

Paclitaxel inhibits the progression of cervical cancer by inhibiting autophagy via lncRNARP11-381N20.2

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Abstract. – **OBJECTIVE:** To observe the effect of paclitaxel on the autophagy of human cervical cancer cell lines by the expression regulation of lncRNARP11-381N20.2 as well as to explore the interaction and relationship between autophagy, proliferation, and apoptosis of cervical cancer cells.

MATERIALS AND METHODS: Genome-wide expression profiles of tumors and their susceptibility to drugs were downloaded through TCGA database to find differentially expressed lncRNA RP11-381N20.2 in chemosensitive sensitive and insensitive groups. Expression of RP11-381N20.2 in 60 cervical cancer tissues and 30 normal tissues was detected by qRT-PCR. The relationship between the expression of RP11-381N20.2 and the clinicopathological parameters of lung cancer was statistically analyzed. The recombinant plasmid pcDNA-RP11-381N20.2 and pcDNA-NC of RP11-381N20.2 were transfected into SiHa cells by lipofectamine, respectively. The autophagy and phenotypic effects were observed. Cell proliferation was determined by colony formation assay. Apoptosis was detected by flow cytometry. Western blot was conducted to detect expressions of autophagy-related proteins.

RESULTS: Genome-wide expression profiles of chemotherapy-sensitive and insensitive data in patients with cervical cancer in TCGA database were analyzed by edgeR package, results showed that the expression of lncRNA RP11-381N20.2 was significantly lower in the chemotherapy-insensitive group. qRT-PCR results showed that the expression of RP11-381N20.2 in cervical cancer was decreased, and the total survival time of patients was positively correlated with the expression of RP11-381N20.2. RP11-381N20.2 was associated with TNM (tumor node metastasis) staging and tumor size. Biological functions of SiHa cells showed that the expression of RP11-381N20.2 was negatively correlated with the treatment time and dose of paclitaxel. Colony formation assay showed that paclitaxel could inhibit the proliferation of cervical cancer cells in a dose-dependent manner. Flow cytome-

try showed that paclitaxel induced apoptosis of cervical cancer cells, which was more promoted after combination with RP11-381N20.2. Western blot results suggested that paclitaxel could induce autophagy in cervical cancer cells in a time- and dose-dependent manners. Paclitaxel combined with RP11-381N20.2 could significantly increase apoptosis of cervical cancer cells.

CONCLUSIONS: During the killing process of paclitaxel on cervical cancer SiHa cells, cell autophagy would affect the efficacy, after overexpression of RP11-381N20.2 in SiHa cells, autophagy induced by paclitaxel was inhibited, thereby enhancing the killing effect of paclitaxel on tumor cells.

Key Words:

Cervical cancer, Paclitaxel, lncRNA, RP11-381N20.2, Autophagy, Proliferation, Apoptosis.

Introduction

Cervical cancer is a common malignant tumor of the female reproductive system. With the general survey and public treatment of cervical cancer has been developed, the prevalence of cervical cancer has dropped significantly and the 5-year survival rate has also increased¹. However, as a preventable disease, the incidence of cervical cancer still remains the seventh in all cancers worldwide², the mortality rate ranks the fourth^{3,4}. It is worth noting that studies found that patients with cervical cancer presented a younger age of onset^{5,6}; therefore, the prevention and treatment of cervical cancer is urgent. It is an important issue in clinical research to further study the pathogenesis and look for new therapeutic targets of cervical cancer.

Paclitaxel has been well applied in treating cervical cancer, especially in neoadjuvant chemothe-

rapy for locally advanced or recurrent cervical cancer. Recently, neoadjuvant chemotherapy has become the common treatment for locally advanced cervical cancer, which has achieved good clinical efficacy, but at present, there is no unified chemotherapy regimen in clinical application. The application of paclitaxel in neoadjuvant chemotherapy for cervical cancer was still in the early stage of exploration. Although there are few reports and clinical data in this area, and the long-term follow-up results are lacked, short-term effects of paclitaxel on neoadjuvant chemotherapy is certain and the total effective rate is higher than other chemotherapy regimens. Additionally, its side effects are small, patients are easily tolerated, so there is a very promising application of paclitaxel on neoadjuvant chemotherapy for cervical cancer. However, the best regimen of neoadjuvant chemotherapy for cervical cancer remains to be further determined.

