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Effect of lncRNA LINC00483 on Taxol Resistance of Hepatocellular Carcinoma Cells by Targeting miR-646

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Abstract

Objective: To investigate the effects of lncRNA LINC00483 on the proliferation, migration and invasion of hepatocellular carcinoma cells and taxol resistance, as well as the potential molecular mechanism.

Methods: Hepatocellular carcinoma HCCLM3 cells and taxol resistant HCCLM3/Tax cells were treated with taxol (Tax) of different concentrations (0.08 μmol/L, 0.16 μmol/L, 0.32 μmol/L, 0.64 μmol/L, 1.28 μmol/L, 2.56 μmol/L). CCK8 assay was used to determine the proliferation inhibition rate and IC50 of Tax on HCCLM3 cells. qRT-PCR was carried out to detect the levels of lncRNA LINC00483 and miR-646 in HCCLM3 and HCCLM3/Tax cells. Western blot was applied to detect the expression levels of proteins CyclinD1, p21, MMP2 and MMP9. Transwell assay was used to detect the cell migration and invasion ability. Dual-luciferase reporter assay system was performed to validate the relationship between LINC00483 and miR-646.

Results: The inhibition rate of taxol (Tax) of 0.08 μmol/L, 0.16 μmol/L, 0.32 μmol/L, 0.64 μmol/L, 1.28 μmol/L, 2.56 μmol/L on HCCLM3/Tax cells was significantly lower than that of HCCLM3 cells in a concentration-dependent manner. The IC50 (10.70±0.11) μmol/L of HCCLM3/Tax on Tax was significantly higher than that of HCCLM3 cells (0.49±0.04) μmol/L. In HCCLM3/Tax cells, the level of lncRNA LINC00483 was significantly higher than that of HCCLM3 cells ($P<0.05$), and the level of miR-646 was significantly lower than that of HCCLM3 cells ($P<0.05$). Inhibition of lncRNA LINC00483 or over-expression of miR-646 combined with 0.16 μmol/L Tax treatment inhibited HCCLM3/Tax cell migration and invasion, enhanced inhibition rate of Tax on cell proliferation, up-regulated the level of p21 protein, and down-regulated the level of CyclinD1, MMP2 and MMP9. LncRNA LINC00483 negatively regulated the expression of miR-646 by targeting. Interfering miR-646 reversed the effects of lncRNA LINC00483 inhibition on proliferation, migration, invasion and taxol resistance of HCCLM3/Tax cells.

Conclusions: Inhibition of lncRNA LINC00483 inhibits proliferation, migration and invasion of HCCLM3/Tax cells and reduces the taxol resistance of cells by targeting miR-646. LncRNA LINC00483 is a potential molecular target for hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma, lncRNA LINC00483, miR-646, Proliferation, Migration, Invasion, Taxol resistance.

1. Introduction

The results showed that the competing endogenous RNA (ceRNA), including long-chain non-coding RNA (Circular RNA (circRNA), lncRNA) was abnormally exposed to carcinoma in the hepatocellular and involved in the hepatocellular carcinoma proliferation process, metastasize and drug resistance (Zhang Deyuan et al., 2016). Inhibited hepatocellular cell cell hepatocellular carcinoma Metastases LINC00483 up-regulation, down-regulation, or interference with LINC00493

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expression to colon cancer (Yan Y1. et al. 2019), lung adenocarcinoma (Yang S. et al., 2019) or cervical (Hu P. et al. 2019). and proliferation. LncBase Prediction v.2 predicted the binding position of miR-646 to LINC00483. In hepatocellular carcinoma tissue, MiR-646 is downregulated (Pan H. et al., 2019). The expression and function, however, of LINC00483 and miR-646 in taxol resistance hepatocellular carcinoma cells and the connection between them and the effects on taxol resistance cells in hepatocellular carcinoma are unknown.

In this experiment, the effects of HCCLM3 / Tax and taxol resistance lncRNA LINC00483 and miR-646 were investigated in order to provide a new path to research into hepatocellular carcinoma taxol resistance, in the sense of the proliferation, invasion, and migration. In this study.

