Am J Transl Res 2021;13(2):770-780
www.ajtr.org /ISSN:1943-8141/AJTR0114043

Original Article

Long intergenic non-coding RNA (lincRNA)-01317 suppresses human gastric cancer growth by inhibiting migration and invasion of cancer cells

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Received May 9, 2020; Accepted December 11, 2020; Epub February 15, 2021; Published February 28, 2021

Abstract: Long intergenic noncoding RNAs (lincRNAs) are strongly associated with several kinds of cancer, including gastric cancer. Here, we found significantly decreased lincRNA-01317 levels in cancer tissue compared with paracancer tissue of patients with gastric cancer, and lincRNA-01317 expression levels positively correlated with clinical survival rate. Furthermore, using a gastric cancer cell line and a xenograft mouse model, we found that transfection of a gastric cancer cell line with lincRNA-01317 significantly inhibited the proliferation, migration, and invasion of gastric cancer cells. Finally, we demonstrated that lincRNA-01317 may target KCNQ1, as KCNQ1 was downregulated after transfection of cells with lincRNA-01317. This study aimed to assess lincRNA-01317 as a potential therapeutic target to treat cancers.

Keywords: LincRNA01317, gastric cancer

Introduction

Gastric cancer is the third leading cause of cancer-related deaths and also one of the most prevalent cancers in Eastern Asia [1]. Patients with gastric cancer often display no noticeable symptoms in the early stage; thus, when diagnosed as distant metastasis, gastric cancer is basically incurable at this stage. Targeted chemotherapy significantly improves the gastric cancer patients' survival rate [2]. Nevertheless, severe adverse reactions and complications caused by chemotherapy add to the clinical challenge. Hence, the treatment for the gastric cancer patients requires the invention of new drugs and new combinations of treatments.

Long intergenic noncoding RNAs (lincRNAs) constitute a group of RNAs >200 nucleotides length with limited protein-coding ability [3]. Reportedly, lincRNAs play a vital role in cell biological function, such as development, differentiation, proliferation, metabolism, and invasion [4-7]. Moreover, they are closely associated with gastric cancer occurrence, invasion, and metastasis [8, 9]. The lincRNAs, particularly lincRNA-01317, are novel and non-annotated [10], and of great research value.

Our study demonstrated that lincRNA-01317 is significantly downregulated in cancerous tissue compared with paracancerous tissue. After transfection of gastric cancer cell lines with lincRNA-01317, migration, proliferation, and invasion of the cells were compromised, indicating that lincRNA-01317 play an important role in the pathogenesis of gastric cancer and is a potential therapeutic target.

Materials and methods

Human samples

Cancer and paracancer (>5 cm from the edge of the tumor) tissue samples from nine patients who underwent radical gastrectomy for gastric cancer at the Shanghai General Hospital of the Nanjing Medical University from September 2018 to November 2018. Patients (mean age: 52.9 years; range: 26-70 years) underwent nei-

Table 1. Clinical and demographic characteristics of the patients for the study of lncRNAs in tumor tissues and adjacent tissues

Patient no.	Age (years)	Gender	Stage	Grade
1	47	F	T3N1M0	I
2	46	M	T4N0M0	I
3	50	M	T4N2M0	II
4	68	F	T4N2M0	II
5	70	F	T1N0M0	I
6	56	M	T2N0M0	II
7	51	M	T3N0M0	II
8	62	M	T4N1M0	II
9	26	F	T4N0M0	II

ther chemotherapy nor radiotherapy before the surgery. **Table 1** summarizes the characteristics of the patients with gastric cancer enrolled in this study. The gastric cancer tissue microarray was derived from 55 patients with gastric cancer who underwent surgical resection between June 2010 and May 2011, in Shanghai General Hospital and all patients were followed until May 2019. The detailed clinical information for the patients is listed in **Table 2**. The experimental protocol was approved by the Ethics Committee of the Shanghai General Hospital. Before enrollment in the study, each patient signed an informed consent.

Mice

Four-week old female nude mice were obtained from the Model Animal Research Center of Nanjing Universityand housed in the animal experimental center of Shanghai General Hospital. The experimental procedures were in accordance with the Animal Care and Use Committee at Nanjing Medical University.

Cell lines and culture conditions

Human gastric cancer cell lines (AGS and HGC-27) were obtained from the Type Culture Collection of the Chinese Academy of Science (Shanghai, China). The cell lines were maintained in F12 or RPMI 1640 medium containing 10% fetal bovine serum and 1% penicillin-streptomycin in a humidified incubators (5% CO_2) at 37°C.

Public database

TCGAwebsite (https://cancergenome.nih.gov/) was used to search publicly available datasets for recent studies of gastric cancer. The distribution data of the most frequently mutated lincRNAs were obtained from male and female patients with whole human species.

RT-qPCR

Total RNA was extracted using the RNeasy Micro Kit (Qiagen, Hilden, Germany) and reversed transcribed into cDNA using the RT Reagent Kit (TaKaRa, Tokyo, Japan). RT-qPCR amplification was performed in a 20-mL reaction volume containing cDNA, primers, and SYBR Green I Supermix (TaKaRa) using an ABI 7500 Thermocycler (Applied Biosystems, Foster City, CA, USA). Supplementary Table 1 lists the primers for the target genes.

FISH

Unstained 5-μm sections or tissue paraffin chip was used for FISH analysis. LincRNA-01317 and lincRNA-00886 were detected using the single-color probe kit (Abbott Laboratories, Des Plaines, IL, USA). On the first day, the slides were pretreated and hybridized using the VP2000 (SciGene, Sunnyvale, CA, USA), per the manufacturer's instructions. On the following day, the slides were washed using Little Dipper (Abbott Laboratories). The washed slides were counterstained with DAPI (Vector Laboratories, Burlingame, CA, USA) and cover slips were applied using Vectashield mounting medium. Furthermore, the slides were stored at -80°C if not scored immediately.

Lentiviral vector production, titration, and transduction

The full-length lincRNA-01317 sequence is the following: TGCCACCACGTAAGAAGTGCCTTTTGCCTCCCACCATTATTCTGAGGCCTCCTCAGCCATGTGGAACTGATGACACATCTAGAAGACCCTCACCTTATGCTTATGCTGGCCCCTTGATCTTGGCCTCCAGAAATGTATAATGAAGAATCTTGAGGTCCTCCTGGATTACCAAAGTGGGCCCTAAATCCAGTGGCAGAAGACACAGACACAGAGAGGAGACCAGGTGAAGACAAAAGAAGAGGCTGGAGTGATGCAACCATCAGAGAGTGAAAATACTCAGTTACCTCCTGGTTTATGAGGCAATGAAGTATTCCAGCACATAAATATTGACGCTGAGACCCATGGGATGTAGGAGTGCTGAGCACATTTGCAAGACATAAAGACCGAAGAGGTGAATCACTTCAAAGAGAAGGACCAGATTCTCATGGACCCCACTGCCATGCTGGCCAGACATCTTGCTGCCATTGTTTTCCTGTTATTTACTCCCAAACAGATG-

Table 2. Clinicopathologic features in 55 patients with gastric cancer

Variable	No. of patients	lincRNA-01317 density		*P*
		Low	High	
Age, y				
< 65	24	12	12	1.000
≥ 65	31	15	16	
Gender				
Male	28	15	13	0.952
Female	27	14	13	
Differentiation				
Well/moderate	25	10	15	0.745
Poor	30	20	10	
Depth of invasion				
T1-T2	5	2	3	0.003
T3-T4	50	40	10	
Lymph node metastasis				
Yes	51	40	11	0.0026
No	4	3	1	
Tumor stage				
I-II	10	8	2	0.0038
III-IV	45	40	5	

GAGTGTCGCTCTGTCACCCAGGCTGGAGTGCAGTGGCACGATCTCGGCTTACTGCAAGATCTACCTCCCGGGTTCACGCCATTCTCCTGCCTCAGCCTCCCGAGTAGCTGGGACTACAGGCGTCCGCCACCACGCCCGGCTAATTTTTTGTTTTTTTTAGTATAGACGGGGTTTCACCGTGTTAGCCAGGATGGTCTCAATCTCCTGACCTCGTGACCCGCCCGCCTTGGCCTCCCAAAGTGAAGTCTCTTTTCAAAATCTTAATGCTTACCTGTGTTTCTTT. The sequence was synthesized and inserted into lentiviral vector pGCSIL-GFP with T4 DNA ligase. Competent *Escherichia coli* DH5α cells were transformed with the ligated vector. 293T cells were co-transfected with pGC-LV, pHelper 1.0, and pHelper 2.0 plasmids to produce the lentivirus. A549 cells were infected with lentivirus in medium containing polybrene (5 μg/mL). The positively infected cells were sorted by FACS to be further cultured. The level of lincRNA-01317 was detected by RT-qPCR [11].

