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REVIEW ARTICLE

A Novel Long Non-Coding RNA KMU15 Promotes Growth and Chemoresistance of Bladder Cancer

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SUMMARY

Background: **Chemotherapy constitutes one of the most important adjuvant treatments for bladder cancer. However, many patients usually develop chemoresistance during chemotherapy. At present, lncRNA has been confirmed not only to be involved in tumorigenesis and progression, but also in tumor chemoresistance. However, the relationship between lncRNAs and chemoresistance of bladder cancer have been rarely reported.**
Methods: **The novel lncRNA-KMU15 was screened by lncRNAs microarray and determination of IC50 in bladder cancer. The expression of KMU15 was evaluated by qRT-PCR. The correlation between KMU15 and clinicopathological parameters was analyzed from clinical cases. The effects of KMU15 on the biological behavior and chemoresistance were investigated by [^{3}H]-TdR incorporation assay and other experiments. The effects of KMU15 on the growth of xenograft tumors and the survival of nude mice under cisplatin were examined in a xenograft mouse model.**
Results: **We confirmed that KMU15 was expressed higher in bladder cancer tissues than paired control tissues. Moreover, the expression of KMU15 was significantly positively correlated with the grade, stage, metastasis, and recurrence of bladder cancer and was significantly negatively correlated with the prognosis. In addition, KMU15 knockdown could significantly inhibit bladder cell proliferation, adhesion, migration, and chemoresistance and promoted apoptosis. Knockdown of KMU15 inhibited the growth of xenografts in nude mice and significantly prolonged the survival of tumor-bearing mice under cisplatin.**
Conclusions: **The novel lncRNA KMU15, which is highly expressed in bladder cancer tissues, could promote the proliferation and progression and was closely related to the malignant degree of bladder cancer. It could also significantly enhance the chemoresistance of bladder cancer cells. Therefore, it was expected to be a new therapy target for bladder cancer and a potential prognosis biomarker for chemotherapy.**
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KEY WORDS

bladder cancer, long non-coding RNA, chemotherapy, chemoresistance

INTRODUCTION

Bladder cancer (BC) is one of the most common malignant tumors in the urinary system. According to the cancer statistics in 2018, there were about 549,000 new

cases of bladder cancer each year, and nearly 200,000 deaths [1]. Although surgical resection and other systemic treatments for bladder cancer have been developed [2,3], many patients develop drug resistance during chemotherapy, so the treatment efficacy is greatly limited [4]. Therefore, to explore innovative mechanisms of chemoresistance in bladder cancer and, at the same time, to find new prognostic molecular biomarkers and potential therapeutic targets has become an urgent need [5].

Long non-coding RNA (lncRNA) were previously considered to be incapable of exerting biological functions [6]. However, recent studies have shown that lncRNA plays important roles in gene regulation and disease progression [7]. Furthermore, it has been demonstrated to express abnormally and have important biological significance for tumor cell proliferation, apoptosis, invasion, metastasis, and drug resistance [8]. For example, ARLNC1, PCA3, MALAT1, HOTAIR, and NEAT1 are highly expressed in prostate cancer and participate in the tumorigenesis, development, and metastasis of prostate cancer [9,10]. GAS5, H19, and PCAT29 have the effect of inhibiting tumor cell growth and migration [9]. Up to now, only a small number of lncRNAs related to bladder cancer have been previously explored, and lncRNAs involved in the regulation of chemoresistance of bladder cancer are rarely reported. Therefore, it is very important to study the relationship between lncRNAs and the chemoresistance of bladder cancer.

In this study, we analyzed lncRNA microarrays of bladder cancer specimens and screened out lncRNA KMU-15, which is closely related to the chemoresistance of bladder cancer. Then we confirmed the biological functions and clinical value of the novel lncRNA KMU15 and its role in the growth of bladder cancer and chemoresistance. lncRNA KMU15 might become a new biomarker for the prognosis of bladder cancer as well as novel therapeutic targets.

