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ORIGINAL RESEARCH

LncRNA PTCSC3 and lncRNA HULC Negatively Affect Each Other to Regulate Cancer Cell Invasion and Migration in Gastric Cancer

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Background: LncRNA PTCSC3 (PTCSC3) inhibits thyroid cancer, cervical carcinoma and glioma, while its roles in gastric cancer are unknown. Studies have reported that HULC could serve as a potential biomarker for the diagnosis and prognosis of gastric cancer (GC). Our study aimed to investigate the potential interaction between PTCSC3 and HULC in gastric cancer.

Methods: This study enrolled 77 gastric cancer patients at the First Affiliated Hospital of Anhui Medical University from January 2016 to January 2018. RT-qPCR was performed to analyze gene expression levels. Cell transfections were carried out to evaluate gene interactions. Transwell assays and wound healing assays were used to analyze the effects of transfection on cell invasion and migration. Western blotting was also used to illustrate the possibility that lncRNA PTCSC3 and lncRNA HULC negatively affected each other through WNT signal path.

Results: We showed that PTCSC3 was downregulated in tumor tissues of gastric cancer patients in comparison to that in adjacent healthy tissues, and an inverse correlation between the expression levels of PTCSC3 and AJCC stage was observed. LncRNA HULC (HULC) was upregulated in tumor and inversely correlated with PTCSC3 in tumor tissues. Overexpression of PTCSC3 mediated the inhibition of HULC, while overexpression of HULC also mediated the inhibition of PTCSC3. PTCSC3 inhibited, while HULC promoted invasion and migration of gastric cancer cells. In addition, overexpression of HULC attenuated the effects of overexpression of PTCSC3. However, overexpression of PTCSC3 showed no significant effects on cell proliferation. We also found that PTCSC3/HULC affected each other to regulate cell invasion and migration through the Wnt/β-catenin signaling.

Conclusion: Therefore, overexpression of PTCSC3 inhibited the invasion and migration of gastric cancer cells, and the function of PTCSC3 is associated with HULC.

Keywords: gastric cancer, lncRNA PTCSC3, lncRNA HULC, migration, invasion

Introduction

Only a small portion of human genome encodes protein products. Most human genes produce functional RNA transcripts (non-coding RNAs) rather than encoding proteins.[1] Genome-wide screens have identified large number of genes that transcribe ncRNAs.[2] Long ncRNAs (lncRNAs) are a subgroup of ncRNAs >200 nucleotides.[3] It has been demonstrated that lncRNAs are critical players in cell development and differentiation.[4] Studies on the functionality of lncRNAs in

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human genes suggest that regulation of the expression of certain lncRNAs can be applied in the treatment of diseases.[5,6] However, clinical applications of lncRNAs are still limited because of the unknown functions.

Gastric cancer is a common malignancy worldwide.[7] Treatment outcomes of gastric cancer have been improved with the development of surgical resection of primary tumors.[8] However, survival of metastatic gastric cancer patients is still poor due to the lack of radical treatment.[9]

LncRNA PTCSC3 (PTCSC3) inhibits thyroid cancer and glioma. In thyroid cancer, PTCSC3 interacts with Wnt/beta-catenin signaling pathway to regulate cancer cell proliferation and invasion.[10] In glioma, PTCSC3 affects chemosensitivity of cancer cells by interacting with the STAT3/INO80 pathway.[11] PTCSC3 has been reported to be involved in thyroid cancer, cervical carcinoma and glioma, while its roles in gastric cancer are unknown.[10–13]

Highly upregulated in liver cancer (HULC) is a lncRNA that has been demonstrated as an oncogene involved in many human cancers.[14–16] It has been reported that HULC has a high expression level in gastric cancer[17–19] and can promote the proliferation, migration and invasion of gastric cancer cells,[20,21] suggesting that HULC plays an important role in pathogenesis of gastric cancer.

Based on our knowledge, there has been no previous report about the interaction between the two LncRNAs. In this study, we found that the expression of PTCSC3 was altered in gastric cancer, and [illegible]pression was negatively correlated with the e[illegible]pression o[illegible]HULC in tumor tissues by deep sequenc[illegible] analysis. Based on these findings, we wo[illegible]er whet[illegible] the interaction between PTCSC3 and HULC i[illegible]volves [illegible]he pathogenesis of gastric c[illegible]cer, an[illegible] we fir[illegible]ly investigate it accordingly.