LncRNAs (long non-coding RNA) are a class of RNA molecules with a transcript of over 200 nt (nucleotide) in length and they do not encode proteins. Instead, they regulate the expressions of genes at various levels such as epigenetics, transcription, and transcription⁷⁻⁹. LncRNA is widely involved in the process of cell proliferation, differentiation, and apoptosis, and plays an important role in the pathogenesis of many diseases¹⁰. Abnormally expressed lncRNAs are proved to be closely related to the recurrence, metastasis, and prognosis of cervical cancer. Currently, no reports focused on lncRNA RP11-381N20.2.

Autophagy is a process that is highly conserved in eukaryotic cells, which functions as degrading and recycling the long-lived biological macromolecules and damaged organelles. It includes autophagy, micro-autophagy, and chaperone-mediated autophagy¹¹. Physiologically, the body removes senescent, degenerative and necrotic cells, and subcellular structures through autophagy to maintain homeostasis¹². Under disease conditions, the body's autophagy changes. Autophagy has been considered as an approach of cell death induced by death program, and recent studies have found that autophagy can be used as a defense mechanism to clear cytoplasmic damaged organelles and metabolites thus protecting cells¹³. Besides, the protein level of Atg7 and LC-3 cascade are symbols of autophagy. There is little research on the effect of autophagy on cervical cancer.

This study first investigated the effect of RP11-381N20.2 on the autophagy mediated by paclitaxel in the treatment of cervical cancer.

Materials and Methods

Expression Analysis of LncrnaRP11-381N20.2

The TCGA (The Cancer Genome Atlas) database was used to download the information about tumor genome-wide expression and its sensitivity to drugs. The differential lncRNAs in normal and tumor tissues, as well as the differential lncRNAs in chemosensitive and insensitive groups, were analyzed by edgeR package. qRT-PCR (quantitative real-time polymerase chain reaction) was performed to analyze RP11-381N20.2 expression in patients with cervical cancer. This study was approved by the Ethics Committee of Yantai Yuhuangding Hospital.

Cell Culture

The cervical cancer cell line SiHa was cultured in RP-MI1640 medium (Gibco, Rockville, MD, USA) supplemented with 10% fetal bovine serum (FBS, HyClone, South Logan, UT, USA) and penicillin/streptomycin (Thermo Fisher Scientific, Waltham, MA, USA), and maintained at 37°C and 5% CO₂ in a humidified atmosphere. Passage for about 4,5 generations, cells with good growth and strong proliferation were selected for further research. Cells were transfected with Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) at a cell density of about 80% in a 6-well plate, and 8 µL of Lipofectamine 2000 and 4 µg of pcDNA-RP11-381N20.2 dissolved in 500 µL of 1640 medium (Gibco, Rockville, MD, USA) was added to each well. The same amount of Lipofectamine 2000 and pcDNA-NC was added in each well from the experimental group; the medium was replaced 6 h after transfection.

Colony Formation Assay

Transfection time point was considered as the 0 h, the medium was replaced 6 h later, 3×10³ cells per well were seeded in 60-mm dishes for transfection with siRNA 24 h later and cultured at 37°C and 5% CO₂ in a humidified atmosphere. After cell culture for two weeks, the medium was replaced and cells were washed with phosphate buffered saline (PBS, BD Biosciences, San Jose, CA, USA) twice, colonies were fixed with methanol and stained by 0.2% crystal violet (Beyotime, Shanghai, China). Colonies were washed with PBS until the eluent was clear, images were taken for counting.

Cell Proliferation Assay by CCK8

Transfection time point was considered as the 0 h, medium was replaced 6 h later, 2×10^3 cells per well were seeded in 96-well plates, after cultured for 24, 48, 72, and 92 h, cell counting kit-8 (CCK-8, Dojindo, Kumamoto, Japan) assay was performed. At the time of detection, serum-free medium was replaced, 10 μ L of CCK8 was added in each well and incubated at 37°C and 5% CO₂ for 1 h. Absorbance values at 450 nm were detected by the microplate reader (Bio-Rad, Hercules, CA, USA). All experiments were performed in quadruplicate.

