 0.211	0.068
	≥2	5.537 ± 0.182	
Histological grade	G1~G2	5.289 ± 0.107	0.083
	G3	5.513 ± 0.132	
Lymphatic metastasis	N/A	3.043 ± 0.037	0.017*
	A	5.588 ± 0.071	
TNM phasing	N/A	3.117 ± 0.068	0.021*
	A	5.883 ± 0.120	

Note: *$P < 0.05$.

3.3. Effects of silent lncRNA-TUG1 on the transference and invasion of SGC-7901 cells

With instant transfection technique and Lipofectamine® 2000 as medium, lncRNA-TUG1 specific siRNA or NC siRNA was transfected into SGC-7901 cells. qRT-PCR detection proved that lncRNA-TUG1 specific siRNA significantly decreased the expression level of lncRNA-TUG1 (1.000 ± 0.000 *vs.* 0.301 ± 0.012, $P < 0.001$).

After the expression of lncRNA-TUG1 in SGC-7901 cells was successfully silenced, scratch healing test was first applied to detect the effects of lncRNA-TUG1's expression change on the transferring capacity of SGC-7901 cells. Compared with NC group, the transferring capacity of SGC-7901 cells was greatly inhibited (20.651 ± 3.817 *vs.* 75.160 ± 4.332, $P = 0.008$) after the knockdown of lncRNA-TUG1. Further detection in Transwell revealed that silencing lncRNA-TUG1 can substantially weaken SGC-7901's invasion (41.223 ± 3.781 *vs.* 63.574 ± 5.152, $P = 0.007$).

3.4. Effects of down-regulating lncRNA-TUG1 on the expression of miR-144/c-Met in SGC-7901 cells

One of lncRNA's functional mechanisms is that it can combine with various RNA sequences including microRNA through molecular sponge effect so as to silence its functions. It was speculated through bioinformatics search that miR-144 may be one of lncRNA-TUG1's combining targets. In order to verify this, qRT-PCR detection was carried out after the expression of lncRNA-TUG1 was silenced in SGC-7901 cells and it was found that the expression quantity of miR-144's increases considerably. It was also learned through bioinformatics search and literature review that tyrosine kinase receptor c-Met may be one of miR-144's targets. qRT-PCR and western-blot detections were conducted and it was discovered that c-Met's mRNA and protein level showed a significant decrease indicating it was probable that lncRNA-TUG1 inhibited the expression of miR-144 and activated c-Met to promote tumorigenesis (see Table 2).

Table 2
Effects of silencing lncRNA-TUG1 on the expression of miR-144/c-Met in SGC-7901 cells.

Symbol	NC siRNA	TUG1 siRNA
miR-144	1.000 ± 0.000	2.133 ± 0.074
C-Met mRNA	1.000 ± 0.000	0.376 ± 0.0248**
C-Met protein	0.871 ± 0.039	0.420 ± 0.026**

**$P < 0.001$, *vs.* NC siRNA group.

4. Discussion

Millions of people all over the world suffer from gastric carcinoma every year. At present, the morbidity rate of GC ranks high among those of malignant tumors in both China and Western countries [7]. With the development of molecular biotechnology, biological targeted therapy has become an important assistant treatment for GC. Cetuximab [8] and bevacizumab [9] have been successfully used for treating GC. Therefore, the search and study of effective molecular therapeutic targets play an important role in improving the prognosis of GC patients.

Today increasing evidence shows that multiple kinds of noncoding RNA, such as (microRNA) [10] and lncRNA [11] have great effects on cells' physiological and pathological processes. Besides, the abnormal expression of ncRNA in diseases shows enormous potential for drug research and development. So far there have been two type of microRNA: miR-122, miR-34 entering the clinical research stage [12]. lncRNA-TUG1 is a newly found type of lncRNA that can regulate the growth of tissues and the development of various benign and malignant diseases. lncRNA-TUG1 shows a higher expression level in pancreatic tissue and its expression is regulated by glucose langerhans. The knockdown of lncRNA-TUG1 in pancreatic β can facilitate cell apoptosis and suppress insulin secretion [13]. For malignant tumors [14], the abnormal expression of lncRNA-TUG1 has great value in monitoring clinic treatment and evaluating prognosis. The research of Tan *et al.* [15] indicates that the expression of lncRNA-TUG1 is considerably up-regulated in bladder carcinoma tissues, which is correlated with the EMT transformation of tumor cells and postoperative radiotherapy resistance. The results of survival analysis curve also verify that lncRNA-TUG1's high expression indicates relatively short postoperative tumor-free survival time and total survival time. As a result, it is believed that changes of lncRNA-TUG1's expression level bear close correlation with the progress, transference and recrudesce of tumors.

In this study, it is first proved in clinical tissue specimens that lncRNA-TUG1 has a high expression in GC tissue. With different clinical pathological characteristics as subgroups, analyses show that lncRNA-TUG1's high expression is closely related with GC patients' lymphatic metastasis and high TNM phasing. The results of this study is consistent with those concerning osteosarcoma [16] and glioma [17,18]. In order to explore the biological functions of lncRNA-TUG1 in GC cells, the specificity of siRNA is applied to knocking down the expression of lncRNA-TUG1 in SGC-7901 cells and scratch healing test and Transwell detection are carried out to certify that silenced lncRNA-TUG1 can inhibit the transferring and invading capacity of cells. Both histology and cytology experiments demonstrate that lncRNA-TUG1 has certain facilitating effects in the transferring process of GC cells.

The effecting mechanism of lncRNA is quite complicated. One important mechanism is that it can act as molecular sponge and combine with microRNA so as to inhibit its silencing effect on downstream target mRNA [19–21]. Through the search on bioinformatics websites such as Starbase [22], it is learned that miR-144 may be one of lncRNA-TUG1's binding molecules and miR-144 is also certified to have significant anti-GC effects [23–25]. To sum up, we hypothesize that lncRNA-TUG1's facilitating effect on the transference and invasion of GC cells is probably realized by inhibiting the expression and function of miR-144. In order to verify this hypothesis, we apply siRNA transfection technique to knock down the expression of lncRNA-TUG1 in SGC-7901 cells. Through qRT-PCR detection, it is discovered that silenced lncRNA-TUG1 notably enhances the expression of miR-144 in SGC-7901 cells. Further study shows that after silencing lncRNA-TUG1, the expression of c-Met, the downstream target of miR-144 in SGC-7901 cells, which has facilitating effect on the invasion of tumor cells, is also inhibited. So far we have preliminarily ascertained the affecting mechanism of lncRNA-TUG1.

In conclusion, lncRNA-TUG1 manifests a tremendous expressing rise in GC tissue. It is very likely that by inhibiting miR-144, lncRNA-TUG1 indirectly activates the expression of c-Met so as to promote the transference and invasion of GC cells. Thus, lncRNA-TUG1 possesses certain value of research and development in the biological targeted therapy of GC.

Conflict of interest statements

We declare that we have no conflict of interest.

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