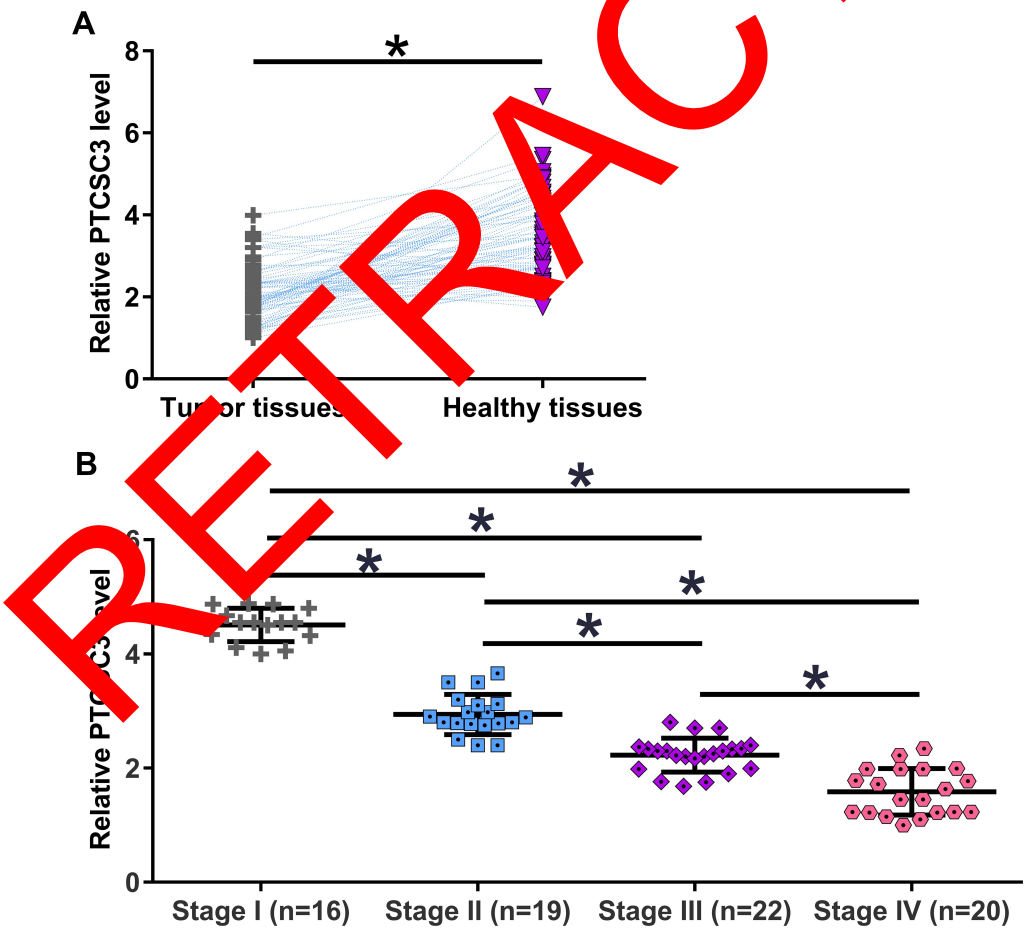

Figure 1 PTCSC3 was downregulated with the increased clinical stages. RT-qPCR results showed that expression levels of papillary thyroid carcinoma susceptibility candidate 3 (PTCSC3) were significantly downregulated in tumor tissues than that in tumor-adjacent tissues (**A**). In addition, expression levels of PTCSC3 were decreased with the increase of clinical stages (**B**). qPCRs were repeated in three technical replicates and average values were presented (*$p < 0.05$).

Materials and Methods

Research Subjects

Our study included 77 gastric cancer patients in The First Affiliated Hospital of Anhui Medical University from January 2016 to January 2018. Inclusion criteria: 1) gastric patients diagnosed by histopathological exam, which was performed by 3 experienced pathologists; 2) patients willing to participate in the study and signed written informed consent. Patients' exclusion criteria: 1) patients with mental disorders; 2) patients who had been treated before admission; 3) patients who were complicated with other diseases. The 77 patients included 49 males and 28 females, and the mean age was 43.4 ± 7.1 years old. According to AJCC (8th edition) staging, there were 16, 19, 22 and 20 cases at stage I, II, III and IV, respectively. This study was approved by the First Affiliated Hospital of Anhui Medical University Ethics Committee.

Human Specimens and Cell Lines

Stomach biopsy was performed. Tumor and adjacent normal tissues were also collected from each patient through biopsy. Human gastric cancer cell lines SNU-1 and AGS were used to perform all in vitro cell experiments. AGS and SNU-1 cells were purchased from ATCC (Manassas, VA, USA). Cells were cultivated with RPMI-1640 Medium containing 10% fetal bovine serum (FBS), and cell culture conditions were 37°C and 5% CO_2.

RT-qPCR

Trizol reagent (Invitrogen, USA) was used for the extraction of total RNAs from tissues and cultivated cells. Synthesis of cDNA was achieved through reverse transcription. Applied Biosystems™ PowerUp™ SYBR™ Green Master Mix was used for the preparation of PCR reaction systems to detect the expression of PTCSC3 and HULC. LightCycler® 96 System (Roche Life Science) was used to carry out PCR. GAPDH was used as endogenous control. The expression levels of PTCSC3 and HULC were normalized to GAPDH using the $2^{-\Delta\Delta CT}$ method.

Cell Transfections

PTCSC3 and HULC expression vectors were provided by GeneCopoeia (Guangzhou, China). SNU-1 and AGS cells were cultivated in RPMI-1640 Medium (10% FBS) at 37°C in a 5% CO_2 incubator for overnight to reach 65–80% confluence before transfection. Lipofectamine 2000 reagent (Invitrogen, USA) was used for transient transfection with 10 nM vectors. Cells with no transfection were used as the control cells. Transfection of empty vector was used as negative control. Cells were harvested at 24 h after transfection for subsequent experiments.

CCK-8 Assay

SNU-1 and AGS cell lines were, respectively, collected at 24 h after transfection to prepare single cell suspensions (3×10^4 cells/mL), and then added into a 96-well plate 1 (100 μL per

Table 1 Association with PTCSC3 and the Clinical Pathological Characteristics of GC Patients

	Group	Cases	High	Low	χ^2	*P* value
Gender	Male	49	24	25	0.27	0.60
	Female	28	12	16		
Age (years)	>45	46	21	24	0.02	0.88
	<45	31	15	16		
Smoking habit	Yes	40	18	22	0.31	0.58
	No	37	19	18		
Lauren classification	Intestinal	43	23	20	0.56	0.45
	Diffuse type	44	20	24		
GC stage					9.71	0.02
	I	16	9	7		
	II	19	9	10		
	III	22	9	13		
	IV	20	7	14		

Note: For analysis of the association between PTCSC3 levels and clinical features, Pearson's χ^2 tests were used.

well) incubated in 37C with 5% CO_2. CCK-8 solution (10 μL; Sigma-Aldrich) was added at 4 h before the end of cell culture. Finally, optical density (OD) values at 450 nm were measured. Each experiment was repeated three times.