MATERIALS AND METHODS

Patients and tissue sample collection

This study was conducted with the approval of the Ethics Committee at the Second Affiliated Hospital of Kunming Medical University, and each patient signed an informed consent before entering the study. All procedures during the study were carried out in accordance with the 1964 Helsinki Declaration and its later amendments and ethical standards. Forty bladder cancer tissue samples were collected for this study from patients who underwent radical cystectomy or transurethral resection of bladder tumors at the Second Affiliated Hospital of Kunming Medical University from January 2014 to January 2018, and data regarding the clinical parameters such as tumor grading and staging was collected retrospectively. We also collected paracancerous tissues from these patients, but for 10 cases who underwent transurethral resection of bladder tumors no paracancerous tissues were collected. All tissue samples were confirmed by pathology after operation. Fresh bladder cancer tissues and their corresponding matched adjacent non-tumor tissues were collected and stored in liquid nitrogen immediately, then transferred to a -80°C freezer. Then, we followed the survival of 220 bladder cancer patients with high or low expression of lncRNA KMU-15 (110 cases/group) from the Second Affiliated Hospital of Kunming Medical University, People's Hospital of Yuxi, and Institute of Biophysics of Chinese Academy of Sciences and used death as the primary outcome. None of the patients had received radiotherapy, chemotherapy or other adjuvant therapy before surgery.

Cell culture

The chemotherapeutic drugs DDP (cisplatin) and DOC (Docetaxel) used in the present study were purchased from TargetMol (Boston, MA, USA). The bladder cancer cell lines T24, EJ, and 5637 were obtained from the cell bank of the Institute of Biophysics of the Chinese Academy of Sciences. Cells were cultured in Dulbecco's Modified Eagle Medium (DMEM, Invitrogen, USA) containing 10% fetal bovine serum (FBS, Gibco, USA), 100 IU/mL penicillin, and 100 mg/mL streptomycin in humidified 5% CO_2 atmosphere at 37°C. Fresh bladder cancer tissues were washed with PBS and added with DMEM. The tissues were cut into pieces of about 1 mm^3 and washed with phosphate buffered solution (PBS). Then, 5 mL of collagenase and penicillin-streptomycin solution was added and placed in a 37°C constant temperature shaker (150 r/minute). When the tissues were flocculated, they were repeatedly washed and centrifuged (1,300 r/minute, 5 minutes/per cycle) and the supernatant was discarded. Complete medium containing DMEM and penicillin-streptomycin solution were added, and the cells were cultured in a cell culture incubator.

Total RNA extraction and quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was extracted by TRIzol reagent (Invitrogen, USA). Quantitative real-time PCR reactions were performed on an ABI 7300 PCR system (Life Technology, USA) following treatment with SuperScript™ III Platinum™ SYBR™ Green One-Step qRT-PCR Kit (Invitrogen, USA) according to the manufacturer's instructions. The primer sequences for lncRNA KMU15 were as follows:

lncRNA KMU15 forward,
5′-CCCCAGTCACTGTTGAGGTC-3′;
reverse,
5′-AGCTTCGAAAGCGTTGAGGA-3'.

GAPDH was used as an internal control for the expression analysis of lnc-KMU15. The primer sequences for GAPDH were as follows:

forward primer,
5'-GCACCGTCAAGGCTGAGAAC-3';
reverse primer,

5'- TGGTGAAGACGCCAGTGGA-3'.
The PCR conditions were as follows: pre-denaturation at 95°C for 5 minutes; 95°C for 15 seconds, 60°C for 30 seconds, and 40°C for 1 minute, for a total of 40 cycles. Real-time quantitative analysis of the expression of target genes was conducted using the $2^{-\Delta\Delta Ct}$ method. Each experiment was performed in triplicate.

Construction and transfection of lentiviral vector
The lentiviral vector interference sequence of the lncRNA KMU15 gene was designed from http://rnaidesigner.thermofisher.com/rnaiexpress/.
We selected the three highest-ranking interference sequences and synthesized the primers (Table 1). The constructed lentiviral vector was co-cultured with Lipofectamine 3000 Reagent (Invitrogen, USA) in Opti-MEM medium (Gibco, USA) to form a DNA-lipofectamine 3000 complex. The medium was then changed to complete medium containing 10% FBS and high sugar DMEM. After 48 hours, the supernatant was collected for transfection. T24 or 5637 cells were plated in a six-well plate, and then the supernatant was added into the six-well plate. After incubation for 48 hours, RNA was extracted after fluorescent cell sorting.