Materials and Methods

2.1. Materials

Hepatocellular HCCLM3 cell strains and the HCCLM3 / Tax hepatocellular carcinoma taxol strain were purchased from ATCC; taxol were purchased at the Hyclone, US; si-LINC00483 and negative controls Si-NC; miR-NC, miR-646 (miR-646), pcDNE and the pcDNA-LINC00483 were purchased at the Beijing Solarbio Science&Technology Co. , Ltd.; The transfection reagent of Trizol, trypsine and RNA was bought from the US-based company Sigma-Aldrich; the transfectamine 2000 was bought from Corning, USA; the Takara Biotechnology (Dalian) Co., Ltd. was bought as a transfection reagent, a real time PCR-kit and an inverse transcription-kit, CyclinD D1,p21,MMP2,MMP9 and GAPDH.

2.2. Methods

Cell culture and establishment of HCCLM2/Tax resistant cell lines (Zhou Mingjie et al., 2015)

The HCCLM3 cells were grown in an incubator with a 5-percent CO2 content of 37 ° C in DMEM medium containing 10% FBS100U / mL of penicillin-100μg / ml of streptomycin. Literature reports [6] that HCCLM3 cells' taxol resistance is caused by intermittently inducing taxol concentration. In the DMME culture medium containing 0.05μM taxol, the cells in the logarithmic growth stage were cultured. The culture tool has been dismissed after 24 hours. The D-hanks solution was used for 3 washings and was then cultivated using the new method of cultivation. The cells have been crossed over again and again. The cells were screened once again at 0.05μM medium in taxol cultivation when the cells returned to the logarithmic growth stage. Then 0.1, 0.15 and 0.2μM taxols were screened for 3 and 10 months. to obtain hepatocellular carcinoma taxol resistance HCCLM3/Tax cells. HCCLM3/Tax cells were then cultured in DMEM culture medium containing low concentrations of taxol (0.02μM).

CCK8 assay for inhibition of cell proliferation and IC50

After taxol treatment or/and transfection, HCCLM3 and HCCLM3/Tax cells were seeded at 5×103 cells/well in 96-well microplate,100μL cells/well. After overnight culture, taxols (Tax) at final concentrations of 0.08 μmol/L, 0.16 μmol/L, 0.32 μmol/L, 0.64 μmol/L, 1.28 μmol/L and 2.56 μmol/L were added to the culture medium for 48h. 10μL CCK8 solution was added to each well for 2h. The absorbance at 450 nm (A) was determined by microplate reader. Inhibition %= (A value of control group-A value of experiment group) / A value of control group × 100%. The IC50 for 50% inhibitory concentration was calculated.

Detection of expression of lncRNA LINC00483 and miR-646 by real-time PCR

The total RNA of HCCLM3 and HCCLM3/Tax cells The reverse primers are as follows: miR-646 upstream primary: 5'-ACTCGGCAGCAGCCTGCCTG-3'; reverse primers: 5'-CTCAACTGGTG GTGGCGTGCATTGCASTCAGTCGTAGTCGTTCGASTA, extracted by Trizol reactant, then synthesized with CDNA following Real-time PCR instructions and detected ncRNA LINC00483 and miR-646 by reaction according to Real-time PCR directives.: 5'-GCTGAACCGGAACAGGACAT-3'; reverse primer 5'-CCAGTTCACAGCAACTCACG-3'; U6 upstream primer 5'-CTCGCTTCGGCAGCACA-3'; reverse primer 5'-AACGCTTCacGATTGCGT-3; GAPDH upstream 1 5'-GACTCATGACCAGTCCATGC 3'; back 1 5'-AGAGGGATGATGTCTG-3'; The study of data was carried out by 2- to Ct process..