Cell viability assays

Cells of control and experimental groups was seeded in each well of the plate to compare cell growth kinetics using the CCK-8 (Dojindo, Kumamoto, Japan) [12]. After incubating the plate for 24-96 h, measure the absorbance at 450 nm using a microplate reader (Thermo Scientific, Waltham, MA, USA), and the absorbance values were normalized to the values of the cells at 0 h.

Plate colony-formation assay

The 6-well plates were inoculated with 1000 cells per well and cultured for 7 days. After being fixed with paraformaldehyde, the colonies were stained with 5% crystal violet for >1 hour. The colonies were photographed and counted using a dissecting microscope. Colony-counting software was used to scan the images of each plate [13].

Cell migration and invasion assay

Cell migratory capacity was assessed using the 8 μm pore size 24-well transwell system (Corning, Corning, NY, USA). In this study, 3×10^5 cells were seeded in the upper chamber and allowed to migrate for 24 h. Cells in the chamber were fixed with methanol and stained with 0.1% crystal violet (C8470, Amresco, Dallas, TX, USA), and photographs were taken [13]. For the invasion assay, 2×10^4 cells were inoculated in serum-free medium in the upper chamber coated with Matrigel matrix (BD Biosciences, USA). After 24 h, the upper chambers were fixed and stained as described before. The cells that had migrated to the reverse side of the upper chambers were photographed [14]. Five fields were selected randomly to count migrated or invaded cells.

Cell wound healing

For the wound-healing experiment, the cells were first cultured to confluence in 6-well plates. The culture was then scratched in the center of the well with a 200-μL microtubule tip. The cells were washed with PBS and incubated with serum-free medium. After 24 h, representative images were captured. The width of the healed area was quantified and compared with the baseline values. All experiments were independently repeated in triplicate [14].

Xenograft model of human colon cancer

AGS or HGC-27 human colon cancer cells (5 × 10^6 cells in 100 mL phosphate-buffered saline [PBS] per mouse) were injected intraperitoneally into the flanks of mice. The tumor volume was calculated using the formula (length × width^2 × 0.5) every three days. At day 10, the mice were euthanized with pentobarbital sodium (200 mg/kg), and tumors were excised for further examination.

Prediction of lincRNA-01317 binding

The website http://rtools.cbrc.jp/ was used to predict the binding target-gene or RNA-of lincRNA-01317. The results were verified by RT-qPCR.

Western blot analysis

Cell were harvested and denatured. Proteins were separated by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred ontopolyvinylidene difluoride membranes. Membranes were blocked and incubated overnight at 4°C with anti-KCNQ1 antibody or anti-YIPF antibody (EP1674Y; Abcam, Cambridge, UK). The target protein was detected by an enhanced chemiluminescence western blot detection system (Thermo Fisher Scientific).

Statistical analysis

Results obtained for the two groups in the study were compared using Student's *t*-test. Statistical analysis was performed using GraphPad software (GraphPad, San Diego, CA, USA). $P < 0.05$ was considered statistically significant.

Results

LincRNA-01317 was frequently downregulated in gastric cancer tissue

Globally, the survival rate for gastric cancer is quite low. According to the TCGA tumor database, the five-year survival rate for gastric cancer is 40%, whereas the ten-year survival rate is only 20%. The TCGA database was used to detect lincRNAs that are most prone to mutation in gastric cancer, and their expression in cancerous and paracancerous tissue was verified. The 20 genes that were most susceptible to mutation were selected for the study (Supplementary Table 2). RT-qPCR analysis revealed that two lincRNAs (lincRNA-01317 and lincRNA-00886) were downregulated in the cancerous tissues obtained from the patients compared with the paracancerous tissue samples obtained from the same patients (**Figure 1A** and **1B**). The significance of the observed differences in their expression levels was assessed using Student's *t*-test, based on the presence or absence of a normal distribution in the data, and revealed significant differences in the expression of lincRNA-01317 and lincRNA-00886 between the groups ($P = 0.0315$ and $P = 0.0464$, respectively); however, no significant difference was observed in other mutation-prone lincRNAs (Supplementary Figure 1). FISH was performed in three paired biopsy specimens of patients with gastric cancer to validate the expression levels of lincRNA-01317 and lincRNA-00886 in gastric cancer. **Figure 1C** and **1D** show that lincRNA-01317 expression was markedly increased, along with a higher fluorescence value, and lincRNA-00886 expression was relatively unchanged in the paracancerous tissue compared with the corresponding cancerous tissue. Thus, we focused on the role of lincRNA-01317 in gastric cancer.

Downregulation of lincRNA-01317 positively correlates with poor prognosis in gastric cancer patients

To explore the clinical significance of lincRNA-01317 in gastric cancer, 55 cancer specimens were detected by FISH, and the correlation between lincRNA level and the clinical characteristics was analyzed. The results showed that lincRNA-01317 was downregulated in cancer tissue (**Figure 2A** and **2B**). Moreover, patients with low levels of lincRNA-01317 expression showed lower 5-year disease-specific survival rate than those with high lincRNA-01317 expression (**Figure 2C**). Furthermore, levels of lincRNA-01317 were negatively correlated with the tumor stage and lymph node metastasis (**Table 2**), suggesting that downregulation of lincRNA-01317 is an independent indicator of prognosis in gastric cancer.

Overexpression of lincRNA-01317 suppressed proliferation, migration, and invasion of a gastric cancer cell line in vitro

Given the low expression level of lincRNA-01317 in gastric cancer tissue, we further evaluated