Cell proliferation assay
Cell proliferation was analyzed using the [^{3}H]-Thymidine ([^{3}H]-TdR) incorporation assay. The treated cells were suspended in Roswell Park Memorial Institute (RPMI)-1640 complete medium (Gibco, USA) containing 10% FBS (1 x 10^5 cells/mL). Then, 100 µL of complete medium and 0.1 mL of cell suspension were added to each well of a 96-well plate. After 24 hours, 10 µL of [^{3}H]-TdR (Solarbio, China) was added to each well. After incubation for 4 hours, 5 mL of liquid scintillation cocktail (BOC, USA) was added, and the amount of [^{3}H]-TdR incorporation was analyzed on Triathler liquid scintillation counter (BIOSCAN, USA).

Apoptosis analysis
Apoptosis was analyzed by the Annexin V-FITC/PI Apoptosis Detection Kit (Solarbio, China). Primary cells of bladder cancer treated with DDP were collected by trypsin (5 x 10^5 cells/mL). Cells were resuspended in 500 µL 1 x Binding Buffer. Then 5 µL Annexin V-FITC and 10 µL of PI were added into each tube and incubated at room temperature for 5 minutes in the dark. Apoptosis was analyzed using a flow cytometer (BD Biosciences, USA).

Cell adhesion assay
Cells were seeded in 96-well plates (5 x 10^3 cells/well), which was pre-plated with fibronectin (FN, Sigma, USA). After incubating for 1 hour, the unadhered cells were washed away with PBS. Each well was fixed with 100 µL methanol for 15 minutes, followed by 100 µL Giemsa staining for 15 minutes. The stain was washed and the number of adherent cells was counted under an inverted microscope.

Wound healing assay
Cell migration ability was analyzed using the wound healing assay. Cells were seeded in 6-well plate (5 x 10^5 cells/well), incubated for 24 hours until the cells were covered and then quickly scratched with a sterile pipette tip. The cells were washed 3 times with PBS, and then the serum-free medium was added and cultured in an incubator. After the scratches were formed, the blank area in the scratches was measured to evaluate the migration ability of the cells.

Clone formation assay
Cells were incubated for 48 hours after transfection and seeded in 6-well plates (100 cells/well). After 2 weeks of incubation, the cells were washed twice with PBS, and 5 mL of 4% paraformaldehyde was added to fix the cells for 15 minutes. The fixative was removed and the cells then stained with Giemsa for 10 - 30 minutes. The number of colonies was counted under a microscope.

Xenograft mouse model
The animal experiments in the present study were approved by the Institutional Animal Care and Use Committee of Kunming Medical University (Kunming China). All of these 5-week-old female BALB/C nude mice used in the experiment were obtained from the Institute of Biophysics of the Chinese Academy of Sciences (Beijing, China). Forty nude mice were randomly divided into 4 groups (20/group). The shlncRNA-KMU15-1 vector or the empty vector shCtrl were transfected into T24 cells and 5637 cells, respectively. Then the cell suspensions (5 x 10^6 cells) were subcutaneously injected into the right flanks of nude mice. Tumor volumes of the nude mouse were assessed once a week. Xenograft tumor mice that survived after 30 days were sacrificed. Tumor weights were measured after resection of the tumors. Another 40 nude mice were randomly divided into 4 groups. The xenograft model was constructed according to the above steps. After the tumor was formed, it was routinely raised and treated with DDP (5 mg/kg) to evaluate the survival of the mice.

Statistical methods
All experiments were repeated three times. The data are expressed as the mean ± standard deviation (M ± SD). Analysis of variance (ANOVA) followed by Bonferroni's post-test was performed for multiple comparisons. Kaplan-Meier methods and log-rank tests were performed for survival analyses of both patients and mice. A p-value less than 0.05 was considered to indicate a significant difference. Data analysis and processing were performed using SPSS 20.0 software (IBM SPSS, Armonk, NY, USA).