Flow Cytometric Analysis

The supernatant was aspirated to the centrifuge tube, the treated cells were trypsinized, and the cells were transferred to the appropriate centrifuge tube. They were centrifuged, and the supernatant was removed, washed twice with cold PBS, and resuspended with an AnnexinV binding solution (Bio-Rad, Hercules, CA, USA). 5 μ L of AnnexinV-FITC and 5 μ L of PI (Propidium Iodide) (Bio-Rad, Hercules, CA, USA) stain were added, protected from light for 15 min, and then diluted with 400 μ L of 1 $\times$ binding buffer. They were measured with the machine. Cells were then analyzed by flow cytometry (Partec AG, Arlesheim, Switzerland). Each experiment was in triplicate.

Western Blotting

The total protein was extracted from treated SiHa cells and the protein concentration was determined using the bicinchoninic acid (BCA, Abcam, Cambridge, MA, USA) kit. 40 μ g protein was used to perform gel electrophoresis. The proteins in the gel was transferred to polyvinyl-

dene fluoride (PVDF, Merck Millipore, Billerica, MA, USA) membrane using a wet film transfer apparatus, blocked with 5% skim milk for 1 h, and incubated with the primary antibodies (Cell Signaling Technology, Danvers, MA, USA) overnight at 4°C. Next, they were incubated with the corresponding secondary antibodies (Cell Signaling Technology, Danvers, MA, USA) for 1 h. The ECL (enhanced chemiluminescence) developer (Thermo Fisher Scientific, Waltham, MA, USA) was used for images.

Statistical Analysis

Statistic package for social science (SPSS) 22.0 software (IBM, Armonk, NY, USA) was used for statistical analysis, Kaplan-Meier survival curves for survival analysis. Flow cytometry results were analyzed using Win MDI software. Measurement data was analyzed by *t*-test and expressed as mean $\pm$ standard deviation ($\bar{x} \pm SD$). All *p*-values <0.05 were considered statistically significant; **p*<0.05, ***p*<0.01, and ****p*<0.001.

Results

Relationship Between the Expression of LncRNA RP11-381N20.2 in Cervical Cancer and Clinical Data

Genome-wide expression profiles of chemotherapy-sensitive and insensitive data in patients with cervical cancer in TCGA database were analyzed by edgeR package. The results showed that the expression of lncRNA RP11-381N20.2 was significantly lower in the chemotherapy-insensitive group (Figure 1A and 1B). Then, we

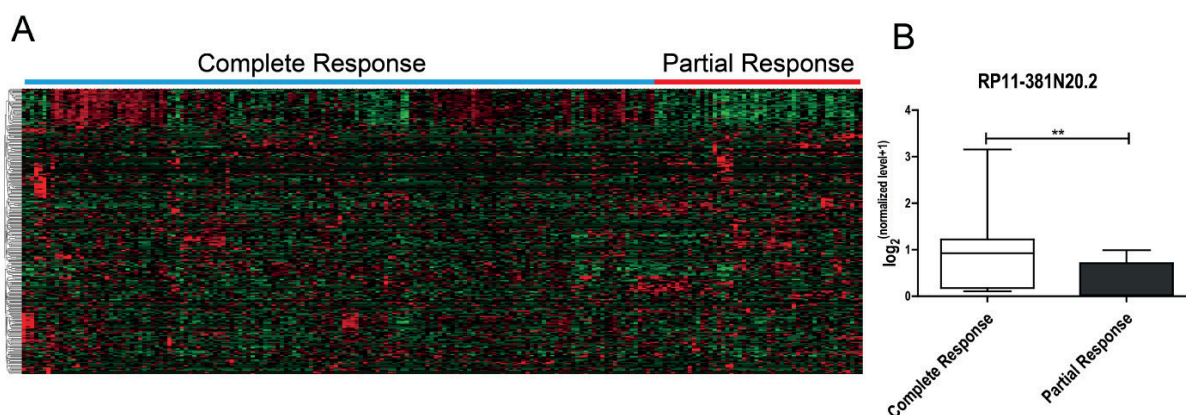


Figure 1. RP11-381N20.2 is highly expressed in chemotherapy-sensitive patients with cervical cancer. **A**, Heat map of differential expressed in chemosensitivity and insensitivity patients with cervical cancer. **B**, Expression of RP11-381N20.2 in the chemotherapy-insensitive group was lower than that in the chemotherapy-sensitive group.

selected 60 cervical cancer tissues and 30 normal tissues, qRT-PCR results revealed that the expression of lncRNA RP11-381N20.2 was lower in cervical cancer tissues (Figure 2A), and it was significantly lower in the chemotherapy-insensitive group than the chemotherapy-sensitive group (Figure 2B). The clinical data of the patients were analyzed and the results showed that the overall survival time of patients was positively correlated with the expression of RP11-381N20.2 (Figure 2C, $p = 0.0443$, HR = 0.4021). In addition, we found that the tumor staging of patients with lower RP11-381N20.2 expression was positively correlated with tumor volume (Table I). These results indicated that RP11-381N20.2 had an inhibitory effect on cervical cancer and was closely related to chemosensitivity.