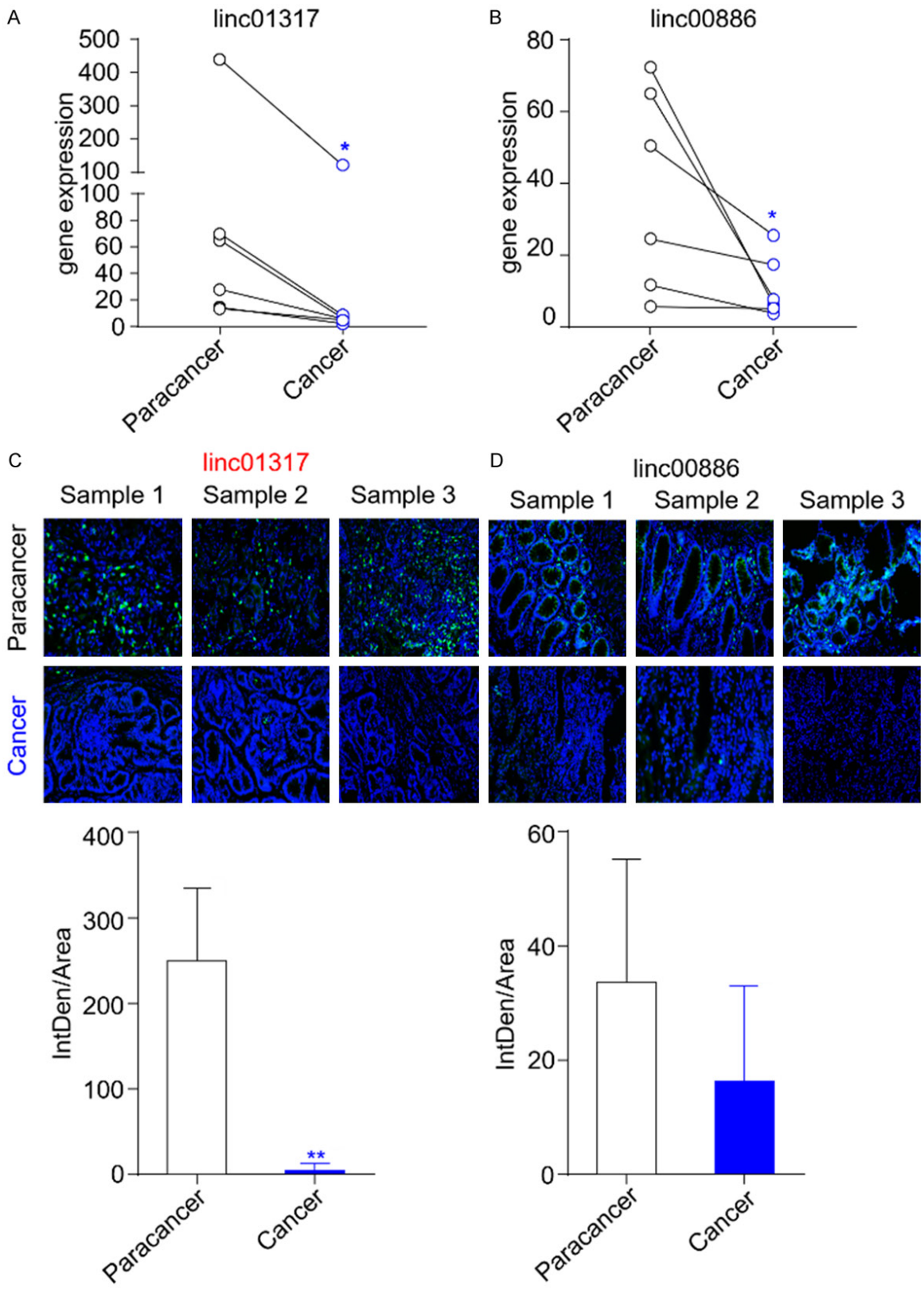

Figure 1. LincRNA-1317 is downregulated in gastric cancer tissue. Levels of lincRNA-01317 (A) and lincRNA-00886 (B) in six pairs of gastric cancer tissue and corresponding paracancer tissue were detected using RT-qPCR. The RT-qPCR results are shown as the mean ± standard error of the mean (SEM). (C) *In situ* hybridization of lincRNA-01317

in paracancer tissue and gastric cancer tissue was performed. Green: lincRNA-01317; blue: nuclei counterstained with 40,6-diamidino-2-phenylindole (DAPI). (D) *In situ* hybridization of lincRNA-00886 in paracancer and gastric cancer tissues was performed. Green: lincRNA-00886; blue: DAPI. The statistical results are shown as the mean ± SEM (*P < 0.05 and **P < 0.01).

the biological role played by this lincRNA in gastric cancer cell lines. We stably transfected AGS and HGC-27 cells with the synthetic lincRNA-01317 sequence (Supplementary Figure 2). For controls, we transfected cancer cells with negative control lincRNA (lincRNA-NC) that did not specifically target any human gene products. After 48 h, the growth of lincrna-01317 transfected cells in both cell lines was slower than that in the NC group. As in the CCK-8 proliferation assay, the proliferation capacity of AGS and HGC-27 cells decreased in the presence of lincRNA-01317 (**Figure 3A**). In addition, overexpression of lincRNA-01317 inhibited the rate of colony formation (**Figure 3B**). To further understand the role of lincRNA-01317 in gastric cancer, transwell migration (**Figure 3C**), wound healing (**Figure 3D**), and invasion (**Figure 3E**) assays were performed. The data show that overexpression of lincRNA-01317 inhibits the migration and invasion of AGS and HGC-27 cells gastric cancer cells.

LincRNA-01317 inhibits tumor growth in a mouse xenograft model of gastric cancer

Given the suppression of cancer cell migration and invasion by lincRNA-01317 *in vitro*, we further assessed whether increased levels of lincRNA-01317 would inhibit tumor formation by gastric cancer cells *in vivo*. LincRNA-01317-overexpressing AGS and HGC-27 cells were subcutaneously implanted into either the left or right posterior flank, respectively, of the same nude mouse (5×10^6 cells per injection site) (**Figure 4A**). Six days after implantation, the cells transfected with linc-NC formed tumors, while the cells transfected with lincRNA-01317 failed to grow or grew slowly (**Figure 4A**), exhibited a marked reduction in tumor size and tumor weight (**Figure 4B** and **4C**) compared with the control group. These data indicated that elevated lincRNA-01317 levels in gastric cancer cells markedly reduced their ability to form tumors.

KCNQ1 emerged as a novel target of lincRNA-01317

Based on the literature [15], we hypothesized that lincRNA-01317 may inhibit the malignant phenotype of gastric cancer cells by regulating genes that control cell proliferation, migration, or invasion. Therefore, we decided to use rtools to find the target RNAs of lincRNA-01317. We found that a variety of genes had binding sites (Supplementary Table 3), and we selected 10 RNAs with the highest scores for RT-qPCR verification, among which KCNQ1 and YIPF showed changes in both cell lines and showed decreased expression in lincRNA-01317-overexpressing cell lines (**Figure 4D**). We then measured the expression of these two genes in the gastric cancer and paracancer tissues, and showed that KCNQ1 expression in the tumor decreased (Supplementary Figure 3A), which was positively correlated with the expression of lincRNA-01317 (Supplementary Figure 3B). Western analysis also confirmed that KCNQ1 levels decreased significantly in the tumor cells (**Figure 4E**). Taken together, these results suggested that lincRNA-01317 reduces the expression of KCNQ1 via the interactions.

Discussion

Increasing evidence has indicated that lincRNAs are critical regulators of cancer-related processes. LincRNA expression shows close correlation with various cancers, and they are function as either tumor suppressor genes or oncogenic genes [16]. During tumor growth and progression, overexpressed or downregulated lincRNAs may potentially target tumor suppressor genes and/or oncogenic genes [17-20]. We first used the TCGA database to identify nearly 200 mutation-prone lincRNAs, and GO analysis revealed that most were new lincRNAs with unannotated functions. The lincRNAs that were most susceptible to mutation and had sequences available were selected. Furthermore, six pairs of tissues were collected from patients with gastric cancer, and RT-qPCR was performed, followed by a paired *t*-test. Two lincRNAs, lincRNA-01317 and lincRNA-00886, were determined to be expressed at a high level in the paracancerous tissues, but at a relatively low expression in the cancerous tissues. Thus, three additional biopsy specimens of patients with gastric cancer were collected and FISH was performed to validate the results.