Transwell Assay

The effects of PTCSC3 and HULC expression vector transfections on cell migration and invasion were explored. Briefly, cells were mixed with serum-free ATCC-formulated RPMI-1640 Medium to prepare single cell suspensions and cell density was adjusted to 3×10^4 cells/mL. Cells were added into the upper chamber with 100 μL per well. Upper chamber was coated with Matrigel (356234, Millipore, USA) prior invasion assay. Lower chamber was added with RPMI-1640 Medium (20% FBS). Cells were cultivated for 13 h, followed by staining of upper chamber membranes with 0.5% crystal violet at room temperature (Sigma-Aldrich, USA) for 15 min. Every test was performed for three times.

Wound Healing Assay

Cells were incubated in a six-well plate for 12 h, the cell layer was scratched with a sterile pipette tip and cultured in RPMI-1640 medium supplemented with 10% FBS for up to 24 h. The images of the cells were pictured under a microscope (Nikon, Japan). Every test was performed for three times.

Western Blotting

Cells were collected using an [illegible]lysis reagent (Beyotime) following the manufacture's instructions to extract total proteins. BAC kit (Beyotime) was used to quantify the protein.

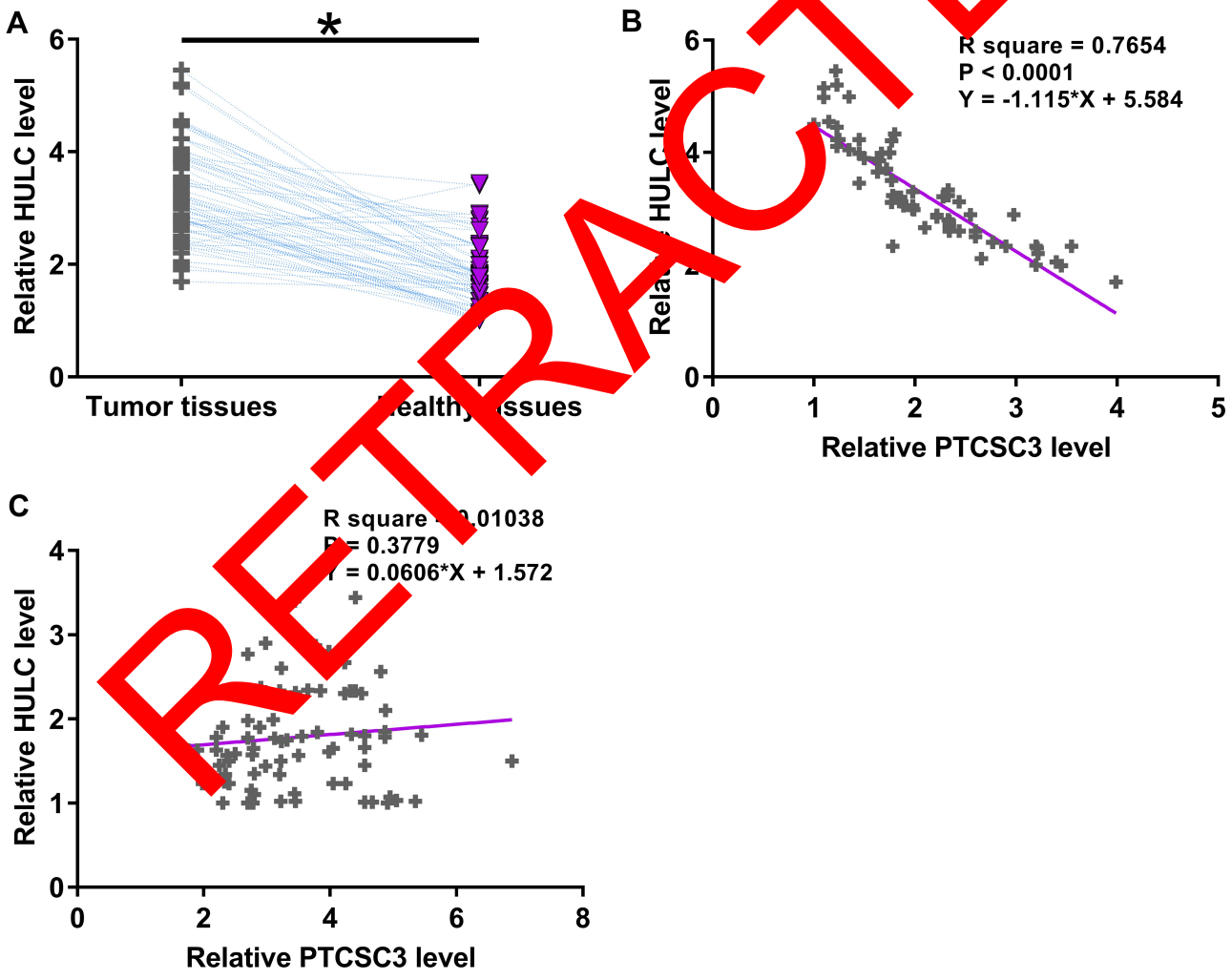

Figure 2 HULC was upregulated in tumor tissues and inversely correlated with PTCSC3. Data of RT-qPCR showed that expression levels of highly upregulated in liver cancer (HULC) were significantly upregulated in tumor tissues (**A**). qPCRs were repeated in three technical replicates and average values were presented (*$p < 0.05$). Pearson's correlation coefficient showed that expression levels of PTCSC3 and HULC were significantly and inversely correlated in tumor tissues (**B**), but not in tumor-adjacent tissues (**C**).

