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LINC01296 promotes the proliferation and invasion by regulating microRNA-760 expression and predicts poor prognosis of hepatocellular carcinoma

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Abstract. – OBJECTIVE: The aim of this study was to investigate the role of LINC01296 in the progression of liver cancer (LCa) and to explore its possible molecular mechanisms.

PATIENTS AND METHODS: TCGA database was used for information mining to verify the expression of LINC01296 in liver tumor tissues and normal tissues. The levels of LINC01296 in 4 pairs of LCa and adjacent tissues, as well as normal liver cell lines and liver cancer cell lines, were detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). The Chi-square test was performed to analyze the clinical characteristics of tumor samples and LINC01296 expression. Meanwhile, the Chi-square test was used to explore the relationship between different clinical features and the expression of LINC01296. Liver cancer cell lines were screened and transfected with siRNA-LINC01296 and microRNA-760 inhibitor, as well as corresponding negative controls, respectively. Cell counting kit-8 (CCK-8) and Transwell assays were used to determine the effects of LINC01296 on the proliferative and invasive capacities of cells. Furthermore, the regulatory association between LINC01296 and microRNA-760 was verified by the Dual-luciferase reporter assay.

RESULTS: LINC01296 expression was remarkably higher in LCa tissues than that of normal liver tissues. Meanwhile, LINC01296 expression was associated with poor prognosis of LCa. Patients with high LINC01296 expression were more likely to have lymph node metastasis. In vitro experiments showed that the knockdown of LINC01296 significantly inhibited the proliferation and migration of HCC cells. Meanwhile, microRNA-760 was remarkably lowly expressed in cancer tissues and cells. Subsequent experiments indicated that LINC01296 was regulated by miR760 in LCa tissues, and high expression of linc0129 could limit microRNA-760 expression. Furthermore, the inhibition of microRNA-760 in HCC cells reversed the effect of LINC01296 knockdown on cell proliferation and invasion.

CONCLUSIONS: LINC01296 could promote the proliferation and invasiveness of hepatoma cells by inhibiting the expression of microRNA-760. Moreover, its expression was closely related to lymph node metastasis and poor prognosis of LCa.

Key Words
LINC01296, MicroRNA-760, Liver cancer, Clinical prognosis.

Introduction

As a highly malignant primary tumor, liver cancer (LCa) is the second most common malignant tumor. The incidence of LCa ranks sixth among all malignant tumors[1,2]. In Asia and Africa, LCa is one of the leading causes of death due to high hepatitis virus infection rate[3,4]. Currently, effective treatments have been achieved for LCa patients, including surgery, radiotherapy, liver transplantation, and other technologies. However, the 5-year survival rate of LCa patients remains low[5]. In addition, there are still a large number of patients who have not benefited from current cancer treatment, including surgery and chemotherapy[6]. Kudo et al[7] has found that a number of encoded proteins are closely related to LCa, such as AFP. However, the mechanism of oncogene aberration and the LCa progression have not been fully explained. Therefore, exploring the underlying mechanisms of deterioration and poor prognosis of hepatocellular carcinoma (HCC) can provide new targets for diagnosis and treatment.

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With the application of large-scale high-throughput sequencing technology in recent years, long-chain non-coding RNA (lncRNA) has become a hot spot in cancer research. LncRNA is a kind of RNA with more than 200 bp in length, with no protein-coding function[8]. It has been found to be involved in the biological processes of various tumors, including proliferation, migration, invasion, and autophagy[9]. Hajjari et al[10] have demonstrated that lncRNA plays a pivotal role in a variety of tumors. For example, HOTAIR gene SNP mutation[11] leads to increased tumor susceptibility, which has been used as a marker of poor prognosis in pancreatic cancer. LINC01296 is a newly discovered long-chain non-coding RNA. It has been found to promote the proliferation and metastasis of tumor cells in colorectal cancer, lung cancer, and bladder cancer. Meanwhile, LINC01296 is closely related to the clinical prognosis of tumors[12-15]. As a newly discovered oncogene, the role of LINC01296 in LCa has not been fully elucidated.

In this research, we investigated the role and mechanism of LINC01296 in HCC. Through database mining and clinical sample corre[illegible]n analysis, we found that LINC01296 was[illegible] expressed in LCa patients and was correlate[illegible]th poor clinical prognosis of LCa patients. Fur[illegible] more, cell experiments indicated that LINC01[illegible] promoted the proliferative abili[illegible]d invasiv[illegible] ness of LCa cells. The inhibiti[illegible]pression of LINC01296 remarkably [illegible]ressed[illegible] prolif-eration and migration ab[illegible]s of LC[illegible]. Fur-thermore, we detected tha[illegible]oR[illegible] be used as a downstr[illegible]gene[illegible]C01296 and played a pivotal ro[illegible]the progre[illegible]of LCa in-duced by LINC0[illegible]