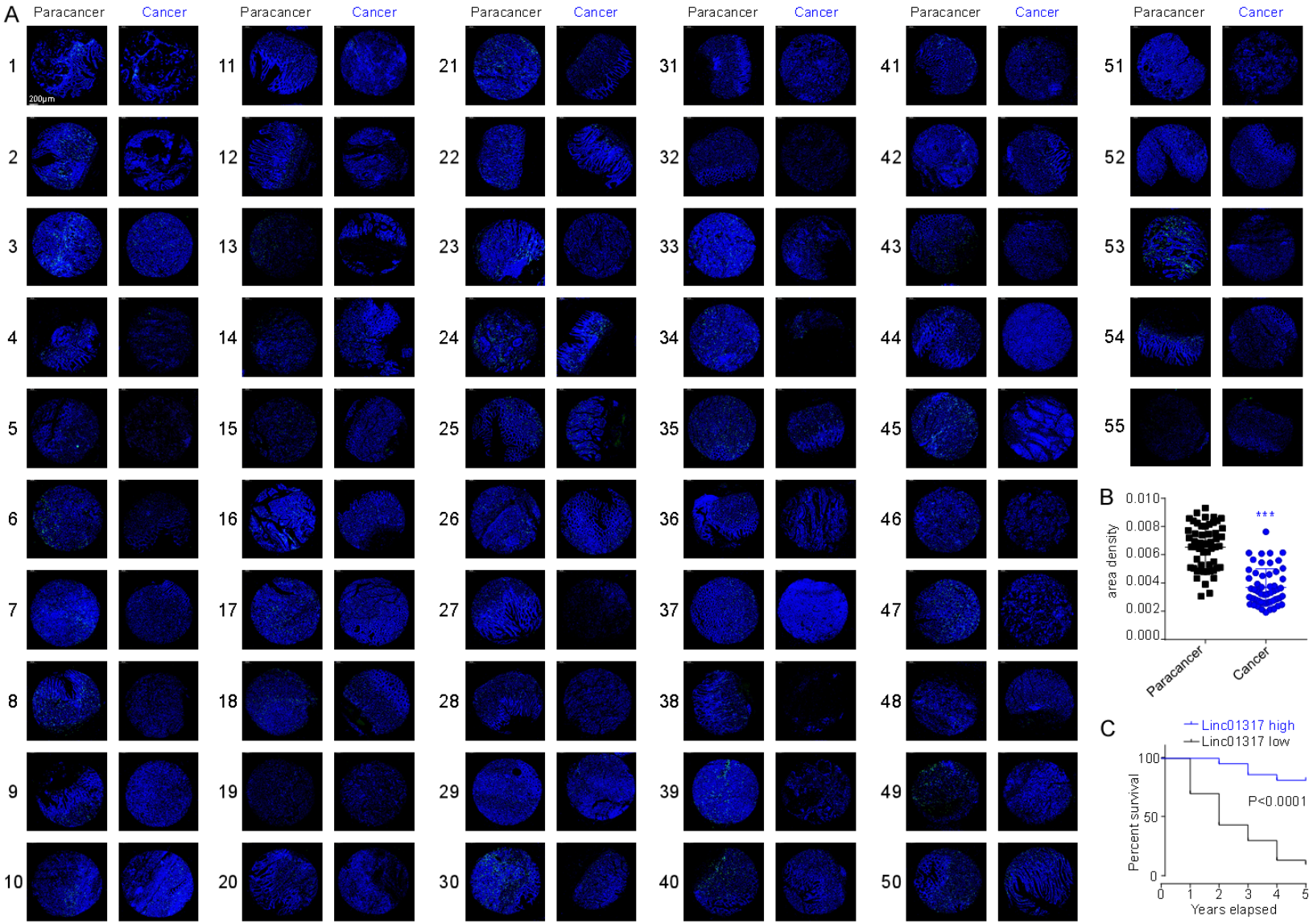

Figure 2. LincRNA-01317 is downregulated in cancer tissue from patients with gastric cancer and is an indicator of poor prognosis. (A) *In situ* hybridization of lincRNA-01317 in paracancer and cancer tissue from 55 advanced-stage gastric cancer patients. (B) The results of statistical analysis of the data in (A) are shown as the mean ± SEM (***P < 0.001). (C) Low expression level of lincRNA-01317 significantly (log rank, P < 0.0001) correlates with poor progression-free survival in this patient cohort.

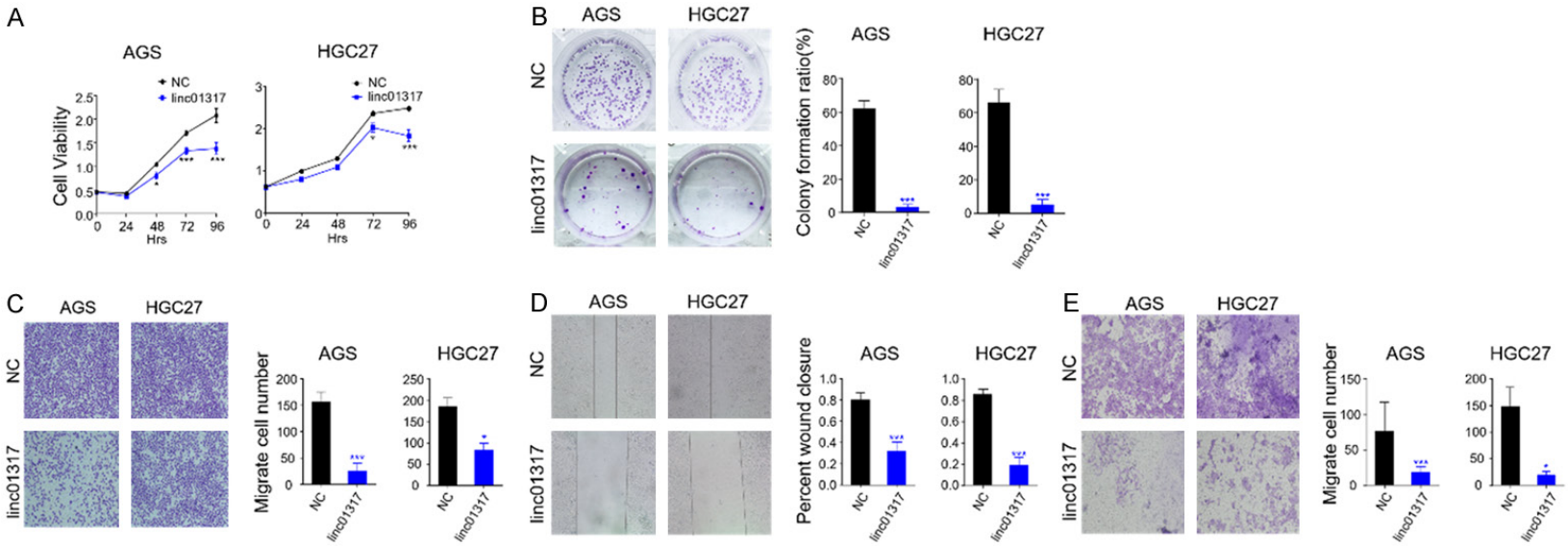

Figure 3. LincRNA-01317 inhibits AGS and HCG27 cell proliferation, migration, and invasion. (A) Stable lincRNA01317-expressing AGS and HCG27 cells were established and linc-NC-expressing cells were control groups. Cell viability and proliferation were evaluated by the CCK-8 assay at 24, 48, 72, and 96 h. Results of statistical analysis are shown as the mean ± SEM (*P < 0.05 and ***P < 0.001). (B) The proliferative ability of lincRNA-01317-expressing AGS and HCG27 cells and NC control cells was assessed via a plate colony-formation assay. The results of statistical analysis are shown as the mean ± SEM (***P < 0.001). (C) LincRNA-01317-expressing AGS and HCG27 cells could migrate on transwell inserts for 24 h. The cells that had migrated into the lower chambers through the filter were quantitated by gentian violet staining and expressed as the total number of cells in the lower wells. Cell mobility and invasion were assessed by wound-healing assay (D) and transwell migration through Matrigel. (E) The results of statistical analysis are shown as the mean ± SEM (*P < 0.05 and ***P < 0.001).

