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Effect of LINC00460 Targeting Micro Ribonucleic Acid-380-5p on Malignant Biological Behaviors of Cervical Cancer C33A Cells

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ABSTRACT The researchers aimed to evaluate the effect of LINC00460 targeting micro ribonucleic acid (miR)-380-5p on the malignant biological behaviors of cervical cancer C33A cells. Compared with C33A group, si-LINC00460 group and miR-380-5p group had significantly lower proliferation and invasion abilities and protein expressions of cyclin D1, CDK2 and vimentin as well as higher apoptosis ability and E-cadherin protein expression (P<0.05). MiR-380-5p declined significantly at the expression level in pcDNA-LINC00460 group by contrast to that in pcDNA-NC group (P<0.05). Compared with si-LINC00460 group, si-NC group presented a significantly raised miR-380-5p expression (P<0.05). In comparison to those in anti-miR-NC group, the proliferation and invasion abilities, together with cyclin D1, CDK2 and vimentin at the protein expression level, were significantly increased, and the apoptosis ability and E-cadherin protein expression were attenuated significantly in anti-miR-380-5p group (P<0.05). Down-regulating LINC00460 expression affects cervical cancer C33A cells from the aspect of inhibiting their multiplication and invasion while facilitating their apoptosis by facilitating miR-380-5p expression.

INTRODUCTION

As the most ubiquitous malignancy occurring in women, cervical carcinoma shows an increasing trend in the prevalence rate annually, posing serious threats to the life and health of patients (Nayak et al. 2019; Karan et al. 2020). Cervical cancer is mainly attributed to the activation of proto-oncogenes resulting from various factors such as genetics, fertility, endocrine and radiation, while the inactivation and apoptosis of tumor suppressors contribute to the uncontrolled proliferation of tumor cells (Burmeister et al. 2022). At present, cervical cancer is mainly treated by surgery, radiotherapy and chemotherapy, but the high recurrence rate seriously affects the prognosis (Wang et al. 2021).

MiRNAs, one of the proteins free of coding function, play their roles by modulating the expressions of target genes through transcription (Li et al. 2020). They have been closely implicated in regulating tumor genes (Morgan et al. 2020; Wu et al. 2021). The biological behaviors of various tumor cells, such as proliferation, differentiation and apoptosis, are mediated by miRNAs (Gao et al. 2021). In recent years, extensive attention has been paid to miRNAs which essentially participate in the treatment of cervical cancer (Huang et al. 2020). However, there are few reports on miR-380-5p about its effect on cervical cancer.

Long-chain non-coding RNAs (lncRNAs), a type of RNAs unable to encode proteins, are capable of regulating gene expression through epigenetics and transcription, thus exerting biological effects (Wang et al. 2020; Zhao et al. 2020). LncRNAs have been reported to mediate the occurrence and development of tumors and regulate multiple biological behaviors of tumor cells (for example, invasion, metastasis and apoptosis) (Guo et al. 2020; Zhang et al. 2020). They can bind RNA-binding proteins to form compounds, acting as tumor suppressors or oncogenes through modulating the expressions of their downstream target genes, thus regulating the biological activities of tumor cells, such as proliferation and invasion, and participating in the process of tumor formation (Xia et al. 2021). LINC00460 is located at the chromosome 13q33.2 (Hu et al. 2019). It participates in regulating the biological functions of oral squamous cell carcinoma, lung cancer, gastric cancer and other tumors (Chen et al. 2022). In the case of non-small cell lung cancer, lowering LINC00460 expression can inhibit cell invasion plus propaga-

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tion (Ding et al. 2021). Nonetheless, no reports on the expression or function of LINC00460 in cervical cancer have been published yet.

Objectives

This study focused on cervical cancer C33A cells to explore the expressions of LINC00460 and miR-380-5p and the impact of LINC00460 targeting miR-380-5p on the malignant biological behaviors of these cells, aiming to lay a valuable experimental foundation for future treatment in clinic.

METHODOLOGY

Cell Lines

Human cervical cancer cell lines (HCC94, C33A, Hela and SiHa cells) were purchased together with human normal cervical epithelial cell line (HaCaT cells) from Shanghai Cell Bank, Chinese Academy of Sciences (China).