[illegible]tients and [illegible]hods

GEP[illegible]Datab[illegible]

[illegible]A d[illegible]ase (http://GEPIA.cancer-pku.cn/ind[illegible] was [illegible] to assess the level of [illegible]NC012[illegible]d the[illegible]gnosis of patients. GEPIA data[illegible] used to mine and analyze the[illegible]e sequen[illegible]g data from TCGA and GTEx. As[illegible]blic database, GEPIA contains 9736 tu-m[illegible] and 857 normal tissue samples. [illegible]e database can be used to analyze differen-[illegible]y expressed genes in tumors, including gene c[illegible]ession analysis, gene OS and DFS sur-vival curve analysis, and gene and clinical stage correlation analysis. GEPIA's tumor information comes from the TCGA database and contains 33 tumor types, including tumor tissue and normal tissue data sets and corresponding clini[illegible]

Sample Collection

Primary LCa samples and [illegible]-cancerous samples were collected from pa[illegible] who underwent LCa resection fro[illegible] Decem[illegible]16 to October 2018 in Guangx[illegible]ternational Medical Hospital. A t[illegible] of 40[illegible]amples enrolled in the study[illegible] LCa[illegible]re diagnosed in accordance with t[illegible]id[illegible]s of th[illegible]mer-ican Association[illegible]the[illegible] of Liv[illegible]isease. The diagnosis[illegible]LCa was[illegible]ed[illegible] imaging techniques[illegible]FP screenin[illegible]nwhile, the collected[illegible]pl[illegible]e confirmed[illegible]s LCa by the pathologic[illegible] exam[illegible] notification, informed consen[illegible]s obtained[illegible] each subject. This st[illegible]approved by th[illegible]angxi International [illegible]ng Medical Hospital Ethics Committee.

[illegible] Culture

[illegible]man imm[illegible]l normal liver cell line (L02) and[illegible] lines (HepG2, Hep3B, Huh7, SMMC[illegible]) were purchased from the Chi-ese Academy of Science Cell Bank (Shanghai, [illegible]. All cells were cultured in high glucose [illegible]o's Modified Eagle's Medium (DMEM; Gibco, Rockville, MD, USA) containing 10% fe-tal bovine serum (FBS; Gibco, Rockville, MD, USA), and 100 U/mL penicillin and streptomy-cin. The cells were maintained at 37°C, in a 5% CO_2 cell culture incubator. All cells were cul-tured regularly, and the number of passages was less than 30.

Cell Transfection

HepG2 and Hep3B cells were used for cell transfection in this study. The cells were first evenly seeded into 6-well plates and transfected at a density of 70%. Cell transfection was carried out according to the manufacturer's instructions of Lipofectamine 2000 (Thermo Fisher Scientific, Inc., Waltham, MA, USA). The transfection ef-ficiency was verified by quantitative Real-Time Polymerase Chain Reaction (qRT-PCR) 48 h later.

Small Interfering RNA and Plasmid Construction

LINC01296 gene was amplified using KOD DNA polymerase and cloned into the pEX-3 vector. Wild type and mutant LINC01296 were constructed using the pmirGLO vector. Small interfering RNAs (si-RNAs) and corresponding

controls (si-NC) were purchased from GenePharma (Shanghai, China), while mimics and inhibitors of microRNA-760 and negative controls (NC) were purchased from Guangzhou Ruizhou (Guangzhou, China).

qRT-PCR

Total RNA in tissues and cells was extracted using TRIzol Reagent (Invitrogen, Carlsbad, CA, USA). Extracted mRNA was reverse transcribed using high-capacity transcription kit (Thermo-Fisher Scientific, Waltham, MA, USA). Subsequently, qRT-PCR was performed in strict accordance with Taq Green qRT-PCR kit (TaKaRa, Dalian, China). MiRNAs were reverse transcribed using TaqMan MicroRNA Reverse Transcription kit, and qRT-PCR was performed using TaqMan Universal qRT-PCR Master Mix (Applied Biosystems, Foster City, CA, USA). GAPDH and U6 were used as internal references for mRNA and miRNA, respectively. The relative expressions of the genes were determined using the $2^{-\Delta\Delta Ct}$ method[17]. The primer sequences used in this study were as follows: LINC01296, F: 5'-GGCAGGATTCGCGTCCTTACGC-3', R: 5'-GCTCGGATGGTCCGACCGA-3'; miR-760 RT: 5'-GTTGGCGCCAACTTCGTCGAC[illegible]3', F: 5'-AGTTCGCGGTGTGTGCGTCC-3'; U6 RT: 5'-GCTTCGGCAGCACATATACTAAAAT-3', F: 5'-CGCTTCAGAATTTGCGTGT[illegible]3'; GAPDH: F: 5'-CGCTCTCTGCTCC[illegible]TC-3', R: 5'-ATCCGTTGACTCCGAC[illegible]CAC

Dual Luciferase Reporter Assay

Hep3B cells were first seeded into 24-well plates. Then the cells were co-transfected with mimic-microRNA and mimics respectively, with pGL3 containing wild-type or mutant copies of LINC01296. 48 hours after transfection, luciferase activity was determined by the dual luciferase reporter system (E1910; Promega, Madison, WI, USA).