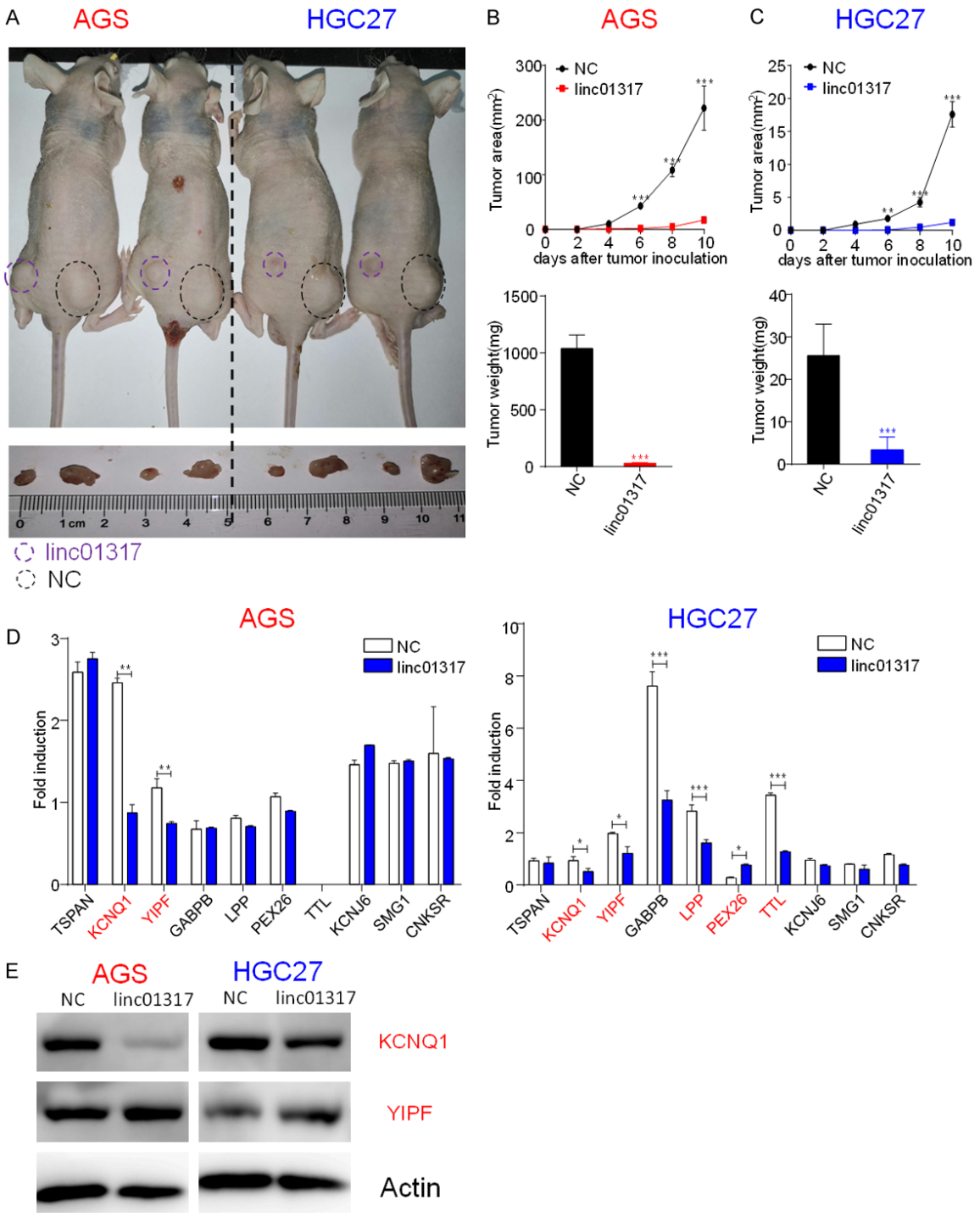

Figure 4. LincRNA-01317 inhibited AGS and HCG27 cell tumor growth *in vivo*. LincRNA- and linc-NC-transfected AGS and HCG27 cells (5×10^6) were injected subcutaneously into the left or right posterior flank, respectively, of the same nude mouse (as indicated). A. Photographs were taken 10 days after tumor-cell implantation. B. Tumor sizes were measure with a vernier caliperare and were shown as mean ± SEM. C. Tumor weight is also shown as mean ± SEM. Four mice were used in each experiment and repeated twice, for a total of eight or more mice. D. Candidate target gene expression measured by RT-qPCR in lincRNA-01317 and linc-NC-transfected AGS and HCG27 cells. Data are representative of two independent experiments (*$P < 0.05$ and ***$P < 0.001$). Western analysis showed that levels of total and cleaved caspase-3 were significantly downregulated in both lincRNA-01317-expressing cell lines. β-actin served as control. D. KCNQ1 and YIPF expression levels were measured by western analysis in lincRNA-01317- and linc-NC-transfected AGS and HCG27 cells. KCNQ1 was downregulated in both lincRNA-01317-expressing cell lines. E. Western analysis of levels of KCNQ1 and YIPF. β-actin was used as the control.

It was confirmed that lincRNA-01317 was expressed at a high level in the paracancerous tissue and at a markedly low level in the cancerous tissues. Furthermore, lincRNA-00886 was expressed at a negligible level in the paracancerous tissues and not at all in the cancerous tissue. Therefore, this suggests the involvement of lincRNA-01317 in the development and progression of gastric cancer and possible applications in diagnostics or targeted therapy. In gastric tissues, Yan et al. showed that lincRNA-00470 promotes tumors growth [21] and linc-00629 inhibits tumor growth [22]. We observed a significant inhibition of cell growth, migration, and invasion with overexpression of lincRNA-01317, suggesting that lincRNA-01317 function as a tumor suppressor in gastric cell lines. Furthermore, lincRNA-01317 expression in tissue samples from 55 gastric cancer patients and the survival rates of the patients showed that lincRNA-01317 was closely correlated with the progression of gastric cancer and could be used as a new biological marker and target.

The general function of lincRNAs is to modulate their targets by direct or indirect binding of RNAs [17, 18]. As these are new lincRNAs with unannotated functions, they are not described in the existing literature. Based on the bioinformatics analysis, we predicted several lincRNA-01317 targets. Our results suggested that KCNQ1, which is a tumor suppressor gene [23], might be a novel target of lincRNA-01317 in gastric cancer cells. Overexpression of lincRNA-01317 significantly down regulated KCNQ1 RNA level. In conclusion, this study may serve as a basis for future studies regarding biological characteristics and the applications of lincRNA-01317.

Acknowledgements

This work was supported by the Science and Technology Committee of Songjiang District, Shanghai (19SJKJGG140).

Disclosure of conflict of interest

None.

Abbreviations

lincRNAs, Long intergenic noncoding RNAs; TCGA, The Cancer Genome Atlas; RT-qPCR, Quantitative reverse transcription-polymerase chain reaction; FISH, fluorescence in situ hybridization; CCK-8, cell counting Kit-8.

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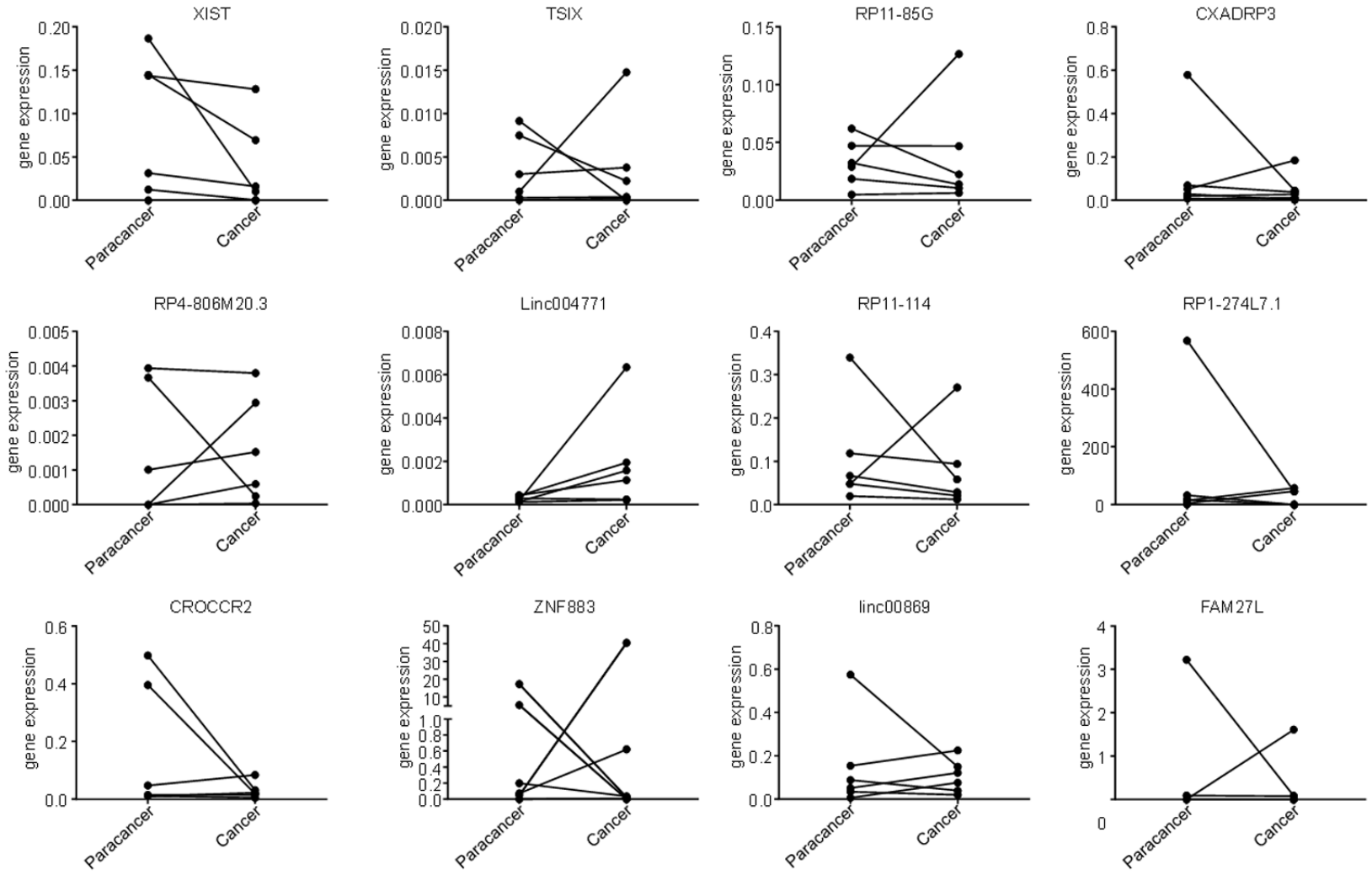
Supplementary Table 1. Primer sequences for real time PCR (5'-3')