Cell transfection

2.3. HCCLM3 / Tax cells were seeded in 6 tank plates in 2 to 105 cells per well in the logarithmic growth process and moved when cells were fused into a single layer. Lipofectamine 2000 reagent package described all the si-NC, si-LINC00483 and si-LINC00583+anti-miR-646 transfections transfactions transfectant vectors in cells in HCCLM3, pcDNA-LINC00483 and si-LINC00483+anti-miR-646 and were registered as Si-NC group, si-LINC00483 Group, miR-646, pcDNA-LINC00483 group, Si-LINC00483+anti-miR-group transfection package After 48h of transfection the cells were collected.

Detection of cell migration and invasion by Transwell experiment

Migration experiment: The HCCLM3 / Tax Cells were cultivated in the logarithmic step of development.

The DMEM Medium containing 0.16 µmol / L taxol was diluted to 1,001 cells / mL in the serum-free medium. In the upper chamber of Transwell were inserted 100 µL cells, in a 5 % CO2 incubator during 2 hours 500 µL medium containing 10% FBS and 0,16 mmol / L taxol was applied to the lower culture well. A cotton swab washed away the non-migrating cells in the upper chamber. Formaldehyde was applied to the cells and crystal violet was dyed. Five microscopically tracked and counted fields.

Invasion experiment: The Matrigel was diluted at 0.16 µmol / L taxol at 4 ° C with serum-free DMEM Medium. It was applied to the top chamber and solidified for 3 hours at 37 ° C. The following steps were the same as the migration experiment.

Western blot assay

Treated groups of HCCLM3/Tax cells at Methods 1, 2 and 3 have been collected, cells have been divided, protein extracted and concentrations measured. SDS-PAGE, skimmed milk powder membrane transfer and locking was done for 2 hours at room temperature. Added and burnt to 4 ° C overnight prime anticorps (CyclinD D1 1:1000, P21 1:1000, MMP2 1:2000, MMP9 1:1000, GAPDH 1:3000) Wash 3 times, 5 minutes per time with a PBST buffer solution, then add secondary antibodies and incubate for 1h at room temperature. Create and take imagery. With GAPDH as an internal guide, level of protein was analyzed.

Double luciferase reporting system experiment

Wild-type (WT-LINC00483) and mutant-type (MUT-LINC00483) lncRNA LINC00483 reporter vectors were then transferred to HCCLM3 / Tax cells with miR-NC or miR-646 for 48h in line with methods 1, 2, and 4 and then collected and lysed cells, and centrifuged surplus was obtained and luciferase activity was observed at supernatant. Relative activity of firefly luciferase against sea renal luciferase production as an internal comparison has been measured.

2.4. Statistical treatment

Data are presented as a mean value ± standard deviation (total value). The statistical program SPSS19.0 was used for the analysis of the results; the independent sample t-test was used to compare intergroups and the multi-group comparison was made with single factor variances. The statistically relevant differential was P<0.05.

Results

2.1. Effects of taxol at different concentrations on inhibition rate of HCCLM3 and HCCLM3 cells

Treatment of hepatocellular carcinoma HCCLM3 The inhibition rate for HCCLM3 / Tax was gradually increased with increased concentration, but with the highest inhibition rate of 2.56 µmol / L HCCLM3 / TAX, the taxol carcinoma HCCLM3 / Tax (Tax) at concentrations of 0.08 µmol / L, 0.16 µmold / L, 0.32 µmol / L, 0.75 µmol / L and 0.32 µmol / L and 2.56 µmol / L showed the taxol inhibition rate (Tax). Tax injections of HCCLM3 / Taxes were gradually Updated. It was slightly lower (31,36%±3,25%) than the HCCLM3 level (82,14%±8,21%). Tax cell IC50 was 0.49± 0.04 µmol / l and Tax cells were 10.70±0.11 µmol / L as shown in Table 1. Tax cell IC50 was 0%49±0.25. The findings have shown a slightly lower tax rate on HCCLM3 / Tax cells than on HCCLM3 cells. For subsequent studies, which did not have a substantial impact on cells, the concentration was selected 0.16 µmol / L Tax at 10% inhibition of HCCLM3 / Tax.