Reagents and Apparatus

Small interfering RNA targeting LINC00460 (si-LINC00460) plasmid, si-negative control (si-NC) plasmid, pcDNA-NC plasmid, pcDNA-LINC00460 plasmid, miR-380-5p mimics, miR-NC plasmid, anti-miR-380-5p plasmid, anti-miR-NC plasmid and dual-luciferase reporter gene vector sourced from Guangzhou RiboBio Co., Ltd. (China). Sequences of primers for polymerase chain reaction (PCR) came from Shanghai Sangon Bioengineering Co., Ltd. (China). Inverted fluorescence microscope was bought from Shanghai Xinmao Instrument Co., Ltd. (China).

Cell Culture

HaCaT cells plus HCC94, C33A, Hela and SiHa cells were inoculated in the medium containing 10 percent fetal bovine serum, penicillin (100 μg/mL) and streptomycin (100 μg/mL). Then the medium was incubated using an incubator under 5 percent CO_2 at 37°C for 24 h and replaced once every 2 days. When the cells adhered to the wall and covered the bottle bottom, they were digested, and subsequent experiments were conducted on those in the logarithmic growth phase.

Cell Grouping plus Transfection

C33A cells were transfected using Lipofectamine™ 2000 kit (Thermo Fisher Scientific, USA) and then divided into C33A group (normal culture without any plasmid transfection), miR-380-5p group (receiving transfection with miR-380-5p mimics), si-NC group (subjected to si-NC plasmid transfection), si-LINC00460 group (undergoing transfection of si-LINC00460 plasmid), anti-miR-380-5p group (transfected with anti-miR-380-5p plasmid), miR-NC group (with miR-NC plasmid transfected), and anti-miR-NC group (subjected to anti-miR-NC plasmid transfection). 24-h culture was performed for all cells before experiments.

Determination of Expressions of LINC00460 and miR-380-5p in Cells by Reverse Transcription PCR (RT-PCR)

TRIzol reagent supplied by Thermo Fisher Scientific (USA) was utilized for extraction of total RNA from cells *as per* the instructions of the kit, followed by acquisition of cDNA through reverse transcription using the reverse transcription kit (Qiagen, Germany). The primer sequences involved: LINC00460 F: 5'-AGAAAGACTGAGCGTGGGA-3', R: 5'-GTCATTTTGGAGGCTGGAA-3'; β-actin F: 5'-CTCCATCCTGGCCTCGCTGT-3', R: 5'-GCTGTCACCTTCACCGTTCC-3'; miR-380-5p F: 5'-CTCGCTTCGGCAGCACA-3', R: 5'-CAGTGCGTGTCGTGGAGT-3'; U6 F: 5'-CTCGCTTCGGCAGCACA-3', R: 5'-AACGCTTCACGAATTTGCGT-3'. The primers were centrifuged and added deionized water, followed by mixing well and preparation into stock solution (100 μmol/L). Then a working solution (final concentration: 10 μmol/L) was prepared by diluting the forward and reverse primers. The following conditions were set for PCR: 10 min of 95°C pre-denaturation, together with 20 s of 95°C denaturation and 34 s of 60°C annealing for 40 cycles. The $2^{-\Delta\Delta CT}$ method was adopted for the analysis of LINC00460 and miR-380-5p expression levels.

Measurement of Cell Proliferation Ability by Methyl Thiazolyl Tetrazolium (MTT) Assay

C33A cells were taken from each group and inoculated at 5×10^4 /well in density into a 96-well plate. After 24, 48 and 72 h of culture, MTT solution was added with the medium discarded. DMSO solution was supplemented after 4 h of culture.

Finally, a microplate reader provided by Thermo Fisher Scientific (USA) was employed to measure the absorbance at 570 nm, and experiments were repeated 3 times to take the mean.