Cell Proliferation

Cell proliferation was measured according to instructions of CCK8 assay (Beyotime Institute of Biotechnology, Shanghai, China). Briefly, the cells were seeded into 96-well plates at a density of 1000 cell. After culture for 0, 24, 48 and 72 h, respectively, 10 uL of CCK-8 reagent was added to each well. Then, the cells were incubated for 2 h in a 37°C incubator. Absorbance at 450 nm was measured by a SpectraMax M5 microplate reader (Molecular Devices, Eugene, OR, USA).

Transwell Assay

The transwell assay was used to determine cell invasive ability. Serum-free medium suspended transfected cells (1×10^5) were inoculated into the upper chamber of matrix gel-coating inserts. Meanwhile, 600 uL of 10% FBS medium was added in the lower chamber as a chemoattractant. After that, the transwell chambers were incubated for 48 h. Lower layer penetrating cells were collected and fixed with 4% paraformaldehyde for 30 minutes, followed by staining with 0.5% crystal violet for 30 minutes at room temperature. After being washed with phosphate-buffered saline (PBS), the invading cells were observed under an x71 inverted microscope (Olympus, Tokyo, Japan). Finally, the number of invading cells was counted.

Statistical Analysis

GraphPad Prism 7.0 software (GraphPad Inc., San Diego, CA, USA) was used for all statistical analysis. All experiments were repeated for at least 3 times. The analysis of variance and *t*-test were used to evaluate the results of qRT-PCR, luciferase reporter gene assay, CCK8 assay, and Transwell assay. A Chi-square test was performed to evaluate the association between gene expressions with clinical samples. One-way ANOVA was applied to compare the differences among different groups, followed by the post-hoc test (Least Significant Difference). The correlation between LINC01296 and miR-760 was analyzed using the Pearson correlation. The overall survival was plotted using the Kaplan-Meier method and checked by the log-rank test. $p<0.05$ was considered statistically significant.

Results

LINC01296 is Remarkably Up-Regulated in LCa Samples and Cell Lines and Leads to Poor Prognosis

We first compared the level of LINC01296 in LCa through the GEPIA database. The results found that the expression of LINC01296 significantly increased in LCa tissues (Figure 1A). Furthermore, LINC01296 expression was remarkably higher in cancer tissues than of adjacent normal tissues (Figure 1B). At the cellular level, compared with human normal liver cell line LO2, the expression of LINC01296 remarkably increased in LCa cell lines (HepG2, Hep3B, Huh7, SMMC-7721) (Figure 1C). HepG2 and Hep3B cells were chosen for subse-