Paclitaxel Inhibits the Proliferation of Cervical Cancer Cells While Promoting Apoptosis

To determine the effect of paclitaxel on the viability of cervical cancer cells, CCK8 and colony formation assays were carried out. The CCK8 assay showed that the proliferation of SiHa cells treated with different concentrations of paclitaxel was gradually decreased with the increasing dose of paclitaxel (Figure 2D). The colony formation assay showed that, with gradually increased doses of paclitaxel culturing with cervical cancer cells, the number of observed colonies was significantly decreased (Figure 2E). It suggested that paclitaxel was capable of inhibiting the prolifera-

tion of cervical cancer cells. Next, to further study the effect of paclitaxel on apoptosis of cervical cancer cells, we conducted the flow cytometry for detecting apoptosis. The results showed that paclitaxel induced apoptosis in a dose-dependent manner (Figure 2F).

Expression of RP11-381N20.2 Decreases After Paclitaxel Treatment

The expression of RP11-381N20.2 was found to be relatively higher in SiHa cells detected by qRT-PCR (Figure 2G), so we selected SiHa cells for overexpression experiments. After transfection of pcDNA-NC and pcDNA-RP11-381N20.2 into SiHa cells, the expression of RP11-381N20.2 was significantly increased, the transfection efficiency was proved to be good (Figure 2H). To explore the correlation between paclitaxel and RP11-381N20.2, SiHa cells were cultured in medium containing different doses of paclitaxel and we found that the expression of RP11-381N20.2 was reduced with the increased paclitaxel dose (Figure 2I). Similarly, in the medium containing the same dose of paclitaxel, the longer the culturing time, the lower the expression of RP11-381N20.2 (Figure 2J). These results indicated that RP11-381N20.2 can promote the inhibitory effect of paclitaxel on cervical cancer.

RP11-381N20.2 Promotes the Antitumor Effect of Paclitaxel

After transfection of RP11-381N20.2 into cells containing paclitaxel medium, apoptosis of cervi-

Table I. Correlation between the expression of RP11-381N20.2 and clinicopathological characteristics in patients with cervical cancer (n = 60).

Clinicopathologic features	Number of cases	RP11-381N20.2 expression		p-value
		Low (n=30)	High (n=30)	
Age (years)				0.1904
<50	35	20	15	
≥50	25	10	15	
Histology				0.4383
Squamous	31	14	17	
Other type	29	16	13	
Tumor size				0.0200*
<4 cm	29	10	19	
≥4 cm	31	20	11	
FIGO stage				0.0371*
I-II	26	9	17	
III-IV	34	21	13	
Lymph node metastasis				0.1079
No	22	14	8	
Yes	38	16	22	