	Primers for real time PCR	
RP11-383M4.6	forward	AGAGGCAGCAGAAGAGGAGGAAG
	reverse	TTGGCGATGGTCTTGACTGAATCC
LINC01098	forward	AGCAGCCGAGACAGAGCAGAG
	reverse	GGTGGATGAACGCCAGATAGCTTC
RP11-434D2.7	forward	AGAGGCAGCAGAAGAGGAGGAAG
	reverse	TTGGCGATGGTCTTGACTGAATCC
LINC00969	forward	GCACAGCCAGAGGACAACACATC
	reverse	ACGTAGGAGGCATTCTCGACACC
LINC00886	forward	CTAGGATTACAGGCACGCACCAC
	reverse	AGGCTGAGGCAGGTGGATCAC
HCG17	forward	GCCACACCGTAGTCATAGAGCAAG
	reverse	GGAGGAACAGCCGTGTCATCAAG
RP11-85G18.6	forward	AGAGGCAGCAGAAGAGGAGGAAG
	reverse	TTGGCGATGGTCTTGACTGAATCC
PGM5P2	forward	CGAGATCGTGGTGCAGATGGC
	reverse	GGAGACCGCAGGTGTTGACAAG
LINC00869	forward	TTCGGTCTTGCCTTGAACACATCC
	reverse	CCTCCTCCTCCTCCTCCTCCTC
FAM27L	forward	GGCTCCGGCCTGACTTCTCC
	reverse	CTTGGCTGGAGTGTGGTCATCTTG
ZNF883	forward	ATCCCTGACCCAGCATCAGA
	reverse	TCCGGGTAAAGGACTTACCACA
LINC01317	forward	AGGCGGAGTGTCGCTCTGTC
	reverse	GAGGCAGGAGAATGGCGTGAAC
CROCCP2	forward	CTGGCGGACTCCTCTTCCTCTC
	reverse	GAGTAACTTGTGGCAGGCGTGAG
RP1-274L7.1	forward	CGAGGCGTGCGGTTCTTCTG
	reverse	TCCTTCCGTCCGTAGCGTACAG
RP11-114H24.7	forward	AGAGGCAGCAGAAGAGGAGGAAG
	reverse	TTGGCGATGGTCTTGACTGAATCC
LINC00477	forward	TCCACTTCTGCCACTCCTGAGAC
	reverse	GCTATGACCATATCGCTGCACTCC
RP4-806M20.3	forward	CGCACGCCTCTCAACTACATCC
	reverse	AGGACCACCAAGGACCACAGG
CXADRP3	forward	TGCTTGCTCTAGTGCTCATTGGTC
	reverse	GCTTCTGGCAGCGGACGTAC
TSIX	forward	TGGATGGCTTCAATGTCTGGCTTC
	reverse	CTGAGGCAGGAGAATGGTGTGAAC
XIST	forward	TCCAGTTCTGTCGCAGTGTTCAAG
	reverse	GCAAGACCTTCAGCCGCCATC
TSPAN	forward	CCTTGGAGTCGAGTCAGGGT
	reverse	CCCGAAGTAGGTAAGAGTCACC
KCNQ10T1	forward	GAGGCTTTCAAAGTACAGGGG
	reverse	CAAGGAGTCAATCTCAGCGTC
YIPF	forward	GTTCCATCAGAGATGCTCATGTC
	reverse	GCAAAGGAGGCTCTTCATCAAA

GABPB	forward	TGGGAAAGAGGTTGCTAGAAGC
	reverse	GTGGAGGGGTGATGTTCCAAG
LPP	forward	CCCGGTAGTTGCTCCAAAAC
	reverse	CCCTGTACTTTGAAAGCCTCTTC
PEX26	forward	GTGCTCCCTGTGTGTTGTG
	reverse	GGGACCTGGTAATACTGAAGGAC
TTL	forward	AACGAGCTGTGCTACAAGGTC
	reverse	GCGTGGTCGATGAGGAAGA
KCNJ6	forward	GACAGAATCCATGACTAACGTCC
	reverse	CTGGCCTGCTTAGGCAACTTT
SMGL	forward	GGCCTCGAAACTGATAACATGA
	reverse	ACTTTTCCGTCGGCTACTTATG
CNKSR	forward	GACTGCCTGCAACAATATGTCC
	reverse	CTGGTGTCCAATCCGTGTGAC
GAPDH	forward	GCCACCCAGAAGACTGTGGATGGC
	reverse	CATGTAGGCCATGAGGTCCACCAC