Transwell Assay on Invasion Ability of Cells

C33A cells taken from each group were seeded at 6×10^4/mL in density into a 24-well plate. Subsequently, 500 μL of medium supplemented with 10 percent fetal bovine serum was added, prior to digestion and dilution (5×10^5) of cells. Another 24-well plate was applied to inoculate the diluted cell suspension into the Transwell chamber, followed by placement on a culture plate containing fetal bovine serum (10%) and culture using a normal incubator for 24 h. Then the chamber was taken out, in which the cells were eliminated. Finally, a microscope manufactured by Olympus (Japan) was used to observe the plate and count the invading cells.

Measurement of Cell Apoptosis Ability by Flow Cytometry

A 96-well plate was employed for inoculation of C33A cells from each group (6×10^4/mL in density). Subsequent to 24-h culture, serum-free medium containing 5 μg/mL adriamycin was added for 48-h culture of the cells, which were then harvested. After washing twice with PBS, they underwent resuspension in binding buffer (500 μL) and sufficient mixing with Annexin V-FITC and then PI both in a volume of 5 μL, followed by 10 min of room-temperature incubation in dark. The apoptosis rate was determined by means of flow cytometry (Bio-Rad, USA) repeated 3 times.

Western Blotting for Detection of Protein Expressions of cyclin D1, Cyclin-Dependent Kinase 2 (CDK2), Vimentin and E-cadherin

C33A cells from all groups were inoculated at a density of 3×10^5/mL into a 6-well plate. The adherent cells were collected and digested with trypsin to obtain cell samples, followed by lysis with RIPA and 10-min centrifugation at 12,000 rpm in a centrifuge tube. Then the protein content in the harvested supernatant was determined. Later, protein samples were subjected to loading with prepared spacer gel (5%) together with separation gel (8%), 100 min of electrophoresis and wet transfer process for transfer onto a PVDF membrane for 2 h. Next, 5 percent blocking buffer was added for 1 h of membrane blocking at room temperature, and primary antibodies against cyclin D1, CDK2, vimentin, E-cadherin and internal reference β-actin were used for incubation at 4°C overnight. Afterwards, 2 h of incubation was implemented with HRP-labeled secondary antibodies added. Finally, the membrane was immersed in ECL solution and then imaged.

Dual-luciferase Reporter Assay

TargetScan7.1 (an online target gene prediction software) displayed that miR-380-5p bound LINC00460 in the 3'-untranslated region (3'-UTR). Wild-type sequences (wt-LINC00460 3'-UTR) together with mutant sequences (mut-LINC00460 3'-UTR) were designed and synthesized, and gene fragments were cloned into pmirGLO luciferase reporter vector to construct LINC00460 3'-UTR dual-luciferase reporter vector (pmirGLO-wt-survivin) and mutant vector (pmirGLO-mut-survivin).

Lipofectamine™ 3000 reagent (Thermo Fisher Scientific, USA) was applied to co-transfect C33A cells with miR-NC or miR-380-5p plasmid plus wt-LINC00460 and mut-LINC00460, and the luciferase activity was detected 48 h later. Grouping for transfection is listed in Table 1. Moreover, C33A cells underwent separate transfection of pDNA-NC, pcDNA-LINC00460, si-NC and si-LINC00460. Following transfection for 48 h, RT-PCR was executed to examine miR-380-5p expression level.

Statistical Analysis

Statistical analysis was accomplished *via* Prism 8.0 (GraphPad, USA). Data such as expression levels of LINC00460 and miR-480-5p, proliferation, invasion and apoptosis abilities, as well as protein expression in cells were described in the form of

Table 1: Grouping for co-transfection

Co-transfection	miR-NC	pmir GLO-wt-LINC00460 3'-UTR
Co-transfection	miR-380-5p	pmir GLO-wt-LINC00460 3'-UTR
Co-transfection	miR-NC	pmir GLO-mut-LINC00460 3'-UTR
Co-transfection	miR-380-5p	pmir GLO-mut-LINC00460 3'-UTR

mean ± standard deviation (x ± s). Comparisons of data among groups and between two groups were carried out through one-way analysis of variance and *t*-test, respectively. P<0.05 represented statistically significant differences.

RESULTS

Expressions of LINC00460 and miR-380-5p in Cells

In comparison to those in HaCaT cells, LINC00460 expression rose significantly, while miR-380-5p expression declined significantly in human cervical cancer HCC94, C33A, Hela and SiHa cells, especially in C33A cells (P<0.05) (Fig. 1).