RESULTS

lncRNA KMU15 was up-regulated in bladder cancer tissues and was closely related to chemoresistance

We first sequenced and analyzed the lncRNA microarray of bladder cancer specimens, and screened out 10 lncRNAs with the most significant overexpression from the expression profiles. The expression of these lncRNAs was knocked down with different siRNAs in bladder cancer cell line T24. DDP was added to detect the half maximal inhibitory concentration (IC50) of T24 cells. The results showed that the IC50 was significantly reduced in T24 cells after knockdown of the third lncRNA compared to the other 9 lncRNAs (Figure 1A), which indicated that the expression of lncRNA KMU15 may be closely related to DDP resistance in bladder cancer. We used the RNAfold web server software to analyze the novel lncRNA sequence, and constructed the spatial structure pattern of the lncRNA (Figure 1B), and named it lncRNA KMU15. Next, we examined the expression of lncRNA KMU15 in the cancer tissues and the paired adjacent non-tumor tissues of 30 patients with bladder cancer. The results showed that the expression of lncRNA KMU15 was significantly increased in 26 cases of bladder cancer tissues (Figure 1C). The results suggested that the expression of lncRNA KMU15 had significant positive correlations with the occurrence of bladder cancer.

High expression of lncRNA KMU15 is a potential unfavorable prognostic factor for bladder cancer

To investigate the association between the expression of lncRNA KMU15 and various clinicopathological parameters of bladder cancer, we collected 40 bladder cancer tissues with different grades and stages. The pathological results showed that there were 20 cases in the G1 grade, 12 cases in the G2 grade, and 8 cases in the G3 grades. Among them, 26 cases were Ta-T1 stage and 14 cases were T2-T4 stage. The expression of lncRNA KMU15 in bladder cancer tissues was detected by qRT-PCR. The results showed that the higher the grade of bladder cancer, the higher the expression of lncRNA KMU15 (Figure 2A). Moreover, the expression of lncRNA KMU15 in tumor tissues of patients with T2-T4 stage was significantly higher than that of patients with Ta-T1 stage (Figure 2B). We also followed up the bladder cancer patients with high and low expression of lncRNA KMU15 (110 cases/group). The results showed that the survival rate of patients with high expression of lncRNA KMU15 were significantly lower than that of patients with low expression of lncRNA KMU15 (Figure 2C). In addition, we compared the expression levels of lncRNA KMU15 in two primary bladder cancer specimens and recurrent tumor specimens. The results showed that the expression level of lncRNA KMU15 was significantly elevated in recurrent bladder cancer tumor tissues (Figure 2D). In addition, we also found that the expression of lncRNA KMU15 was significantly increased in bladder cancer tissues after lymph node metastasis (Figure 2E).

Knockdown of lncRNA KMU15 suppresses bladder cancer cell growth and enhances DDP chemosensitivity *in vitro*

The lentiviral vectors were transfected into bladder cancer cell lines T24 and 5637. The expression of lncRNA KMU15 were detected by qRT-PCR to screen for bladder cancer cell lines with stably low expression of lncRNA KMU15. The results showed that the expression of lncRNA KMU15 was significantly down-regulated in T24 and 5637 cells in the shlncRNA-KMU15 transfected group; shlncRNA-KMU15-1 has the strongest inhibitory effect on lncRNA KMU15 expression (Figure 3A). Subsequently, we extracted and cultured primary tumor cells from 6 patients with bladder cancer, and knocked down the expression of lncRNA KMU15 using shlncRNA-KMU15-1. We found that the IC50 of DDP in 6 groups of bladder cancer cells was significantly decreased after lncRNA KMU15 knockdown, and the chemosensitivity of bladder cancer cells to DDP was significantly enhanced (Figure 3B). Next, we selected T24 and 5637 cells with stably low expression of lncRNA KMU15 after being transfected with shlncRNA-KMU15-1 and analyzed the cell proliferation ability by [^{3}H]-TdR incorporation assay. The results indicated that the proliferation of both bladder cancer cells was significantly inhibited after lncRNA KMU15 knockdown (Figure 3C). In addition, we collected 2 clinical specimens of bladder cancer. The primary cells were cultured and transfected with shlncRNA-KMU15-1. The results of apoptosis analysis showed that the apoptosis rate of tumor cells was significantly increased after DDP treatment. After lncRNA KMU15 knockdown, the apoptotic rate of tumor cells was significantly increased under DDP treatment (Figure 3D). Finally, we knocked down the expression of lncRNA KMU15 in bladder cancer cell lines and evaluated the biological functions including adhesion, migration, and colony formation abilities of tumor cells after silencing lncRNA KMU15. The results showed that the biological functions of adhesion (Figure 3E), migration (Figure 3F), and clone formation (Figure 3G) of 3 bladder cancer cell lines were significantly inhibited after lncRNA KMU15 knockdown ($p < 0.01$).