Protein samples were separated by 10% SDS-PAGE, and equal amount of protein was transferred onto PVDF membranes. Membranes were then incubated with primary antibody (anti-β-catenin 1:500, abcam) at 4°C for 24 h. Then, the membranes were further incubated with secondary antibodies (1:1000) at room temperature for another 2 h. The bands were visualized by an ECL. GAPDH was used as internal control.

Statistical Analysis

Three biological replicates were included in each experiment. Comparisons among different cell treatment groups were performed using one-way ANOVA and Tukey's test. Gene expression levels in paired tumor and adjacent normal tissues were compared by paired *t* test. Correlations between PTCSC3 and HULC were analyzed by Pearson's correlation coefficient. The 77 patients were divided into high (n = 34) and low (n = 33) PTCSC3 level groups with the median expression level of PTCSC3 in tumor tissues as a cutoff value. Associations between patients' clinical data and the expression levels of PTCSC3 were analyzed by Chi-squared test. Differences with $p < 0.05$ were statistically significant.

Results

PTCSC3 Was Downregulated with the Increased Clinical Stages

RT-qPCR results showed that the expression levels of PTCSC3 were significantly lower in tumor tissues in comparison to that in tumor-adjacent healthy tissues in the 77 gastric cancer patients (Figure 1A, $p < 0.05$). In addition, the expression levels of PTCSC3 were decreased with the increase of clinical stages (Figure 1B, $p < 0.05$). Chi-squared test (Table 1) showed that the expression levels of PTCSC3 in tumor tissues were closely associated with patients' clinical stage (stage I–IV, $p < 0.0001$), but not age (> or ≤45 years old, $p > 0.05$), gender (male or female, $p > 0.05$), tumor differentiation (high or low, $p > 0.05$), Lauren classification (intestinal or diffuse type, $p > 0.05$) and smoking habit (yes or no, $p > 0.05$).

HULC Was Upregulated and Inversely Correlated with PTCSC3 in Tumor

HULC was significantly upregulated in tumor tissues compared with that in tumor-adjacent healthy tissues in the 77 gastric cancer patients (Figure 2A, $p < 0.05$). Results of Pearson's correlation coefficient indicated that

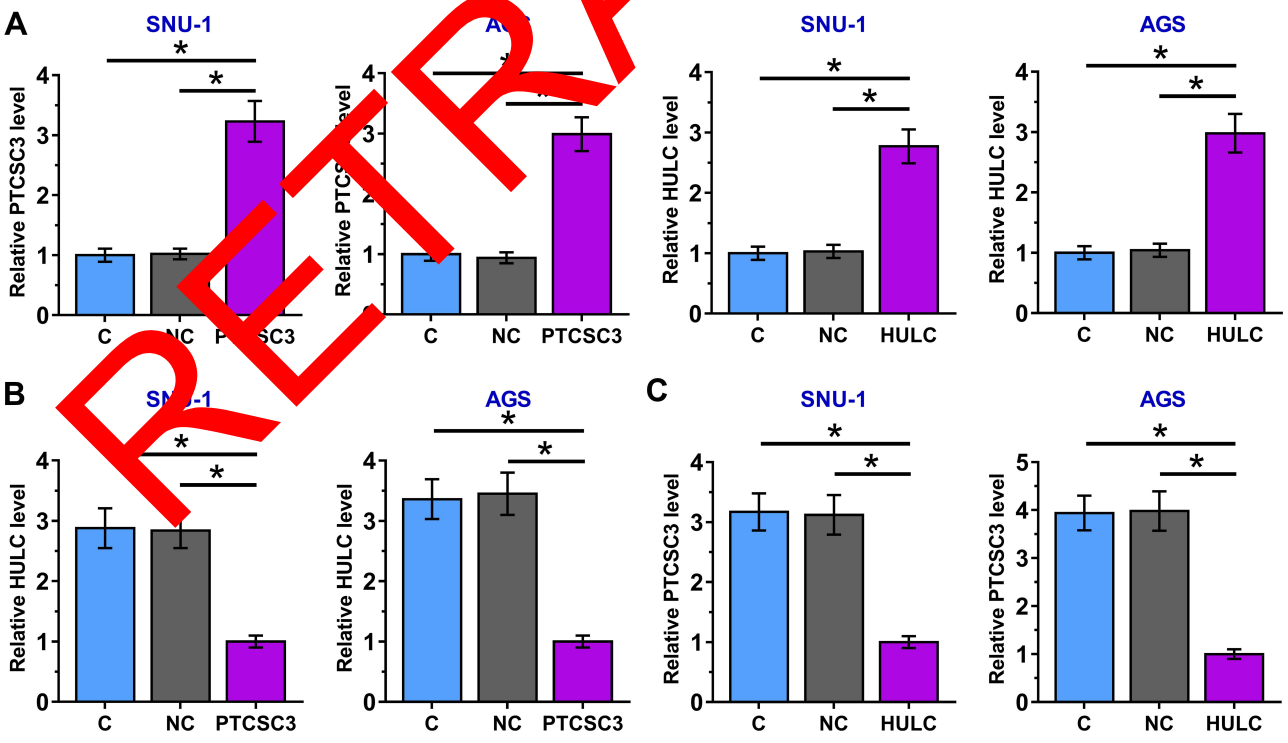

Figure 3 PTCSC3 and HULC negatively affected each other in gastric cancer cells. Overexpression of PTCSC3 and HULC in cells of SNU-1 and AGS cell lines were achieved at 24 h after transfection (**A**). In addition, overexpression of PTCSC3 resulted in inhibited the expression of HULC (**B**), and overexpression of HULC also mediated the inhibition of PTCSC3 (**C**). Experiments were performed in three independent replicates and mean ± SD values were presented (*$p < 0.05$).