Table 1. **Effects of Taxol at Different Concentrations on Inhibition Rates of HCCLM3 and HCCLM3/Tax Cells ($\bar{x}$±s,n=9)**

Grouping	Taxol concentration						IC50 (µmol/L)
	0.08 µmol/L	0.16 µmol/L	0.32 µmol/L	0.64 µmol/L	1.28 µmol/L	2.56 µmol/L	
HCCLM3	13.25±1.42	27.33±2.47	41.65±4.23	56.87±5.63	69.55±6.32	82.14±8.21	0.49±0.04
HCCLM3 /Tax	5.48±0.54*	8.36±0.81*	14.22±1.36*	18.21±1.33*	23.12±2.41*	31.36±3.25*	10.70±0.11*
t	15.343	21.893	18.520	20.049	20.593	17.253	261.690
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Note: compared with HCCLM3 group, *P<0.05

2.2. Expression of lncRNA LINC00483 and miR-646 in hepatocellular carcinoma taxol resistance cells

Hepatocellular carcinoma HCCLM3 cells and hepatocellular carcinoma taxol resistance cell HCCLM3/Tax were detected. The results showed LncRNA LINC00483 was considerably higher for HCCLM3 / Tax compared (P<0.05) to HCCLM3 cells (and miR-646 content was slightly less for HcCLM3 / Tax compared with that for HCCLM3 (P<0.05). For more detail, see Table 2.

Table 2. **Expression of lncRNA LINC00483 and miR-646 in Hepatocellular Carcinoma Taxol-resistant Cells ($\bar{x}$±s, n=9)**

Grouping	LINC00483	miR-646
HCCLM3	1.00±0.06	1.00±0.05
HCCLM3/Tax	2.85±0.28*	0.44±0.04*
t	19.381	26.237
P	0.000	0.000

Note: compared with HCCLM3 group, *P<0.05

2.3. Effect of inhibiting the expression of lncRNA LINC00483 in combination with taxol (0.16 μmol/L) on the proliferation and migration and invasion of hepatocellular carcinoma taxol resistance cell HCCLM3/Tax

The lncRNA LINC00483 content in the HCCLM3 / Tax Cells group decreased, the cell injection rate increased, the amount of migration and invasion increased, compared to Tax+si-NC group Tax+si-LINC00483 cells

Cells have reduced, protein content in Cyclin D1, MMP-2 and MMP-9 has decreased, the p21 level has increased and statistically significant differences have increased (P < 0.05). See Figure 1 and Table 3, respectively. The findings showed LINC00483 inhibition rate in combination with 0.16 μmol / L Tax treatment inhibited HCCLM3 / Tax cell propagation, migration, and invasion and enhanced the rate of taxol inhibition on cells.

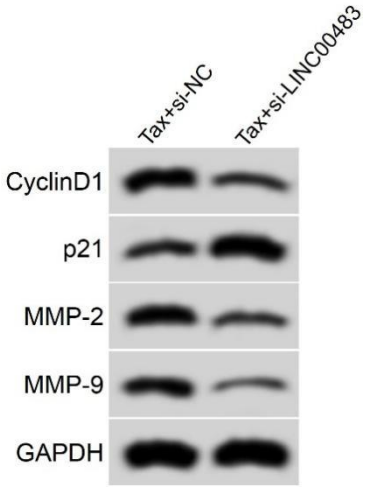

Figure 1. **Expression of Proteins Related to Proliferation, Migration and Invasion**

Table 3. **Effects of Inhibition of lncRNA LINC00483 Combined with Taxol Treatment on Proliferation, Migration and Invasion of HCCLM3/Tax Cells（ $\bar{x}$±s, n=9 ）**