Effects of Down-Regulating LINC00460 Expression on Proliferation, Invasion and Apoptosis of C33A Cells and Its Influences on Cyclin D1, CDK2, Vimentin and E-cadherin in Cells at the Protein Expression Level

The cell proliferation, invasion and apoptosis abilities, together with cyclin D1, CDK2, vimentin and E-cadherin protein expressions, showed no significant differences between C33A and si-NC groups (P>0.05). Significantly weaker cell proliferation and invasion abilities and lower protein expressions of cyclin D1, CDK2 and vimentin, along with significantly stronger cell apoptosis ability and E-cadherin protein expression, were observed in the si-LINC00460 group contrasted with those in the C33A group (P<0.05) (Fig. 2).

Role of Up-Regulating miR-380-5p Expression in Affecting Proliferation, Invasion and Apoptosis of C33A Cells and Its Influences on Protein Expressions of cyclin D1, CDK2, Vimentin and E-cadherin in Cells

The cell proliferation, invasion and apoptosis abilities and protein expressions of cyclin D1, CDK2, vimentin and E-cadherin presented no significant differences between miR-NC group and C33A group (P>0.05). The MiR-380-5p group had significantly lower cell proliferation and invasion abilities and protein expressions of cyclin D1, CDK2 and vimentin as well as significantly higher cell apoptosis ability and protein expression of E-cadherin than the C33A group (P<0.05) (Fig. 3).

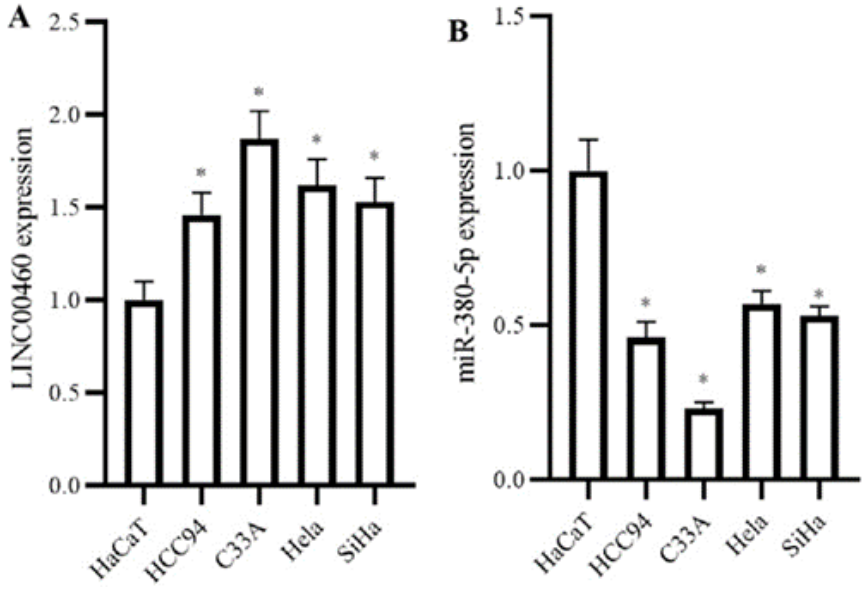

Fig. 1. Expressions of LINC00460 and miR-380-5p in cells. A: Cellular LINC00460 expression. B. Cellular miR-380-5p expression. *P<0.05 *vs.* HaCaT cells