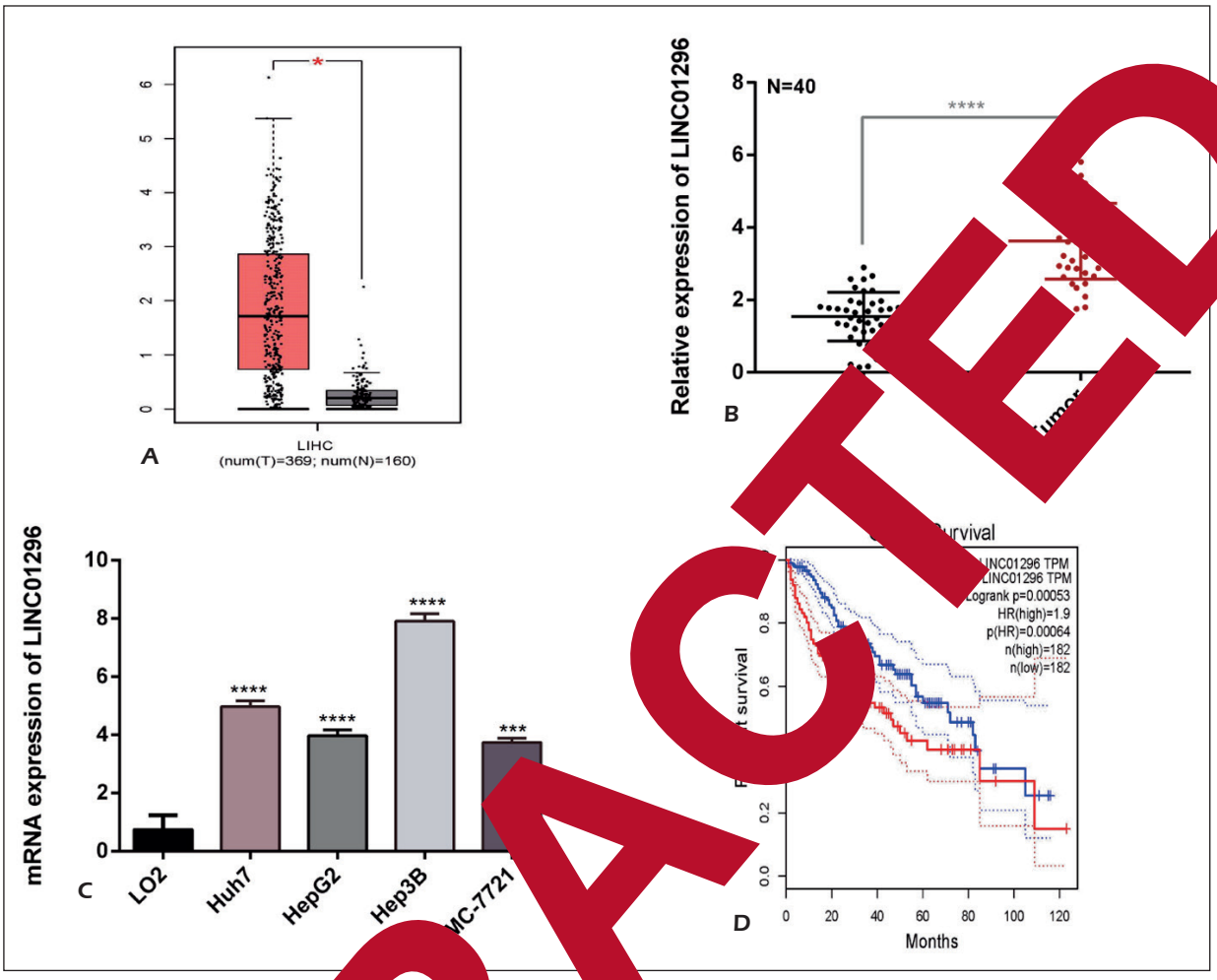

Figure 1. LINC01296 is highly ...essed in ... cancer tiss...s and cell lines and is associated with poor prognosis. **A**, The expression level of LINC0129... ...ver canc... ...higher than that in normal liver tissues by GEPIA database. **B**, The expression of LINC01296 i... liv... ...er ... ...es ... ...er than that in adjacent normal tissues by qRT-PCR. **C**, QRT-PCR showed that the expressio... ...LINC... ...iver cancer cell lines was higher than that of normal liver cell line. **D**, The overall survival (OS) of patien... ...higher e... ...n of LINC01296 was significantly worse than that of patients with lower expression. (*p<0.05, ***p... ****p<0.000...

quent experi...ts. Throu... GEPIA prognostic analysis, ...ound that the l... LINC01296 was correlat... ...ith the overall survi... of patients. The overa... ...rvival ... of patients with higher expressio... ...INC0... was si...ificantly worse than that of pati... ...lower ...ession (Figure 1D). This ...icated ... LINC... ...6 played a pivotal role in ...gressi...

LIN...1296 Is Associated with Lymph ...asis in Clinical HCC

We further analyzed the relationship between ...linical features of LCa patients and the level o...C01296. The results demonstrated that in pati...ts with lymph node metastasis, the highest expression rate of LINC01296 was 86.7%. However, in patients with LCa without lymph node metastasis, the highest expression rate of LINC01296 was only 28%. There was a significant difference between the two groups (p<0.05) (Table I). Among other clinical indicators, like age, sex, HBV infection, the AFP level and the tumor TNM stage of patients were not significantly correlated with the expression of LINC01296.

Down-Regulation of LINC01296 Inhibits Proliferation and Migration of Hep3B and HepG2 Cells

Small interfering RNA (si-RNA) was used to target the expression of LINC01296 in the knockdown cells. The transfection efficiency was verified by qRT-PCR (Figure 2A).

Table I. Correlation between the clinicopathologic characteristics and LINC01296 expression in hepatocellular carcinoma.

Characteristics			LINC01296		
		No.=40	Low expression (n=20)	High expression (n=20)	*p*-v
Age (y)	<55	12	8	4	
	≥55	28	12	16	
Sex	Male	31	14	17	0.705
	Female	9	6	3	
HBV	No	15	7	8	.4
	Yes	25	13	12	
Serum AFP level (ng/mL)	<20	11	4	7	0.077
	≥20	29	16	13	
Lymph node metastasis	No	25	18	7	
	Yes	15	2	13	
TNM Stage	I+II	21	12	9	0.752
	III+IV	19	8	11	