Grouping	LINC00483	Inhibition rate (%)	Number of migration cells (piece)	Number of invasion cells (piece)	CyclinD D1 protein	p21 protein	MMP-2 protein	MMP-9 protein
Tax+si-NC	1.00±0.07	8.65±0.84	113.56±9.58	98.36±9.22	0.69±0.06	0.32±0.03	0.62±0.06	0.53±0.05
Tax+si-LINC00483	0.53±0.05*	45.12±4.22*	52.03±5.12*	44.18±4.28*	0.27±0.03*	0.78±0.07*	0.21±0.02*	0.18±0.02*
t	16.391	25.428	16.994	15.990	18.783	18.120	19.448	19.498
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Note: compared with Tax+si-NC group, *P<0.05

2.4. LINC00483 regulates miR-646 expression by targeting

The sequence of miR-646 includes binding sites that complement the LINC00483 lncRNA, as predicted by LncBase Recommended v.2, see Figure 2. The results of a double luciferase study showed that the relative firefly luciferase activity in the wild miR-646 group WT-LINC00483 was considerably reduced (P<0.05) in relation to

The miR-NC group did not substantially alter the relative activity of luciferase in the MUT-LINC00483 mutant as shown at Table 4. qRT-PCR findings showed that LINC00483 over-expression substantially reduced miR-646 content (P<0.05); LINC00483 inhibitors were up-regulated, miR-646 content (P<0.05) see table 5. This indicates that LINC00483 changes miR-646 by addressing negatively.

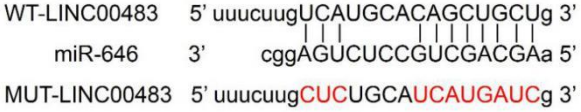

Figure 2. **Sequence of LINC00483 Contains Nucleotide Sequences Complementary to miR-646**

Table 4. **Dual-luciferase Reporter Assay System（ $\bar{x}$±s, n=9 ）**

Grouping	WT-LINC00483	MUT-LINC00483
miR-NC	0.98±0.06	0.99±0.07
miR-646	0.46±0.04*	1.00±0.05
t	21.663	0.349
P	0.000	0.732

Note: Compared with miR-NC group, $^{*}P$<0.05

Table 5. **lncRNA LINC00483 Regulates the Expression of miR-646 ($\bar{x}$±s, n=9)**

Grouping	miR-646
pcDNA	1.00±0.05
pcDNA-LINC00483	0.53±0.05*
si-NC	0.98±0.06
si-LINC00483	2.71±0.26#
F	436.740
P	0.000

Note: compared with pcDNA group, $^{*}P$<0.05; compared with si-NC group, $^{\#}P$<0.05

2.5. Effect of miR-646 over-expression in combination with taxol (0.16 μmol/L) on the proliferation and migration and invasion of hepatocellular carcinoma taxol resistance cell HCCLM3/Tax

The content of miR646 in HCCLM / Tax3 cells has increased substantially, as compared with the Tax+miR-NC group, in the Tax+miR-646 Group, cell inhibition.

rate was significantly increased, the expression of the number of migration and invasion cells was significantly decreased (P<0.05), as was the increase in the expression of p21. For more detail, see Figures 3 and 6. That suggests that miR-646 over-expression inhibits proliferation, migration and HCCLM3 invasion, and improves the taxol resistance of cells in HCCLM / Tax3.

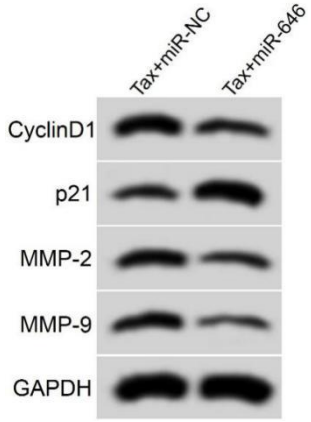

Figure 3. **Expression of Proliferation and Migration and Invasion Associated Proteins**

Table 6. **Effects of Over-expression of miR-646 Combined with Taxol Treatment on Proliferation, Migration and Invasion of HCCLM/Tax3 Cells ($\bar{x}$±s, n=9)**