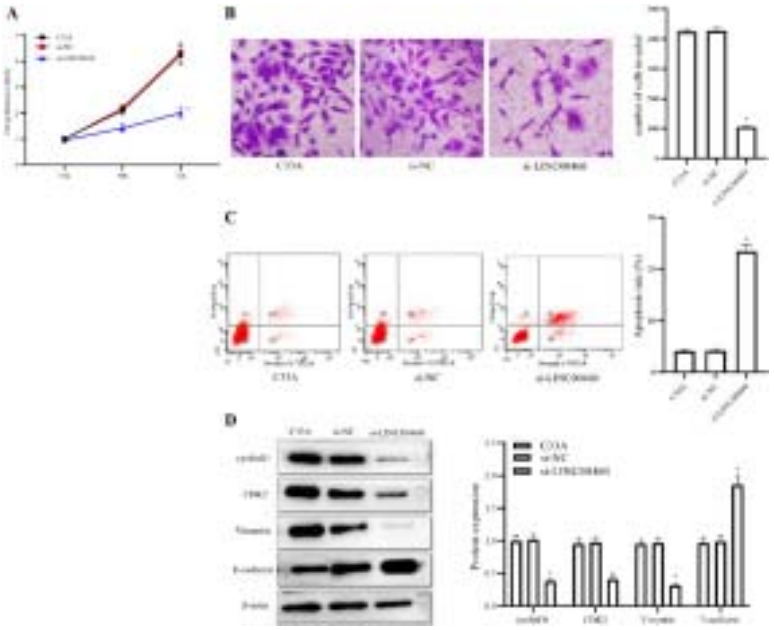

Fig. 2. Effects of down-regulating LINC00460 expression on C33A cell proliferation, invasion and apoptosis together with its influences on protein expressions of cyclin D1, CDK2, vimentin and E-cadherin in cells. A: Cell proliferation ability. B: Cell invasion ability. C: Cell apoptosis ability. D: Protein expressions of cyclin D1, CDK2, vimentin and E-cadherin in cells. *P<0.05 *vs*. C33A group

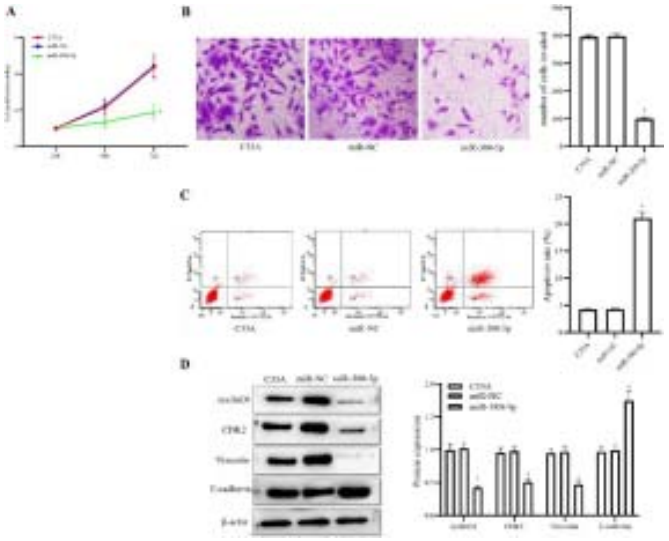

Fig. 3. Role of up-regulating miR-380-5p expression in impacting C33A cell proliferation, invasion and apoptosis and its influences on protein expressions of cyclin D1, CDK2, vimentin and E-cadherin in cells. A: Cell proliferation ability. B: Cell invasion ability. C: Cell apoptosis ability. D: Protein expressions of cyclin D1, CDK2, vimentin and E-cadherin in cells. *P<0.05 *vs*. C33A group

Prediction and Identification of Targeting Relationship between LINC00460 and miR-380-5p

As revealed by the software, the LINC00460 3'-UTR possessed base complementary binding sites with miR-380-5p. The miR-380-5p group exhibited significantly reduced luciferase activity compared with the miR-NC group after transfection with wild-type LINC00460 (LINC00460-WT) ($P<0.05$), whereas no significant difference was found between the two groups after transfection with mutant LINC00460 (LINC00460-MUT) ($P>0.05$), according to the luciferase assay results. The results of RT-PCR denoted that miR-380-5p expression was significantly lower in the pcDNA-LINC00460 group than in the pcDNA-NC group ($P<0.05$). Moreover, significant elevation of miR-380-5p expression was detected in the si-NC group in comparison to that in the si-LINC00460 group ($P<0.05$) (Fig. 4). The above findings indicated that LINC00460 can negatively regulate miR-380-5p expression.