Supplementary Table 2. Most susceptible to mutation in TCGA

Symbol	Name	Cytoband	Type	# Affected Cases in Cohort	# Affected Cases Across the GDC	# Mutations
XIST	X inactive specific transcript (non-protein coding)	Xq13.2	lincRNA	43/206 (20.87%)	554/10202	54
TSIX	TSIX transcript, XIST antisense RNA	Xq13.2	lincRNA	25/206 (12.14%)	345/10202	32
RP11-85G18.6	RP11-85G18.6	10p12.1	lincRNA	21/206 (10.19%)	321/10202	30
CXADRP3	coxsackie virus and adenovirus receptor pseudogene 3	18p11.21	lincRNA	17/206 (8.25%)	191/10202	17
RP4-806M20.3	RP4-806M20.3	20q13.32	lincRNA	15/206 (7.28%)	127/10202	15
CTD-2139B15.2	CTD-2139B15.2	5p15.1	lincRNA	14/206 (6.80%)	117/10202	9
LINC00477	long intergenic non-protein coding RNA 477	12p12.1	lincRNA	13/206 (6.31%)	128/10202	11
RP11-114H24.7	RP11-114H24.7	15q24.3	lincRNA	12/206 (5.83%)	188/10202	12
RP1-274L7.1	RP1-274L7.1		lincRNA	11/206 (5.34%)	160/10202	12
CROCCP2	ciliary rootlet coiled-coil, rootletin pseudogene 2	1p36.13	lincRNA	11/206 (5.34%)	260/10202	11
AC015849.16	AC015849.16	17q12	lincRNA	10/206 (4.85%)	139/10202	10
CTD-2066L21.3	CTD-2066L21.3	5p13.3	lincRNA	10/206 (4.85%)	108/10202	10
LINC01317	long intergenic non-protein coding RNA 1317	2p22.3	lincRNA	9/206 (4.37%)	146/10202	9
CTD-2206N4.2	CTD-2206N4.2	17q12	lincRNA	9/206 (4.37%)	139/10202	11
ZNF883	zinc finger protein 883	9q32	lincRNA	9/206 (4.37%)	112/10202	9
FAM27L	family with sequence similarity 27-like	17p11.2	lincRNA	9/206 (4.37%)	114/10202	8
LINC00869	long intergenic non-protein coding RNA 869	1q21.2	lincRNA	9/206 (4.37%)	138/10202	9
PGM5P2	phosphoglucomutase 5 pseudogene 2	9p11.2	lincRNA	8/206 (3.88%)	149/10202	8
RP11-147L13.11	RP11-147L13.11	17q24.2	lincRNA	8/206 (3.88%)	105/10202	8
HCG17	HLA complex group 17 (non-protein coding)	6p22.1	lincRNA	8/206 (3.88%)	79/10202	7
RP11-313I2.11	RP11-313I2.11	11q14.3	lincRNA	7/206 (3.40%)	140/10202	6
LLNLR-249E10.1	LLNLR-249E10.1	19p13.12	lincRNA	7/206 (3.40%)	84/10202	7
LINC00886	long intergenic non-protein coding RNA 886	3q25.31	lincRNA	7/206 (3.40%)	75/10202	7
RP11-32B5.8	RP11-32B5.8	15q11.2	lincRNA	7/206 (3.40%)	102/10202	7
RP11-266K4.9	RP11-266K4.9	12p13.31	lincRNA	6/206 (2.91%)	38/10202	6
LINC00969	long intergenic non-protein coding RNA 969	3q29	lincRNA	6/206 (2.91%)	127/10202	6
RP11-651P23.5	RP11-651P23.5	3q25.1	lincRNA	6/206 (2.91%)	80/10202	6
RP11-434D2.7	RP11-434D2.7	17p11.2	lincRNA	6/206 (2.91%)	110/10202	6
XXbac-BPG308J9.3	XXbac-BPG308J9.3	6p22.1	lincRNA	6/206 (2.91%)	124/10202	6
LINC01098	long intergenic non-protein coding RNA 1098	4q34.3	lincRNA	6/206 (2.91%)	87/10202	6
RP11-383M4.6	RP11-383M4.6	9q21.32	lincRNA	6/206 (2.91%)	221/10202	6
AC022007.5	AC022007.5	3p25.3	lincRNA	6/206 (2.91%)	49/10202	5
RP11-306013.1	RP11-306013.1	6q25.2	lincRNA	6/206 (2.91%)	71/10202	6
RP11-219A15.2	RP11-219A15.2	17p11.2	lincRNA	5/206 (2.43%)	106/10202	5
RP11-699L21.1	RP11-699L21.1	3q29	lincRNA	5/206 (2.43%)	44/10202	5
AC016995.3	AC016995.3	2p22.1	lincRNA	5/206 (2.43%)	45/10202	5
AC005522.7	AC005522.7	7q11.23	lincRNA	5/206 (2.43%)	40/10202	6
MIR99AHG	mir-99a-let-7c cluster host gene	21q21.1	lincRNA	5/206 (2.43%)	51/10202	5
LINC00336	long intergenic non-protein coding RNA 336	6p21.31	lincRNA	5/206 (2.43%)	54/10202	5
RP11-813I20.2	RP11-813I20.2	14q22.3	lincRNA	5/206 (2.43%)	57/10202	5
RP11-147L13.13	RP11-147L13.13	17q24.2	lincRNA	5/206 (2.43%)	68/10202	6
SPACA6P-AS	SPACA6P antisense RNA	19q13.41	lincRNA	5/206 (2.43%)	53/10202	5
AC005863.1	AC005863.1	17p12	lincRNA	5/206 (2.43%)	42/10202	5
FLJ33360	FLJ33360 protein	5p15.31	lincRNA	5/206 (2.43%)	80/10202	5
AC004702.2	AC004702.2	17p11.2	lincRNA	5/206 (2.43%)	55/10202	5
KANTR	KDM5C adjacent non-coding transcript	Xp11.22	lincRNA	4/206 (1.94%)	47/10202	5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RP4-806M20.3
Linc004771
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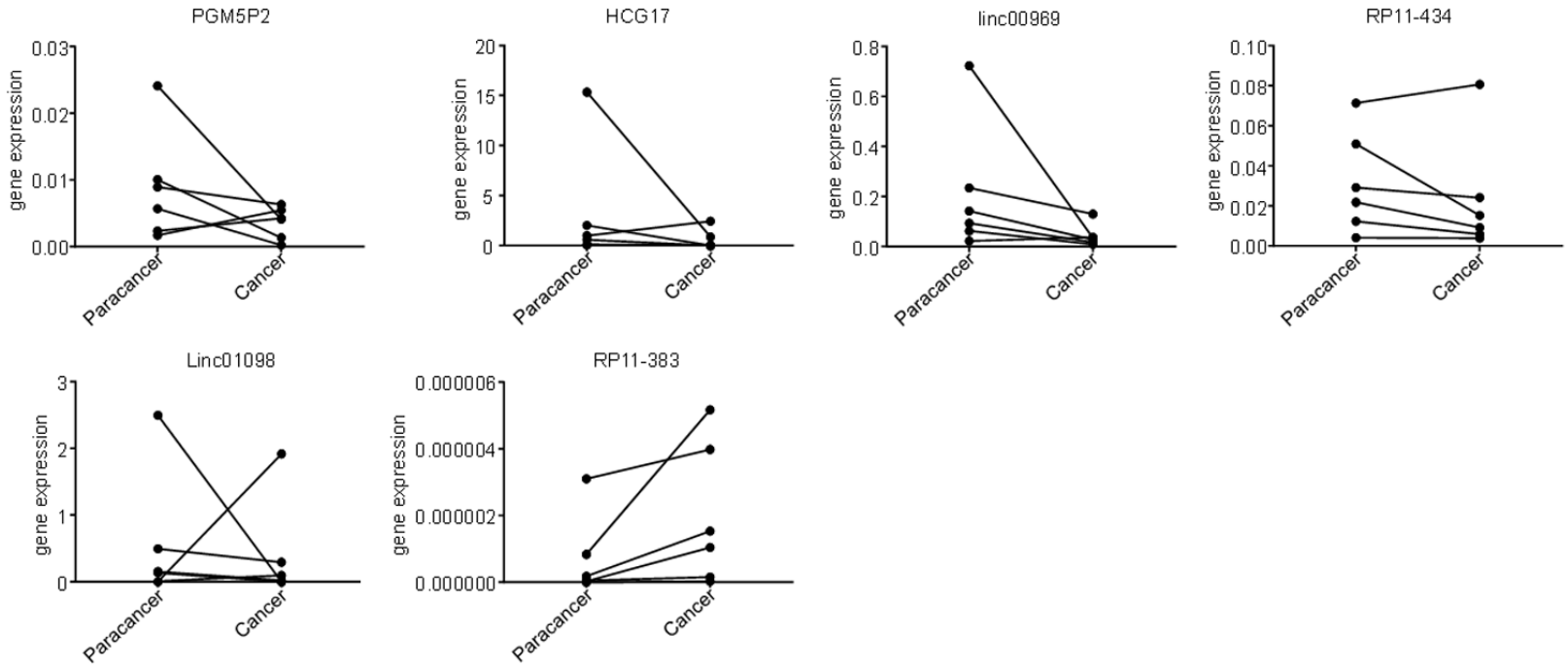
CROCCR2
ZNF883
linc00869
FAM27L
gene expression
Paracancer
Cancer



Supplementary Figure 1. RT-qPCR results of lincRNA expression. The induction of lincRNA expression in paired samples was measured using RT-qPCR. Samples were collected and lysed, and RNA was extracted for the RT-qPCR assay. Data were pooled from six paired independent samples and expressed as mean ± SEM with $P < 0.05$.

A

GCGGCCGCTGCCACCACGTAAGAAGTGCCTTTTGCCTCC
CACCATTATTCTGAGGCCTCCTCAGCCATGTGGAACTGAT
GACACATCTAGAAGACCCTCACCTTATGCTTATGCTGGCCC
CTTGATCTTGGCCTCCAGAAATGTATAATGAAGAATCTTGA
GGTCCTCCTGGATTACCAAAGTGGGCCCTAAATCCAGTGG
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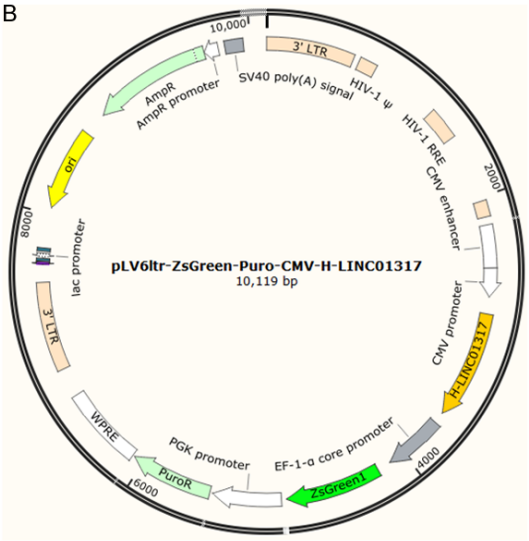
B



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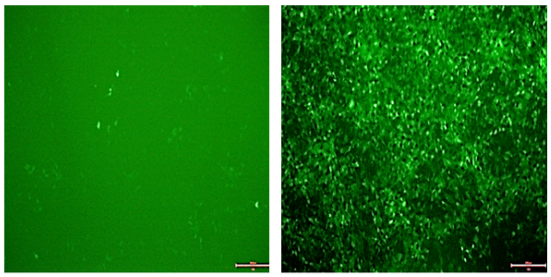

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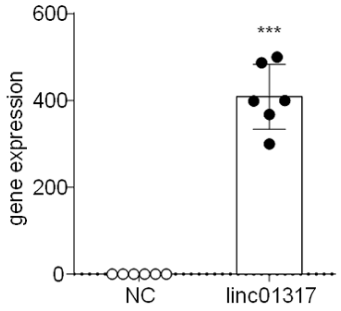
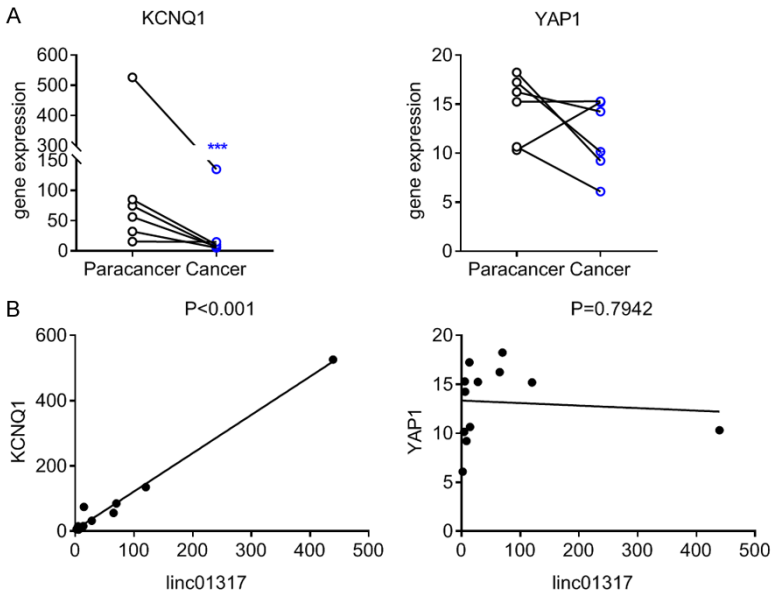


Supplementary Figure 2. Tumor cell line transfected with plasmid encoding lincRNA-01317. A. Nucleotide sequences of lincRNA-01317 from human samples. B. LincRNA-01317 plasmid was constructed. C. Tumor cell line successfully transfected with plasmid encoding lincRNA-01317. D. Levels of lincRNA-01317 in NC (control) and lincRNA-01317 cell lines.