Knockdown of lncRNA KMU15 inhibits bladder cancer growth *in vivo* and improves survival rate of xenograft tumor mice treated with DDP

Cells with stable low expression of lncRNA KMU15 were injected subcutaneously into nude mice, and the volume of xenograft tumors was measured periodically. The results showed that the volume and weight of xenograft tumors formed by the two bladder cancer cells were significantly reduced after lncRNA KMU15 knockdown (Figure 4A, 4B, 4C, and 4D). Finally, bladder cancer cell lines T24 and 5637 transfected with shlncRNA-KMU15-1 or shCtrl were injected subcuta-

Table 1. Interference sequence of lncRNA KMU15.

	Sequence (5` to 3`)
shlncKMU15-1	**TGCCAGAGCTTCTGCTGCCA**
shlncKMU15-2	**CCAGCCCTACTAAATTCAAC**
shlncKMU15-3	**TGGAAATGGCTTTGGAGCCC**

neously into nude mice. DDP was injected periodically after tumor formation and the survival of the mice was monitored. The results showed that the chemosensitivity of xenograft tumor to DDP was significantly enhanced after knockdown of lncRNA KMU15. Mice survival rates under DDP treatment was significantly improved (Figure 4E, 4F).

DISCUSSION

Bladder cancer patients who develop resistance to chemotherapy have limited therapeutic options at present. Therefore, it is necessary to identify novel targets for prevention and therapy of chemoresistant bladder cancer [11]. In this study, we found a novel lncRNA KMU-15 closely associated with chemoresistance in bladder cancer. Besides, we verified that lncRNA KMU15 is overexpressed in clinical specimens.

Chemotherapy might have unrealized clinical benefits for bladder cancer patients who are masked due to a lack of biomarkers in the selection of drug-responsive patients, and it is difficult to predict the clinical outcomes of chemotherapy in patients with bladder cancer [12]. Here, we showed that reduced expression of lncRNA KMU15 significantly inhibits chemoresistance in bladder cancer cells. The expression of lncRNA KMU-15 was significantly increased in bladder cancer tissues with recurrence and lymph node metastasis. In addition, we first found that lncRNA KMU15 was significantly positively correlated with the grade and stage of bladder cancer, and was negatively correlated with the survival prognosis. Therefore, lncRNA KMU15 has a predictive potential in chemoresistance and tumor progression of bladder cancer patients. It is advisable to evaluate lncRNA KMU15 expression in bladder cancer to identify patients who might benefit from chemotherapy or might be progressed.

Numerous studies have shown that aberrantly expressed lncRNAs can play an important role in tumorigenesis and metastasis [13,14]. We first studied the biological function of lncRNA KMU15 in bladder cancer. The present study revealed that the proliferation, adhesion, and migration ability of bladder cancer cells were significantly inhibited after knocking down the expression of lncRNA KMU15, and this situation was also confirmed *in vivo*. Knockdown of lncRNA KMU15 significantly inhibited the growth of xenograft tumors in nude mice.