Grouping	miR-646	Inhibition rate (%)	Number of migration cells (piece)	Number of invasion cells (piece)	CyclinD1 protein	p21 protein	MMP-2 protein	MMP-9 protein
Tax+miR-NC	1.01±0.06	9.32±0.91	112.05±9.66	95.36±9.52	0.67±0.06	0.31±0.03	0.61±0.06	0.55±0.05
Tax+miR-646	2.85±0.28*	33.14±3.32*	61.25±6.42*	53.14±5.37*	0.32±0.03*	0.72±0.07*	0.28±0.03*	0.22±0.02*
t	19.277	20.758	13.139	11.588	15.652	16.151	14.758	18.384
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Note: compared with Tax+miR-NC group, *P<0.05

2.6. Interference miR-646 reverses the inhibition effect of LINC00483 on taxol resistance in HCCLM3/Tax cells

The content of miR-646 in HCCLM3 / Tax cells was reduced by + + si-LINC00483+anti-miR-646, while the cell-inhibition rate was reduced compared to the Tax+si-LINC00483 + anti-miR-646 community., the number of migration and invasion cells was Increased, CyclinD1, MMP2, and MMP9 expression were enhanced and p21 expression decreased, with statistically significant differences (P<0.05). This indicates that miR-646 interferes reverse the effects of lncRNA LINC00484's inhibition of HCCLM3 / Tax cell proliferation, migration, invasion, and taxol resistance.

Figure 4. **Expression of Proteins Related to Proliferation, Migration and Invasion**

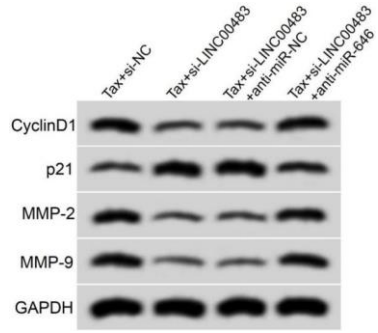

Table 7. **Interfering the Expression of miR-646 Reverses the Effect of lncRNA LINC00483 Inhibition on Taxol Resistance of HCCLM3/Tax cells ($\bar{x}$±s, n=9)**

Grouping	miR-646	Inhibition rate (%)	Number of migration cells (piece)	Number of invasion cells (piece)	Cyclin D1 protein	p21 protein	MMP-2 protein	MMP-9 protein
Tax+si-NC	1.00±0.06	8.77±0.87	115.47±9.97	96.36±9.58	0.68±0.06	0.30±0.03	0.63±0.06	0.56±0.05
Tax+si-LINC00483	2.78±0.27*	45.36±4.51*	56.39±5.68*	47.12±4.71*	0.26±0.03*	0.77±0.07*	0.23±0.02*	0.19±0.02*
Tax+si-LINC00483+anti-miR-NC	2.81±0.28	46.88±4.62	54.18±5.42	45.39±4.55	0.24±0.03	0.79±0.06	0.22±0.02	0.17±0.02
Tax+si-LINC00483+anti-miR-646	1.55±0.15#	21.03±2.11#	91.22±9.11	79.65±7.81#	0.57±0.05#	0.41±0.04#	0.52±0.05#	0.47±0.04#
F	166.546	268.949	128.099	115.558	223.101	206.864	223.652	285.245
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Note: Compared with Tax+si-NC group, $^{*}P$<0.05; compared with Tax+si-LINC00483+anti-miR-NC group, $^{\#}P$<0.05

Discussion

In China, the annual number of new cases of hepatocellular carcinoma is nearly half as high as worldwide, and its incidence is hidden. The majority at the time of diagnosis are middle-and aged. The rate of resection is low and the rate of repeatability is high. Chemo-embolism of catheter-based hepatic arteries is the preferred treatment for mid and advanced stage patients, but chemotherapy's unspecificity and drug resistance may lead to a lack of care (Feng Huigang et al. 2017). Therefore, in the clinical practice of hepatocells carcinoma, the development of targeted chemotherapeutics for hepatocellular carcinoma is an urgently required issue. Research has shown that different lncRNAs can be expressed differently in hepatocellular tissue carcinoma (Shi Junying et al., 2018). miRNA and lncRNA have been associated with hepatocellular carcinoma resistance, which may be possible therapeutic targets for hepatocellular carcinoma therapy overcoming resistance (Ding B. et al. 2018).