PTCSC3 and HULC were inversely and significantly correlated in tumor tissues (Figure 2B), but not in tumor-adjacent tissues (Figure 2C).

PTCSC3 and HULC Negatively Affected Each Other

The inverse correlation between PTCSC3 and HULC in tumor tissues of patients indicated the potential interactions between these two lncRNAs in gastric cancer. Overexpression of PTCSC3 and HULC in SNU-1 and AGS cells were achieved (Figure 3A, $p < 0.05$). Compared with negative control (NC) and control (C) groups, overexpression of PTCSC3 resulted in inhibited expression of HULC (Figure 3B, $p < 0.05$). Overexpression of HULC also mediated the inhibition of PTCSC3 (Figure 3C, $p < 0.05$).

Overexpression of PTCSC3 Inhibited Gastric Cancer Cell Migration and Invasion, but Not Proliferation Through HULC

Compared with C and NC groups, overexpression of PTCSC3 resulted in reduced migration and invasion of gastric cancer cell, while overexpression of HULC mediated inversely (Figure 4) ($p < 0.05$). Moreover, overexpression of HULC reduced the effects of overexpression of PTCSC3 ($p < 0.05$). However, overexpression of PTCSC3 did not affect cell proliferation (Figure S1).

PTCSC3/HULC Affected Each Other to Regulate Cell Invasion and Migration by Wnt/β-Catenin Signaling

To evaluate the relationship between PTCSC3 and HULC, Western blotting assay was used to predict that HULC with PTCSC3 could regulate cell invasion and migration through Wnt/β-catenin pathway (Figure 5). It showed that overexpression of PTCSC3 inhibited the expression of β-catenin while HULC reversed the effect. And silencing of HULC increased the expression levels of β-catenin. These results suggested that PTCSC3/HULC via Wnt/β-catenin pathway to mediate cell migration and invasion.

Discussion

The application of regulating the expression of lncRNAs in the treatment of gastric cancer is challenged by their obscure functions. Our study reported that PTCSC3 was downregulated in gastric cancer, and overexpression of PTCSC3 may inhibit gastric cancer. The actions of PTCSC3 in gastric cancer are likely mediated by its negative interactions with HULC through Wnt/β-catenin pathway.

HULC is a well-characterized oncogenic lncRNA in cancers.[22] Inhibition of HULC can serve as a therapeutic target for cancer by regulating cancer cell behaviors and increasing chemosensitivity.[23,24] In the development of gastric cancer, HULC was upregulated and resulted in promoted cancer cell migration, proliferation and invasion.[25] In our study, significantly upregulated expression of HULC in tumor tissues of gastric cancer patients was observed. In addition, our in vitro cell migration and invasion assay data also suggested that HULC positively regulated the invasion and migration of gastric cancer cells. Our study further confirmed the oncogenic role of HULC in gastric cancer.

LncRNAs participate in cancer biology by regulating downstream oncogenic or tumor suppression pathways.[26] LncRNAs can also interact with other ncRNAs, such as miRNAs to exert their functions in cancer development.[27] However, reports on the interactions between lncRNAs are limited. To the best of our knowledge, there was no research studying the interaction between PTCSC3 and HULC in gastric cancer. This study explored the interactions between two lncRNAs, which is novel. In the present study, we showed that PTCSC3 was likely a tumor suppressor in gastric cancer, and its roles in gastric cancer are likely to mediate cancer cell migration and invasion. Moreover, the regulatory roles of PTCSC3 are possibly achieved through the negative feedback regulation with HULC. This finding enriched our understandings on gastric cancer. Briefly, HULC promotes cell proliferation of different kinds of tumor cells.[25,28,29] For instance, overexpression of HULC promotes cell proliferation in lung cancer by upregulating sphingosine kinase 1.[19] In contrast, knockdown of HULC resulted in the decreased proliferation of both osteosarcoma and hepatocellular carcinoma cancer cells.[20,21] Similarly, we also found that HULC promotes gastric cancer cell proliferation (data shown in supplementary Figure S1). Interestingly, in this study, overexpression of PTCSC3 did not affect gastric cancer proliferation (data shown in supplementary Figure S1). Therefore, PTCSC3 may interact with multiple factors to achieve regulation on gastric cancer cell behaviors. This hypothesis was also further supported by our finding that HULC overexpression only partially reversed the effects of PTCSC3 overexpression on cancer cell