Down-Regulating miR-380-5p Reversed the Effects of Down-Regulating LINC00460 Expression on C33A Cell Proliferation, Invasion and Apoptosis as well as Its Influences on Protein Expressions of Cyclin D1, CDK2, Vimentin and E-cadherin in Cells

The anti-miR-380-5p group, contrasted with the anti-miR-NC group, displayed significantly enhanced cell proliferative and invasive abilities plus cyclin D1, CDK2 and vimentin at the protein expression level, in addition to significantly lowered cell apoptosis ability and E-cadherin protein expression ($P<0.05$) (Fig. 5).

DISCUSSION

Mo and Lou (2020) reported a distinctly higher LINC00460 expression in the tumor tissues than in the normal adjacent tissues of cervical cancer patients, and was closely associated with tumor cell differentiation, distal metastasis, TNM stage, and lymph node metastasis. In this study, LINC00460 was highly expressed in cervical cancer cells. After silencing LINC00460, the cell proliferative and invasive capabilities markedly declined while the cell apoptosis ability significantly rose, indicating that silencing LINC00460 can regulate the malignant biological activities of cervical cancer cells.

Cyclin D1 and CDK2 are crucial proteins facilitating the cell cycle (Duan et al. 2020). As revealed by the present study, down-regulating LINC00460 led to decreases in cyclin D1 and CDK2 protein expressions, inhibited the interstitial phenotypic marker protein vimentin from expression, and promoted epithelial phenotypic marker protein E-cadherin for expression, indicating that down-regulating LINC00460 can inhibit the epithelial-mesenchymal transition of cervical cancer cells.

MiRNAs can mediate the occurrence and progression of several tumors and their roles in the prevention and treatment of cervical cancer have attracted extensive attention (Shen et al. 2020). It has been reported that various miRNAs covering miR-125, miR-204 and miR-187 are abnormally expressed in cervical cancer, as oncogenes or tumor suppressors (Li et al. 2019; Cao et al. 2020; Hung et al. 2020). Nevertheless, the effect of miR-380-5p on cervical cancer has been rarely exploited. MiR-380-5p was lowly expressed in cervical cancer cells, and its overexpression suppressed their proliferation and invasion but facilitated their apoptosis in this study. Furthermore, it also apparently inhibited the expressions of cyclin D1, CDK2 and vimentin and facilitated that of E-cadherin. Therefore, the overexpression of miR-380-5p can modulate the malignant biological activities of such cells while inhibiting the occurrence of epithelial-mesenchymal transition. Likewise, Han et al. (2019) reported that low miR-380-5p expression existed in cervical cancer tissues plus cells, and after transfection with overexpressed miR-380-5p, cervical cancer cells were markedly suppressed in terms of the proliferation and invasion. The mechanism may be associated with the down-regulated expressions of RHOA and downstream proteins.

LncRNAs exert regulatory effects mainly through binding and inhibiting the expressions of downstream miRNAs (Karagkouni et al. 2021). Highly expressed LINC00662 can affect miR-409-5p expression to repress the propagation and invasion of cervical cancer HCC94 cells, thus working as a tumor suppressor (Wang et al. 2019). The researchers herein uncovered the complementary binding sites between LINC00460 and miR-380-5p. In other words, miR-380-5p emerged as a target gene of LINC00460. Similarly, up-regulating