* $p < 0.05$

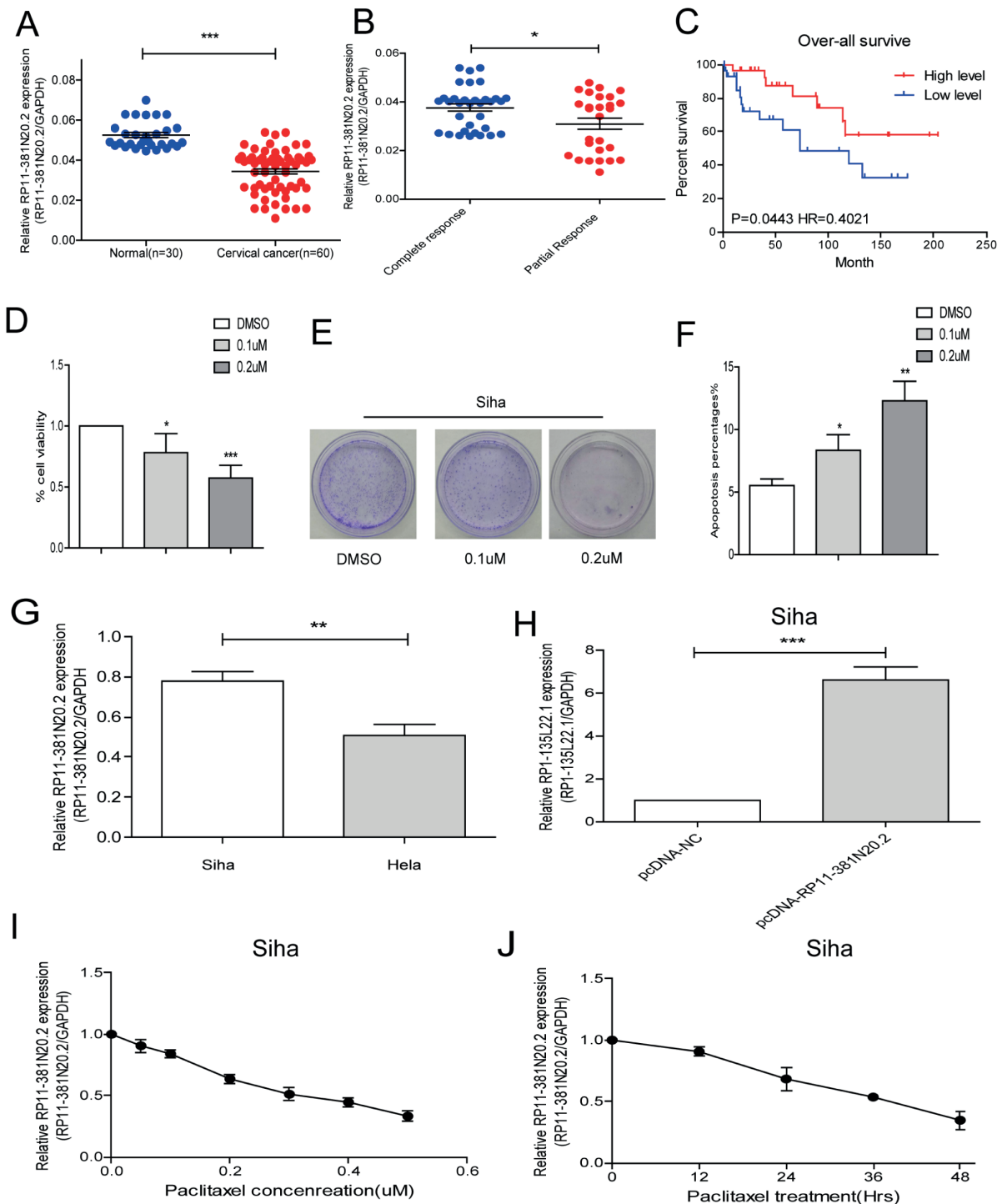


Figure 2. RP11-381N20.2 is lowly expressed in cervical cancer. **A**, RP11-381N20.2 expression in 60 cervical cancer tissues was significantly lower than that of 30 normal cervical tissues. **B**, Expression of RP11-381N20.2 in the chemotherapy-sensitive cervical cancer tissues was higher than that of chemotherapy-resistant cervical cancer. **C**, The overall survival of RP11-381N20.2 in high expression group was higher than that of low expression group. **D**, Cell proliferation after different doses of paclitaxel treatment by CCK8. **E**, Cell proliferation after different doses of paclitaxel treatment by colony formation assay. **F**, Cell apoptosis after different doses of paclitaxel treatment. **G**, RP11-381N20.2 expression in cancer cell lines (SiHa, Hela). **H**, Transfection of pcDNA-RP11-381N20.2 in SiHa. **I**, RP11-381N20.2 expression in SiHa cell line after treatment of different doses of paclitaxel. **J**, RP11-381N20.2 expression in the SiHa cell line after a different treatment time of paclitaxel.