According to recent studies, lncRNA LINC00483 is up-regulated in lung adenocarcinome and it may inhibit the development, migration and invasion of hepatacellular carcinoma by silencing its expression and increase the sensitivity to radio-susceptibility of lung adenocarcinoma (Yang QS. et al., 2019). The gastric carcinoma LINC00483 is often upregulated, leading to the initiation of gastric carcinoma, tumour size, metastatic conditions and weak prediction. It aims at miR-30a-3p and negatively controls the expression and signaling of SPAG9; stimulates MAPK pathways; encouraging, in vitro and in vivo proliferation, invasion and metastatic gastric carcinoma cells (Li D. et al . ,

2018). It has been shown that LINC00483 is associated with tumor metastasis and radiation sensitivity but its expression and function in the carcinoma of hepatocells is unknown. In this analysis, the taxo resistance of cell lines HCCLM3 / Tax is determined to detect the IC50 and taxol inhibition rates at various levels (0.08 µmol / L, 0.16 µmol / L, 0,32 µmol / L, 0.64 µmol / L, 1.28 µmol / L, 2.56 µmol / L). The findings showed, for HCCLM3 / Tax, that the tax inhibition rate was lower than for HCCLM 3 and for that matter, the IC50 was higher than HCCLM3 cells and for lncRNA LINC00483 cells, similar to the assumptions of the above, significantly increased (Yang QS. and other categories, 2019). (Li D. et al., 2018). Si LINC00483 transfection combined with Tax in HCCLM3 / Tax cells has impaired cell migration and invasion, up-regulated p21, down-regulating proteins Cyclin D1, MMP3 and MMP9 and increased the cell proliferating tax rate, indicating that lncRNA LINC00483 can be the possible target for hepatocellular carcinoma chemotherapy sensitisation. Tax cells inhibiting migration and invasion.

In this study, the binding site of miR-646 to lncRNA LINC00483 was predicted by LncBase v.2. Capitalization, colonisation, migration, and invasion of colon carcinomas was inhibited through the down-regulation of the miR-646 expression and gastric carcinoma (Xue M. et al., 2019), the up-regulation of the miR-646 expression, and the cisplatin resistance of gastric carcinoma cells was correlated with this. Studies have shown that individual nucleotide polymorphism in miR-646 is related to hepatocellular carcinoma susceptibility in a large population (Wang R. et al. 2014). miR-646 is a target in a significantly down regulation circ 0000267 for cell growth and migration, and for invasion and apoptosis (Pan H, and al. 2019) with a concentration of circular 0000267 in hepatocellular carcinoma (CDCC). These studies all indicate that miR-646 has proliferation, metastasis, and resistance of the tumor cells. The results of this analysis revealed that miR-646 in HCCLM3 / Tax was substantially less than in cells in HCCLM3 (Dai H. et coll., 2017) (Xue M. et al., 2017)

2019), over-expression of miR-646 in Combination with the Tax prevented HCCLM3 / Tax cell migration and invasion and increased inhibition of cells caused by taxol. The experiment for double luciferase reporting showed that the negative regulation of miR-646 expression by targeting in the LNcRNA LINC00483 reversed the HCCLM3 / Taxcell proliery, migration, invasion and taxol resistances by interfering with miR-5006, confirming the existence of the two in hepatocellular carcinoma in the unique regulatory association.

In this study lncRNA Linc 00483 expression was increased by regulation, miR-646 was decontrolled, and lncRNA Linc 00483 was targeted by miR-646 to modulate HCCLM3 / Tax cell resistance in hepatic cell resistance Tax cell HCCLM3 / Tax to proliferation, migration, invasion and taxol. The main target chemosensitizer in hepatocellular carcinoma should be lncRNA LINC00483.

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