*Statistically significant

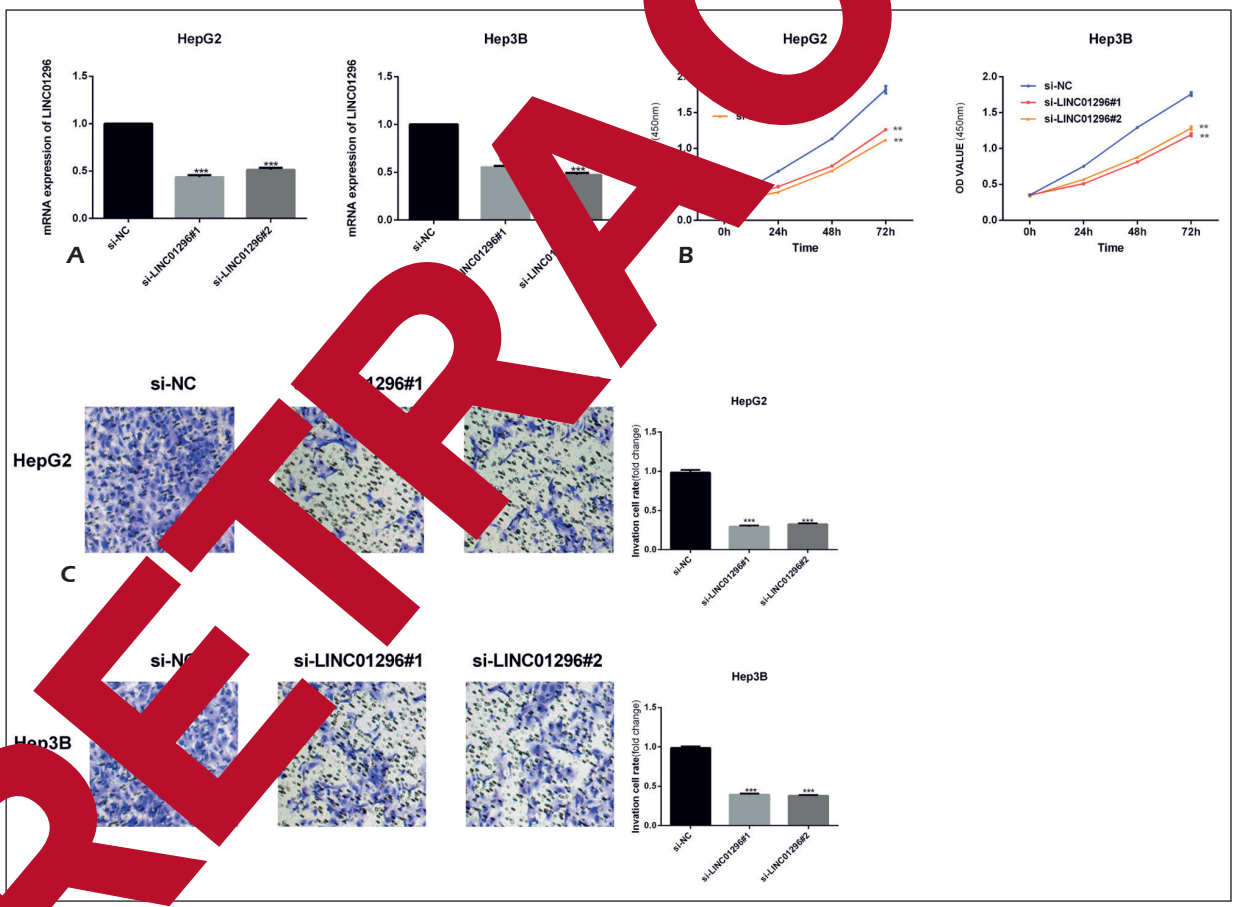

Figure 2. Down-regulation of LINC01296 inhibits the proliferation and invasion of hepatoma cells. **A**, Small interfering RNA down-regulates the expression level of LINC01296 in Hep3B and HepG2 cells. **B**, After down-regulating LINC01296, the proliferation of Hep3B and HepG2 cells was inhibited. **C**, After down-regulating LINC01296, the invasive ability of HepG2 cells was weakened (magnification × 40). **D**, Hep3B cells showed significantly decreased invasive ability after the down-regulation of LINC01296 (magnification × 40) (**p<0.01, ***p<0.001).

Subsequently, the effect of LINC01296 on cell proliferation was detected by CCK-8 assay. The results showed that the proliferation of Hep3B and HepG2 cells was remarkably inhibited after the down-regulation of LINC01296 (Figure 2B). Similarly, the cell invasion ability was measured by the transwell assay. The results indicated that the invasive ability of Hep3B and HepG2 cells transfected with LINC01296 si-RNA was remarkably suppressed as well (Figure 2C). The above results demonstrated that the down-regulation of the expression of LINC01296 could significantly inhibit the proliferative and invasion activity of LCa cells.