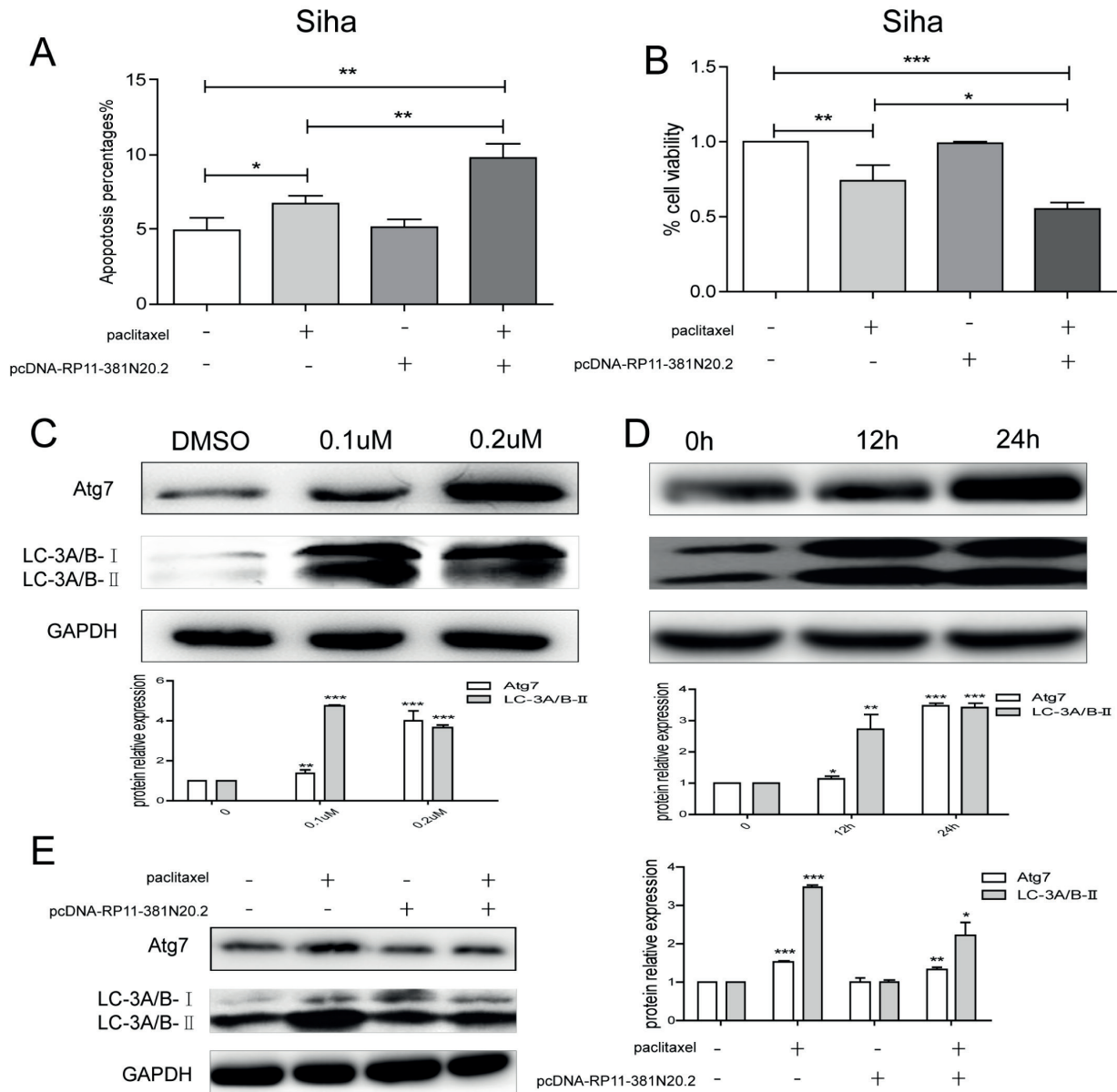


Figure 3. Paclitaxel induces autophagy in cervical cancer cells. High expression of RP11-381N20.2 inhibits autophagy in cervical cancer cells. **A**, Apoptosis of cervical cancer cell after RP11-381N20.2 transfection. **B**, Proliferation of cervical cancer cells after RP11-381N20.2 transfection. **C-D**, Western Blot showed that the protein expression of Atg7, LC3A/B-II and GAPDH after different treatment doses (left) and different treatment time of 10 μ M paclitaxel (right). **E**, Protein expressions of Atg7, LC3A/B-II, and GAPDH in SiHa cells under different treatments of paclitaxel (0.1 μ M) and overexpression of RP11-381N20.2 during cell culture.

cal cancer cells was significantly increased (Figure 3A, the parameter is a percentage). Meanwhile, we found that cells transfected with RP11-381N20.2 into cells culturing in paclitaxel medium also showed a significant reduction in cell proliferation (Figure 3B). These results suggested that the combination of paclitaxel with RP11-381N20.2 could inhibit tumor progression via promoting apoptosis and inhibiting proliferation of cervical cancer cells.