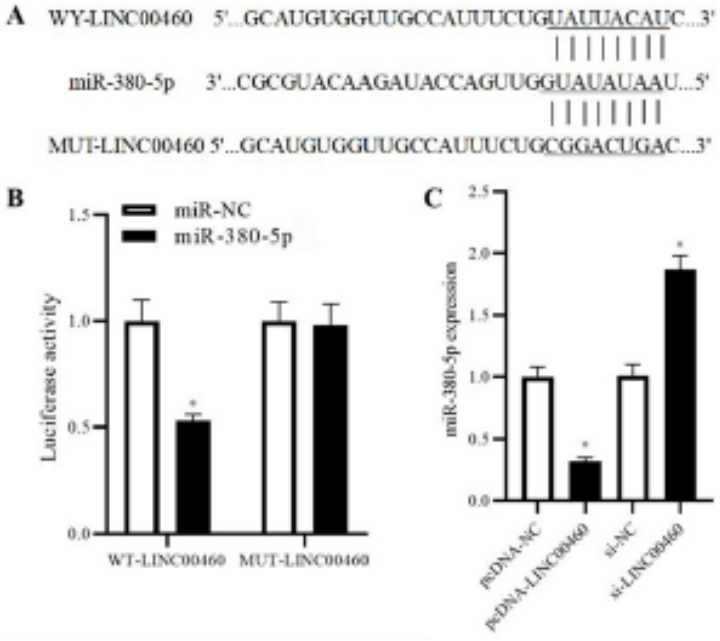

Fig. 4. Dual-luciferase reporter assay for verification of targeting relationship of LINC00460 with miR-380-5p. A: Base complementary binding sites between miR-380-5p and LINC00460 . B: Luciferase activity. C: Detection of miR-380-5p expression *via* RT-PCR

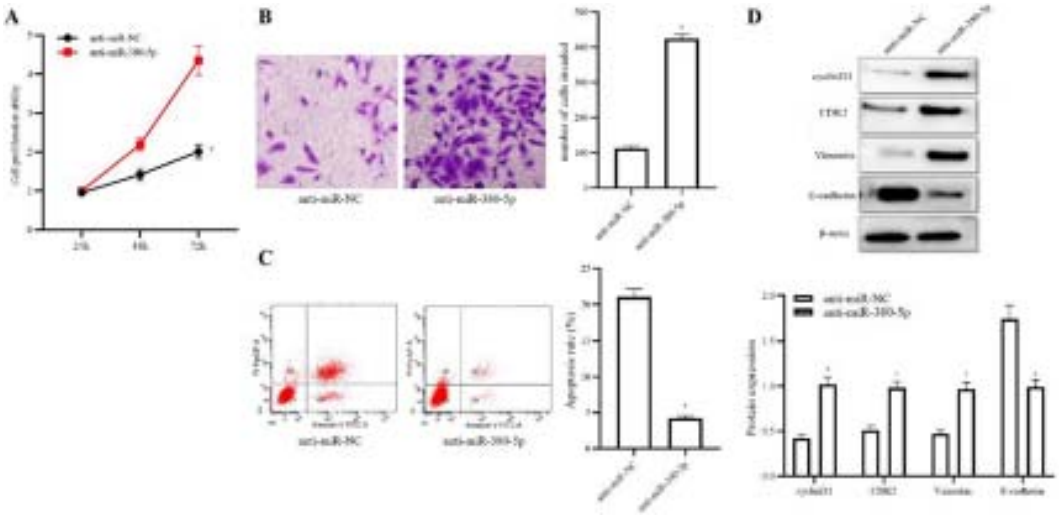

Fig. 5. Down-regulating miR-380-5p reversed the effects of down-regulating LINC00460 expression on C33A cell proliferation, invasion and apoptosis as well as its influences on protein expressions of cyclin D1, CDK2, vimentin and E-cadherin in cells. A: Cell proliferation ability. B: Cell invasion ability. C: Cell apoptosis ability. D: Protein expressions of cyclin D1, CDK2, vimentin and E-cadherin in cells. *P<0.05 *vs.* anti-miR-NC group

LINC00460 suppressed miR-380-5p expression, whereas decreasing LINC00460 promoted the expression of miR-380-5p, indicating a negative regulatory relationship between them. Furthermore, down-regulating miR-380-5p reversed the inhibitory role of down-regulating LINC00460 expression on the proliferation and invasion as well as the pro-apoptotic effect of cervical cancer cells, suggesting that down-regulating LINC00460 expression can regulate the cell proliferation, invasion and apoptosis abilities. The results are probably attributed to the elevated miR-380-5p expression (Cáceres-Durán et al. 2020).

CONCLUSION

In summary, down-regulating LINC00460 expression influences cervical cancer C33A cells from the aspect of inhibiting their multiplication and invasion while facilitating their apoptosis by facilitating the expression of miR-380-5p.

RECOMMENDATIONS

The preliminarily clarified mechanism may be applicable to treat cervical carcinoma in clinic, but in-depth animal and human studies are in need all the same.

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