LINC01296 Is Involved in the Regulation of MicroRNA-760 Expression

The bioinformatics website lncRNASNP database (http://www.lncrnablog.com) predicted that microRNA-760 might be a potential downstream target for LINC01296[18]. The dual luciferase reporter assay confirmed that LINC01296 could bind to the 3'-UTR region of microRNA-760 (Figures 3A, 3B). Subsequently, we performed qRT-PCR in normal liver cell lines and hepatoma cell lines. The results indicated that the le[illegible] of microRNA-760 was remarkably down-re[illegible] in LCa cells (Figure 3C). Similarly, the microRNA-760 level significantly decreased in LCa tissues relative to adjacent normal tissue[illegible] 3D). Furthermore, we performed a li[illegible] sion analysis on the levels of LI[illegible]1296 and microRNA-760 in clinical samp[illegible] linear relationship was observed between t[illegible]ressions of LINC01296 and microR[illegible]-760 ([illegible]3806, $p<0.001$) (Figure 3E).

LINC01296 Affec[illegible]e Pro[illegible]ation, Migration, and In[illegible]n [illegible]Ca Ce[illegible] through MiR7[illegible]

To obser[illegible] the re[illegible]hi[illegible] between LINC01296 [illegible]croRNA-760[illegible] very experiment wa[illegible]lo[illegible] After silenc[illegible]g LINC01296 in HCC ce[illegible]s, we fu[illegible] inhibited microRNA-760 expre[illegible] and detect[illegible]ll proliferation ability [illegible]8 assay. The [illegible]lts showed that the l[illegible]kdown of microRNA-760 alone in Hep3B [illegible] HepG2 cell[illegible]uld enhance the proliferation [illegible]e hepatoma[illegible]ls. Besides, the inhibition of m[illegible]60 in Hep[illegible]nd HepG2 cells could restore the [illegible]ct of LINC01296 silencing on cell proli[illegible]on (Figure 4A). Similarly, we found [illegible]hat the knockdown of microRNA-760 in Hep3B

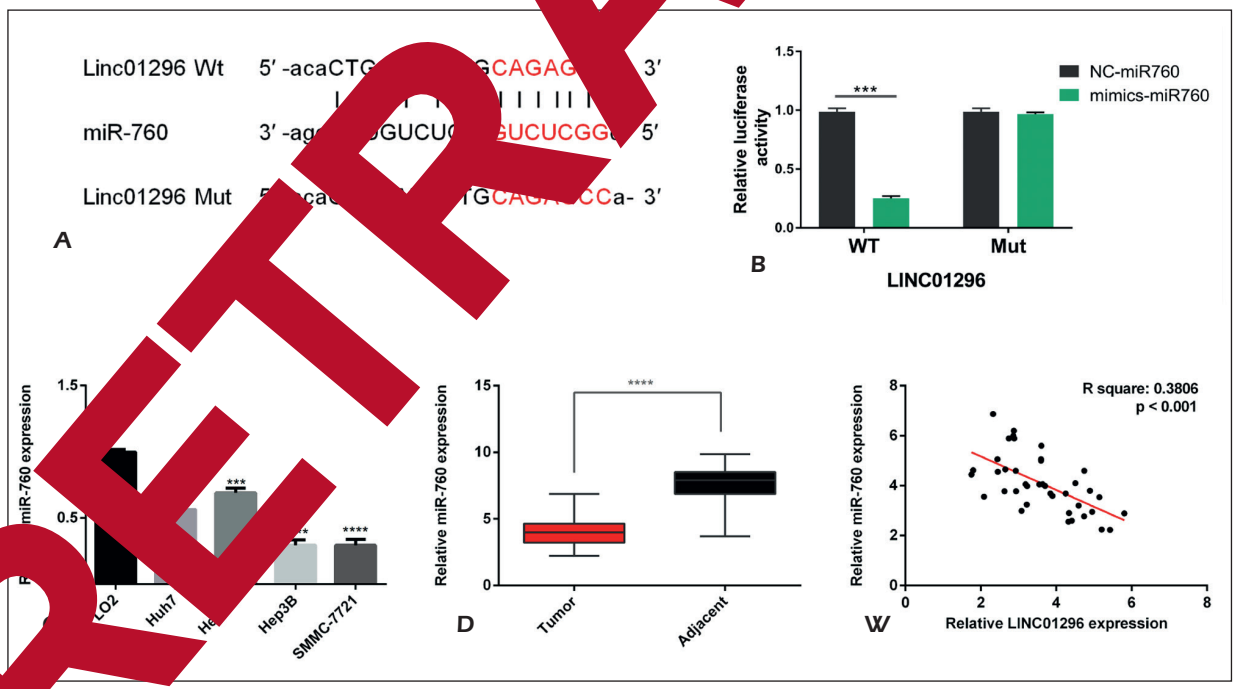

Figure 3. LINC01296 regulates miR-760 expression. **A**, The binding site of miR-760 and LINC01296 is predicted. **B**, Dual-luciferase reporter assays showed that the mutations in LINC01296 binding site abolished the inhibitory effect of mimics-[illegible]760 on luciferase activity. **C**, The expression level of miR-760 in hepatoma cell lines was lower than that in normal liver cell lines. **D**, Compared with adjacent tissues, miR-760 expression was significantly down-regulated in HCC tissues. **E**, The correlation between LINC01296 and miR-760 expression (**$p<0.01$, ***$p<0.001$, ****$p<0.0001$).