Supplementary Table 3. List of RNAs interacting with ENST00000366209 (AC009499.1)

Rank	Ensemble ID	Name	Position (hg19)	MINENERGY				SumEnergy
				MinEnergy	Binding site (query)	Binding site (target)	location	
1	ENST00000597346	KCNQ1OT1	chr11:2629559-2721224	-89.3	671-735	74164-74228	ncRNA	-13370.2
2	ENST00000589042	TTN	chr2:179390717-179672150	-26.3	10-61	21359-21410	CDS	-13110.4
3	ENST00000604411	TSIX	chrX:73012041-73049066	-76.9	549-604	5383-5438	ncRNA	-7658.9
4	ENST00000397910	MUC16	chr19:8959521-9092018	-41.7	194-260	27629-27695	CDS	-6419.4
5	ENST00000607772	CNKSR3	chr6:154708639-154831793	-96.9	569-625	11615-11671	UTR3	-4616.4
6	ENST00000609686	GRIN2B	chr12:13693166-14133053	-34.6	560-610	22345-22395	UTR3	-4529.7
7	ENST00000373191	AGO3	chr1:36396680-36538101	-80.8	544-604	12681-12741	UTR3	-4439.1
8	ENST00000501122	NEAT1	chr11:65190270-65213011	-71.7	671-745	17793-17867	ncRNA	-4280.0
9	ENST00000546474	BRF1	chr14:105675624-105781926	-81.2	557-614	8843-8900	UTR5	-3625.3
10	ENST00000329627	PEX26	chr22:18560690-18588162	-90.2	546-606	6496-6556	UTR3	-3562.8
11	ENST00000295851	ABI2	chr2:204192943-204312446	-82.7	541-607	18801-18867	UTR3	-3502.7
12	ENST00000397345	NEB	chr2:152341854-152591001	-23.1	1-46	9408-9459	CDS	-3496.6
13	ENST00000367255	SYNE1	chr6:152442820-152958534	-23.7	723-778	1184-1239	CDS	-3427.8
14	ENST00000264065	DNAJC10	chr2:183581000-183659191	-65.1	540-605	16339-16404	UTR3	-3401.0
15	ENST00000370754	DST	chr6:56322788-56819385	-28.4	437-486	21972-22021	CDS	-3302.6
16	ENST00000312675	LPP	chr3:187930722-188608460	-95.3	671-737	8490-8556	UTR3	-3287.1
17	ENST00000361354	NCKAP1	chr2:183773844-183903200	-82.0	516-623	6039-6146	UTR3	-3237.5
18	ENST00000564288	MACF1	chr1:39669919-39952849	-21.3	724-775	15819-15870	CDS	-3232.9
19	ENST00000368918	GABPB2	chr1:151043081-151098018	-122.4	532-625	7139-7232	UTR3	-3219.2
20	ENST00000609713	KCNJ6	chr21:38979679-39288749	-96.2	542-606	11628-11692	UTR3	-3179.3
21	ENST00000309955	CFLAR	chr2:201980828-202041410	-79.7	539-608	6109-6178	UTR3	-3125.7
22	ENST00000238831	YIPF4	chr2:32502980-32541663	-93.8	546-607	8229-8290	UTR3	-3091.0
23	ENST00000335251	INTU	chr4:128554088-128647892	-84.7	514-607	11686-11779	UTR3	-3024.2
24	ENST00000367701	ZBTB37	chr1:173838095-173872687	-67.6	574-625	13905-13956	UTR3	-2994.7
25	ENST00000406785	SLC8A1	chr2:40324411-40679209	-26.3	203-250	2800-2847	CDS	-2987.8
26	ENST00000343098	FSIP2	chr2:186603356-186698016	-27.0	559-618	187-246	CDS	-2955.8
27	ENST00000357395	SYNE2	chr14:64319684-64693165	-27.9	673-723	18007-18057	CDS	-2937.9
28	ENST00000429989	TSPAN14	chr10:82213923-82292879	-107.1	514-625	10454-10565	UTR3	-2902.3
29	ENST00000327381	XKR4	chr8:56014950-56454613	-90.5	671-735	10377-10441	UTR3	-2893.7
30	ENST00000355837	AC005154.6	chr7:30587974-30604233	-79.8	536-599	2923-2986	ncRNA	-2875.2
31	ENST00000418539	BCYRN1	chr2:47558200-47571656	-81.1	541-606	2841-2906	ncRNA	-2832.2
32	ENST00000371655	RAB3B	chr1:52373629-52456436	-96.6	546-608	1681-1743	UTR3	-2786.7
33	ENST00000333891	PCLO	chr7:82383330-82792246	-23.2	212-271	8276-8335	CDS	-2785.7
34	ENST00000526775	CACNA1E	chr1:181452717-181777219	-38.5	205-257	8997-9049	UTR3	-2761.3

35	ENST00000261491	DGKH	chr13:42622890-42817032	-86.8	542-606	15361-15425	UTR3	-2754.6
36	ENST00000446231	SMG1	chr16:18816176-18937776	-139.4	533-625	13056-13148	UTR3	-2728.2
37	ENST00000381318	ITSN1	chr21:35014765-35272165	-79.7	543-608	10626-10691	UTR3	-2650.0
38	ENST00000367941	STX7	chr6:132767007-132834201	-62.5	671-728	10309-10366	UTR3	-2646.5
39	ENST00000473989	UBN2	chr7:138916232-138992982	-90.1	671-735	8649-8713	UTR3	-2645.7
40	ENST00000429829	XIST	chrX:73040492-73072588	-33.4	194-256	12309-12371	ncRNA	-2630.3
41	ENST00000366847	FGFR1OP	chr6:167412671-167466201	-90.1	546-603	7075-7132	UTR3	-2600.7
42	ENST00000437048	VPS53	chr17:411909-618096	-70.3	671-735	5150-5214	UTR3	-2574.8
43	ENST00000361565	IPO9	chr1:201798270-201853422	-79.5	542-602	4953-5013	UTR3	-2555.8
44	ENST00000324306	ZKSCAN1	chr7:99613205-99639312	-82.8	547-606	5633-5692	UTR3	-2555.5
45	ENST00000233336	TTL	chr2:113239732-113299316	-101.2	542-607	6733-6798	UTR3	-2553.9
46	ENST00000430027	DLX6-AS1	chr7:96584454-96643377	-51.6	536-610	3577-3651	ncRNA	-2551.9
47	ENST00000443374	RP11-50E11.3	chr10:52384712-52401211	-89.1	536-604	12058-12126	ncRNA	-2525.5
48	ENST00000608999	PPP1R12B	chr1:202317828-202561834	-79.0	544-591	5326-5373	UTR3	-2512.5
49	ENST00000356387	ORAI2	chr7:102073997-102097268	-93.7	543-602	5037-5096	UTR3	-2480.3
50	ENST00000610020	RPAP2	chr1:92764523-92867613	-47.2	573-625	12192-12244	UTR3	-2467.3



Supplementary Figure 3. KCNQ1 and YAP1 expression. A. Levels of KCNQ1 and YAP1 in 6 pairs of gastric cancer tissue and corresponding paracancer tissue were detected using RT-qPCR. The RT-qPCR results are shown as the mean ± SEM. B. Relative expression of KCNQ1, YAP1, and lincRNA-01317 in gastric cancer tissue and corresponding paracancer tissue.