RP11-381N20.2 Inhibits Autophagy Induced by Paclitaxel

Western blot was conducted on cervical cancer SiHa cells treated with paclitaxel. The results suggested that expressions of LC3A/B-I, LC3A/B-II, and Atg7, key proteins that regulated autophagy in cervical cancer cells, were increased in a dose-dependent manner (Figure 3C and 3D). We also found that Atg7 and LC3A/B-II were

up-regulated after paclitaxel treatment, whilst Atg7 and LC3A/B-II were down-regulated after treatment with RP11-381N20.2 (Figure 3E), indicating that RP11-381N20.2 could inhibit paclitaxel-induced autophagy. These experimental results showed that paclitaxel induced autophagy in cervical cancer cells and thus reducing its antitumor effect. RP11-381N20.2 inhibited paclitaxel-induced autophagy.

Discussion

Cervical cancer is the most common gynecologic malignant tumor with an annual increase of about 500,000 cases, there have been high morbidity and mortality. Continuous high-risk human papillomavirus (HPV) infection is the major cause of cervical cancer¹⁴. However, the pathogenesis is not yet clear. Scholars^{15,16} found that macrophage played a dual role in tumor development, it not only promoted the death of cancer cells in the therapy but also enhanced the resistance of cancer cells to chemotherapy. Some studies^{17,18} have shown that overexpression of Beclin1 in cervical cancer cells Hela can promote autophagic cell death; the opposite result was found when silencing Beclin1. Therefore, to clarify the effect of autophagy on the development and treatment of cervical cancer is of great significance, and control of autophagy is expected to become a new target for the treatment of cervical cancer.

With the extensive application of bioinformatics and the comprehensive data sharing, TCGA database has been more and more used in medical research because of its complete data, large sample size, and full-grade prognosis information. Therefore, in this study, Genome-wide expression profiles of tumors and their susceptibility to drugs were downloaded through TCGA database to select the lowly expressed lncRNA RP11-381N20.2 in cervical cancer by the edgeR package to analyze lncRNA map of normal and tumor tissues. Furthermore, we found that RP11-381N20.2 was downregulated in cervical cancer tissues compared with that of normal cervical tissues, which was positively correlated with the overall survival rate. The expression of RP11-381N20.2 was confirmed to be correlated with tumor size and stage in patients with cervical cancer. It suggested that RP11-381N20.2 had an antitumor effect on cervical cancer, and can inhibit the formation of tumor resistance.

As we all know, there have been a large number of clinical data focused on paclitaxel in the

treatment of ovarian cancer, the combination chemotherapy with cisplatin or carboplatin regimen proved to have the best efficacy. However, the application of paclitaxel in the treatment of cervical cancer is still in an exploration period. Currently, studies¹⁹⁻²¹ have shown that paclitaxel induced autophagy in cancer therapy. This study further studied the effect of paclitaxel on the autophagy in the treatment of cervical cancer, and its interaction with RP11-381N20.2. We conducted the colony formation assay and flow cytometry. The results showed that paclitaxel had the ability to inhibit proliferation but increase the apoptosis of cervical cancer cells in a time- and dose-dependent manner. Western blot was utilized to study the correlation between paclitaxel and autophagy. The results suggested that paclitaxel could induce autophagy in cervical cancer cells in a time- and dose-dependent manners. Autophagy was significantly reduced after treatment with RP11-381N20.2. Further study found that paclitaxel combined with RP11-381N20.2 significantly increased apoptosis of cervical cancer cells. It implied that paclitaxel had significant antitumor potential in cervical cancer, a combination of which with RP11-381N20.2 could inhibit autophagy but promote apoptosis of cervical cancer cells.

Conclusions

In summary, paclitaxel has a profound antitumor effect on cervical cancer and can induce autophagy. Our study first investigated that paclitaxel could inhibit the autophagy of cervical cancer *via* RP11-381N20.2, thereby inhibiting its progress. Our findings provided important insight into the usage of anti-cancer agents in combination with autophagy inhibitors. It provides new references in the treatment of cervical cancer to help develop new drugs.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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