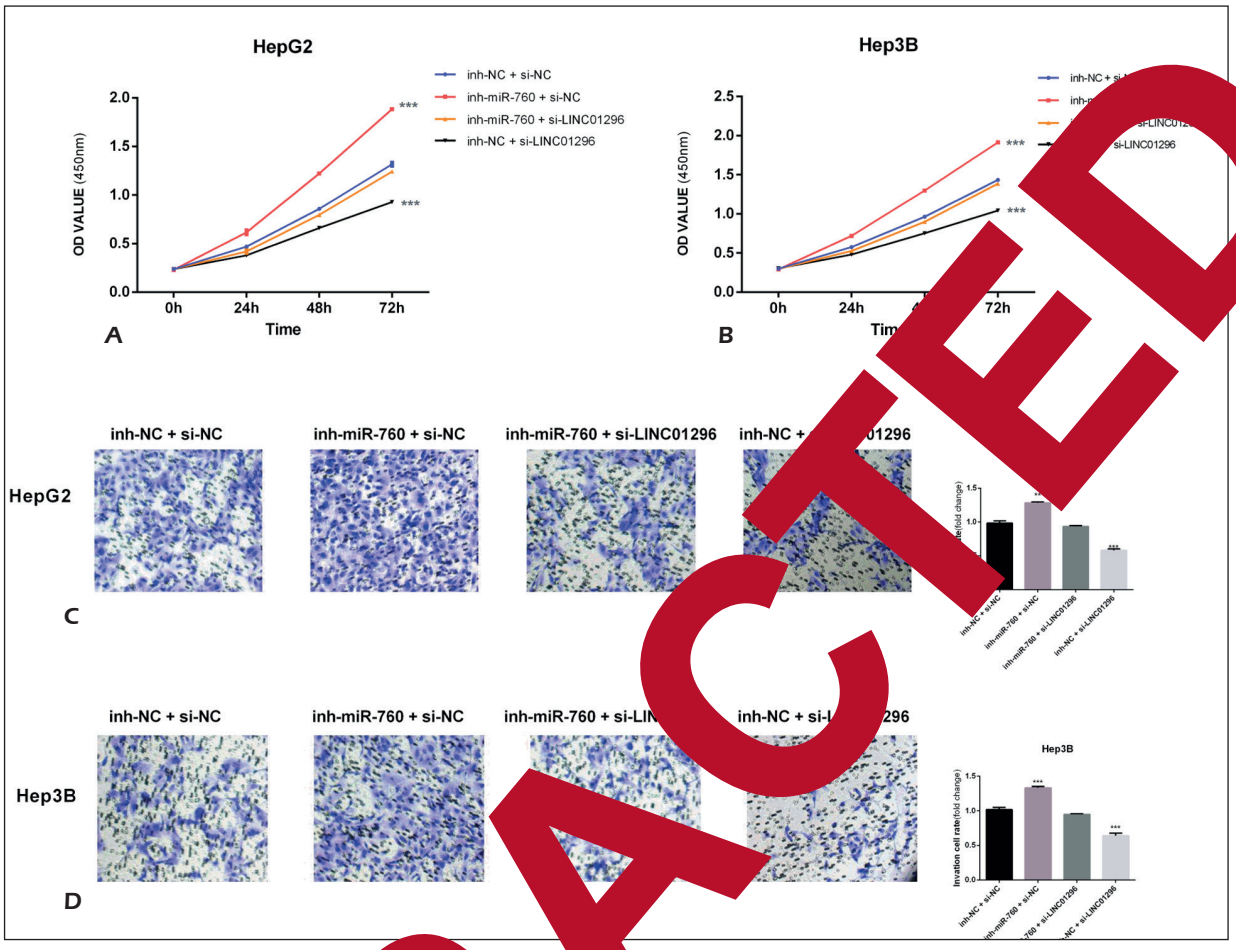

Figure 4. The inhibition of miR-76 can offse ffect of si-LINC01296 on the proliferation and migration of hepatoma cells. **A**, Inh-miR-760 ed the ibition of eration of HepG2 cells by si-LINC01296. **B**, Inh-miR-760 reversed the inhibition of prolif n of He ells by si-L NC01296. **C**, Inh-miR-760 reversed the inhibition of invasive ability of si-LINC01296 on H lls (m). **D**, Inh-miR-760 reversed the inhibition of invasion of Hep3B cells by si-LINC01296 (ma ific 4 $p<0.$ $p<0.001$, ****$p<0.0001$).