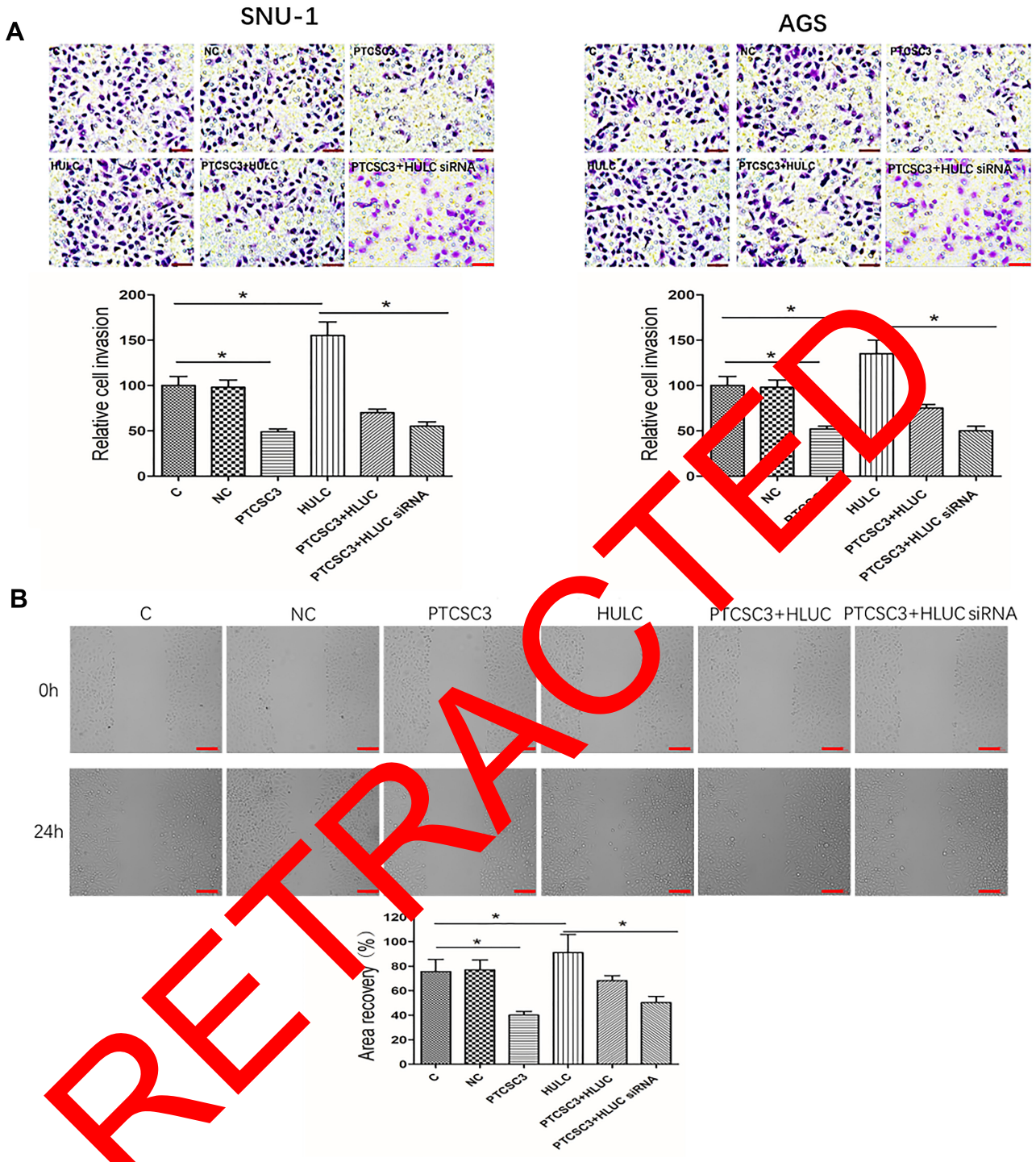

Figure 4 Overexpression of PTCSC3 inhibited gastric cancer cell migration and invasion, but not proliferation through HULC. Overexpression of PTCSC3 resulted in inhibited, while overexpression of HULC led to promoted invasion (**A**) and migration (**B**) of cells of gastric cancer cell lines. In addition, overexpression of HULC attenuated the effects of overexpression of PTCSC3. Experiments were performed in three independent replicates and mean ± SD values were presented. Error bar = 100 μm (*$p < 0.05$).

migration and invasion. Studies have reported that PTCSC3 and HULU do not affect lung tumor tissue.[20,30] In our study, we further demonstrated that PTCSC3 and HULC were significantly and inversely correlated only in tumor tissues but not in tumor-adjacent tissues. We also demonstrated that PTCSC3/HULC affected each other by Wnt/β-catenin to effect tumor cell behaviors. Therefore, the interaction between PTCSC3 and HULC is likely