and HepG2 ce nh the invasion ability of hepatoma cells by tra assay. Meanwhile, the inhibi of microRN significantly reversed ffect of si-LINC01 on the invasion of th patoma s. The above results indicated tha C012 played n important role in the progr CCa by eting microRNA-760.

iscussion

oding RNA has become a hot topin biological tumor research in recent years[19]. study of long non-coding RNA provides new s s for the diagnosis and treatment of malignant mors. Yu et al[20] have found that the up-regulation of LINC00152 is closely related to tongue squamous cell carcinoma. Meanwhile, patients with high LINC00152 expression are more likely to suffer an advanced tumor. Chen et al[21] have indicated that lncRNA salmon regulates the expression of target gene ORC1 by combining with miR-140-5p, thereby leading to the malignant progression of colon cancer. Recent studies have found that some long-chain non-coding RNAs are involved in the mechanism of tumor resistance. For example, lncRNA tp76-as1 induces tumor resistance to chemotherapy drug temozolomide in glioma by regulating the expression of the target gene ALDH1A1[22]. LncRNA PVT1 regulates cisplatin resistance of non-small cell lung cancer through the pvt1-mir-216b-beclin-1 signaling axis[22]. As a newly discovered long non-coding RNA, we detected for the first time that LINC01296 was abnormally highly

Table II. Quantitative PCR primer sequences.

miRNA cDNA			
	miR-760	primer	5'-AACGAGACGACGACAGAC-3
	U6	primer	5'-GCAAATTCGTGAAGCGTTCCATA-
qRT-PCR Primer			
	LINC01296	forward	5'-GAGAAGCAGTGGTGGGTTCC
		reverse	5'-GAGCAACACAGATGAACCGC-3
	GAPDH	forward	5'-TCCTCTGACTTCAACAG CAC-3
		reverse	5'-GAGCAACACAGATGA GC-3'
	miR-760	forward	5'-TATTGCTTAAGAAT GTAG
		reverse	5'AACTCCAGCAGGA TGTGA
	U6	forward	5'-AGAAGGCTGGG ATTT
		reverse	5'-AGGGGCCAT

expressed in LCa tissues and cell line. Meanwhile, LINC01296 expression was remarkably correlated with the survival of patients with LCa. The prognosis of patients with higher LINC01296 expression was remarkably worse than that of patients with lower expression. These findings suggested that LINC01296 might be involved in the progression of LCa. Subsequent cell experiments showed that LINC01296 affected the proliferative and invasion abilities of LCa cells. The inhibition of LINC01296 significantly inhibited the prog of tumor cells. Meanwhile, a summary anal of the clinical data revealed that patients with h LINC01296 expression had a significantly hig probability of lymph node meta This su gested that LINC01296 might i r metastasis by promoting the proli ion an igration of tumor cells. These ab xperim sults all indicated that LINC012 ve in promoting the pro ion

Chen et al[23] ha ound that A plays a pivotal role in t ression of L though miRNA itself ot in the exp ession of proteins, it can participat e progression of tumors by ating the tra ion and translation of target genes. Micro A-760 has been foun inhibi orectal cancer progression by reg g tar ene FOXC1[24]. ROS1 inhibits the prolif d meta s of lung cancer cells by bindi s tar ene[25]. In LCa, Tian et al[26] found t RNA-760 inhibits the resistance of LCa to notherapy through the Notch1/hes /Akt signaling pathway. This makes the drug doxorubicin continuously effective on LCa cells. These studies suggest that 760 plays an important role in malignant tu- In this study, we proved for the first time that microRNA-760 inhibited the progression of LCa through experiments. The existence of binding sites h ce C01296 and microRNA-760 was verifi through base prediction and dual-luci e reporter g say. The results disclo LINC01296 co regulate the level of RNA-760. Meanwhile, a linear expression relonship was o ved between LINC01296 and NA-760 in c cal samples. Subsequent cell- xperimen nfirmed that the inhibition of the microRNA-760 could reverse the effect of 01296 on the proliferative and invaiveness abilities of LCa cells. All these findings that miRNA-760 served as an important gu of LINC01296 in LCa.

To sum up, as a new oncogene in LCa, LINC01296 is highly expressed in LCa and is closely related to LCa lymph node metastasis and clinical prognosis. LINC01296 promotes the proliferation and invasion abilities of LCa cells. Furthermore, miR760 was a key downstream gene of LINC01296, whose transcription level was negatively correlated with LINC01296 expression. In addition, LINC01296 might be a new target for clinical prognosis and treatment of LCa.

Conclusions

LINC01296 can promote tumor progression by inhibiting the expression of microRNA-760, and lead to poor prognosis of the tumor.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

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