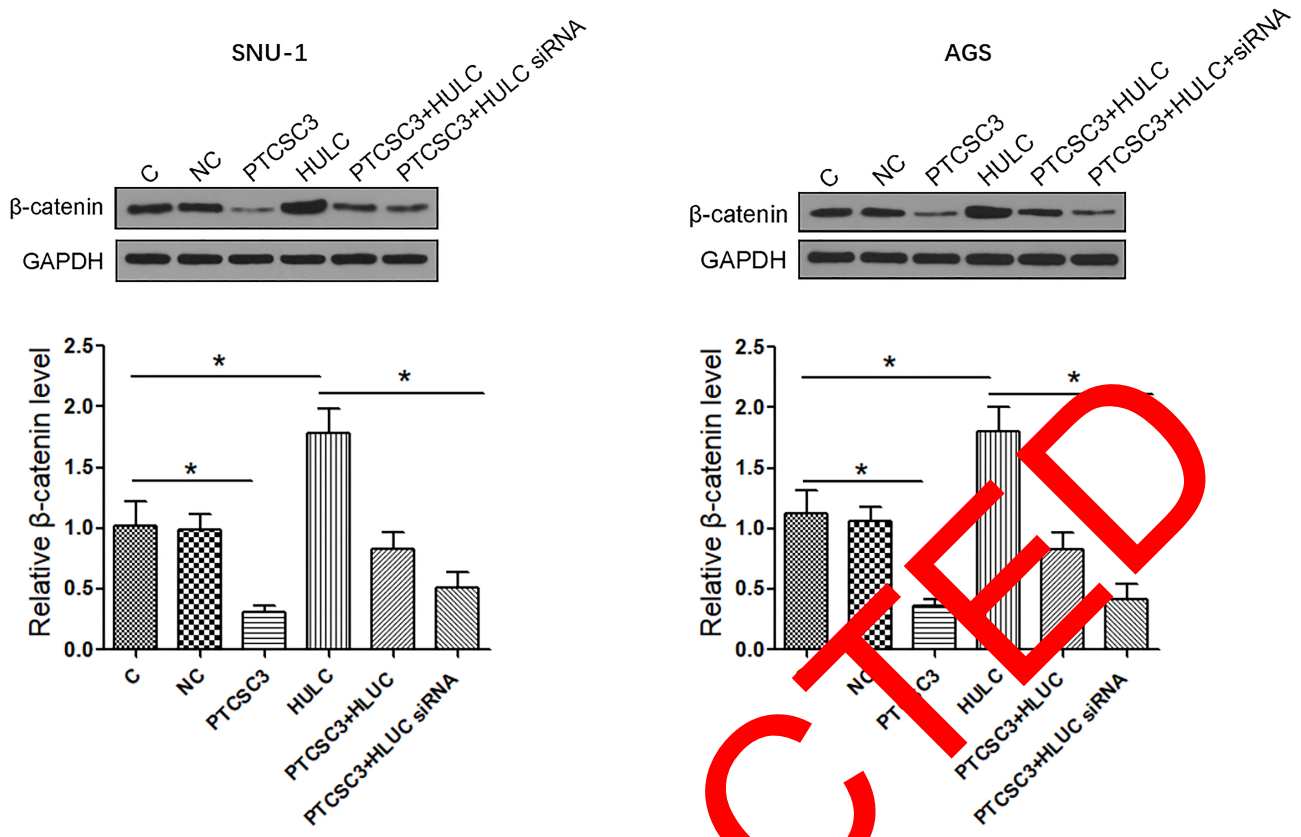

Figure 5 PTCSC3/HULC affected each other to regulate cell invasion and migr... Wnt/β-cate... bit gastric cancer cell migration and invasion HULC. PTCSC3 overexpression resulted in decreased, while HULC overexpression led to promo... β-ca... xpression of cells of gastric cancer cell lines. Experiments were performed in three independent replicates and mean ± SD values were presented. Error bar = ...0 μm.

mediated by certain pathological factors. F... ure stud... s are still needed to identify these factors.

Conclusions

In conclusion, PTCSC3 inh...bits gastric ...ancer invasion and migration. The fun...ion of PTCSC3 ... associated with HULC and ...ulated ...Wnt/β-catenin pathway. Overexpression of PTCS...may be ... therapeutic target of gastric canc... by ...gative... int...acting with HULC.

Disclosu...e

The authors dec...e that they have no competing interests for this work.

References

1. Eddy SR. Non-coding RNA genes and the modern RNA world. *Nat Rev Genet*. 2001;2(12):919–929. doi:10.1038/35103511
2. Mattick JS. Non-coding RNAs: the architects of eukaryotic complexity. *EMBO Rep*. 2001;2(11):986–991. doi:10.1093/embo-reports/kve230
3. Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. *Nat Rev Genet*. 2009;10(3):155–159. doi:10.1038/nrg2521
4. Fatica A, Bozzoni I. Long non-coding RNAs: new players in cell differentiation and development. *Nat Rev Genet*. 2014;15(1):7–21. doi:10.1038/nrg3606
5. Shi X, Sun M, Liu H, Yao Y, Song Y. Long non-coding RNAs: a new frontier in the study of human diseases. *Cancer Lett*. 2013;339(2):159–166. doi:10.1016/j.canlet.2013.06.013
6. Gutschner T, Diederichs S. The hallmarks of cancer: a long non-coding RNA point of view. *RNA Biol*. 2012;9(6):703–719. doi:10.4161/rna.20481
7. Rugge M, Fassan M, Graham DY. Epidemiology of gastric cancer. *Gastric Cancer Cham*. 2015;23–34.
8. Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer*. 2017;20(1):1–19. doi:10.1007/s10120-016-0622-4
9. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. *Lancet*. 2016;388(10060):2654–2664.
10. Wang X, Lu X, Geng Z, Yang G, LncRNA SY. PTCSC3/miR-574-5p Governs Cell Proliferation and Migration of Papillary Thyroid Carcinoma via Wnt/beta-Catenin Signaling. *J Cell Biochem*. 2017;118(12):4745–4752. doi:10.1002/jcb.26142
11. Wang XM, Liu Y, Fan YX, et al. LncRNA PTCSC3 affects drug resistance of anaplastic thyroid cancer through STAT3/INO80 pathway. *Cancer Biol Ther*. 2018;19(7):590–597. doi:10.1080/15384047.2018.1449610
12. Xia S, Ji R, Zhan W. Long noncoding RNA papillary thyroid carcinoma susceptibility candidate 3 (PTCSC3) inhibits proliferation and invasion of glioma cells by suppressing the Wnt/beta-catenin signaling pathway. *BMC Neurol*. 2017;17(1):30. doi:10.1186/s12883-017-0813-6

13. Zhang M, Song Y, LncRNA YL. PTCSC3 suppressed cervical carcinoma cell invasion and proliferation via regulating miR-574-5p. *J Am J Translat Res*. 2019;11(11):7186–7194.
14. Wang C, Jiang X, Li X, et al. Long noncoding RNA HULC accelerates the growth of human liver cancer stem cells by upregulating CyclinD1 through miR675-PKM2 pathway via autophagy. *Stem Cell Res Ther*. 2020;11(1):8. doi:10.1186/s13287-019-1528-y
15. Mercatelli N, Fortini D, Palombo R, Paronetto MP. Small molecule inhibition of Ewing sarcoma cell growth via targeting the long non coding RNA HULC. *Cancer Lett*. 2020;469:111–123. doi:10.1016/j.canlet.2019.10.026
16. Hu Y, Ye S, Li Q. Quantitative Proteomics Analysis Indicates That Upregulation of lncRNA HULC Promotes Pathogenesis of Glioblastoma Cells. *OncoTargets therapy*. 2020;13:5927–5938
17. Esfandi F, Salehnezhad T, Taheri M, et al. Expression assessment of a panel of long non-coding RNAs in gastric malignancy. *Exp Mol Pathol*. 2020;113:104383. doi:10.1016/j.yexmp.2020.104383
18. Qi M, Yu B, Yu H, Li F. Integrated analysis of a ceRNA network reveals potential prognostic lncRNAs in gastric cancer. *Cancer Med*. 2020;9(5):1798–1817. doi:10.1002/cam4.2760
19. Zhang Y, Song X, Wang X, Hu J, Jiang L. Silencing of LncRNA HULC Enhances Chemotherapy Induced Apoptosis in Human Gastric Cancer. *J Med Biochem*. 2016;35(2):137–143.
20. Liu T, Liu Y, Wei C, Yang Z, Chang W, Zhang X. LncRNA HULC promotes the progression of gastric cancer by regulating miR-9-5p/MYH9 axis. *Biomed Pharmacother*. 2020;121:109607. doi:10.1016/j.biopha.2019.109607
21. Xian H, Zhuo Z, Sun Y, Liang B, Zhao X. Circulating long non-coding RNAs HULC and ZNFX1-AS1 are potential biomarkers in patients with gastric cancer. *Oncol Lett*. 2018;16(4):4689–4698. doi:10.3892/ol.2018.9199
22. Li SP, Xu HX, Yu Y, et al. LncRNA HULC enhances epithelial-mesenchymal transition to promote tumorigenesis and meta[illegible] of hepatocellular carcinoma via the miR-200a-3p/ZEB1 signalin[illegible] pathway. *Oncotarget*. 2016;7(27):42431–42446. doi:10.18632/oncotarget.9883
23. Kong D, Wang Y. Knockdown of lncRNA HULC inhibits proliferation, migration, invasion, and promotes apoptosis by sponging miR-122 in osteosarcoma. *J Cell Biochem*. 2018;119(1):1050–1061. doi:10.1002/jcb.26273
24. Zhang Y, Song X, Wang X, Hu J, Jiang L. Silencing of LncRNA HULC Enhances Chemotherapy Induced Apoptosis in Human Gastric Cancer. *J Med Biochem*. 2016;35(2):137–143. doi:10.1515/jomb-2015-0016
25. Zhao Y, Guo Q, Chen J, Hu J, Wang S, Sun Y. Role of long non-coding RNA HULC in cell proliferation, apoptosis and tumor metastasis of gastric cancer: a clinical and in vitro investigation. *Oncol Rep*. 2014;31(1):358–364. doi:10.3892/or.2013.2850
26. Huarte M. The emerging role of lncRNAs in cancer. *Nat Med*. 2015;21(11):1253–1261. doi:10.1038/nm.3981
27. Zhou X, Ye F, Yin C, Zhuang Y, Yu[illegible]ng G. The Interaction Between MiR-141 and lncRNA-H[illegible]in Regula[illegible] Cell Proliferation and Migration in Gastric Can[illegible] *Cell Physiol[illegible]iochem*. 2015;36(4):1440–1452. doi:10.1159/000430109
28. Xin L, Zhou Q, Yuan [illegible] et al. M[illegible]Tase/lncR[illegible]A HULC/FoxM1 reduced cisplatin resi[illegible]nce in gastric c[illegible]er [illegible] suppressing autophagy. *J Cancer Res Cli[illegible] Oncol*. [illegible]9;145(10):2507–2517. doi:10.1007/s00432-[illegible]03[illegible]5-w
29. Takahashi K[illegible]oyama K[illegible]ta Y, et al[illegible]he Interaction Between Long Non-codi[illegible]RNA HULC [illegible]nd [illegible]icroRNA-622 via Transfer by Extrac[illegible]ular [illegible]sicles Regula[illegible] Cell Invasion and Migration in Human Pancre[illegible] Cancer. *J Fron oncol*. 2020;10:1013. [illegible]3389/fonc.202[illegible]01013
[illegible]. Xu J, Zhang Y, You Q, et al. LncRNA PTCSC3 Alleviates the Postoperati[illegible] Distant Recurrence of Gastric Cancer by Suppression of lncRNA [illegible]OXA11-AS. *Cancer Manag Res*. 2020;12:2623–2629. doi:10.2147[illegible]MAR.S229269