Studies have also confirmed that the effect of lncRNA on tumor chemoresistance [15,16]. For example, lncRNA TUG1 could promoted cell growth and chemoresistance of small cell lung cancer [17]. In addition, recent studies have shown that many overexpressed lncRNAs such as lncRNA-HOTAIR [18], lncRNA-MALAT1 [19], lncRNA-CRNDE [20], and lncRNA-XIST [21] could enhance the resistance of colorectal cancer to different chemotherapeutic drugs. Therefore, lncRNAs may be the key to deciphering the intrinsic or acquired resistance mechanisms of bladder cancer. From the above studies, we found that the expression of lncRNA KMU15 might be correlated with the chemoresistance of bladder cancer cells. Furthermore, we found that knockdown of lncRNA KMU15 significantly increased DDP-induced apoptosis in bladder cancer cells. The resistance of bladder cancer cells to DDP was also significantly reduced after knocking down lncRNA KMU15. In addition, interference with the expression of lncRNA KMU15 significantly prolonged the survival of tumor-bearing mice under DDP treatment. Therefore, our results suggest that inhibition of lncRNA KMU15 expression could significantly enhance the chemosensitivity of bladder cancer cells and improve the prognosis. In addition, unlike the lncRNA screening methods described in previous studies [22,23], the screening of lncRNA KMU15 in this study was combined with the detection of drug resistance in bladder cancer cells. Furthermore, lncRNA KMU15 has not been reported in bladder cancer or other types of tumors in the past. This study explored the clinical value and biological function of lncRNA KMU15 for the first time. Our study has been validated in animals, cell lines, and clinical samples, and the results are more convincing. Therefore, the therapeutic strategy targeting lncRNA KMU15 might provide new directions for improving the efficacy of chemotherapy for bladder cancer. However, the mechanism of how lncRNA KMU15 affects chemoresistance in bladder cancer cells is unclear, so we will further explore the molecular mechanism of lncRNA KMU15 to enhance chemoresistance in bladder cancer *in vitro* and *in vivo*.

The sample size of this study is relatively small. Hence, we will take a larger sample size in further studies to validate its clinical value.

CONCLUSION

Our study describes, for the first time, the expression and clinical values of lncRNA KMU15 in bladder cancer. Notably, overexpression of lncRNA KMU15 might be associated with acquisition of a drug-resistant, aggressive, and poor prognostic phenotype of bladder cancer. Knockdown of lncRNA KMU15 inhibits the growth of bladder cancer cells, and significantly reduces the resistance of bladder cancer cells to DDP *in vitro* and *in vivo*. Therefore, our results suggest that the lnc-

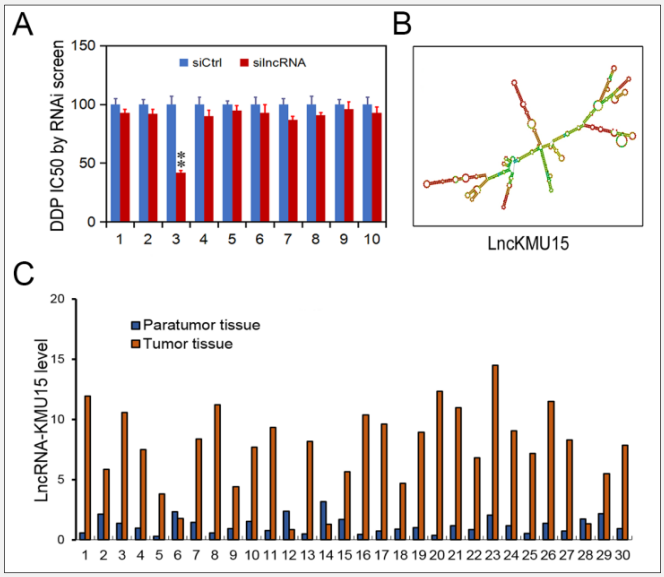

Figure 1. lncRNA KMU15 was up-regulated in bladder cancer tissues and was closely related to chemoresistance.

A. Determination of IC50 detected the resistance of bladder cancer cells to DDP after knockdown of 10 lncRNAs (screened by microarray), and the resistance of DDP decreased after knockdown of the third lncRNA (lncRNA KMU15). ** p < 0.01; B. The spatial structure pattern diagram of lncRNA KMU15; C. qRT-PCR confirmed the expression of lncRNA KMU15 in bladder cancer tissues.

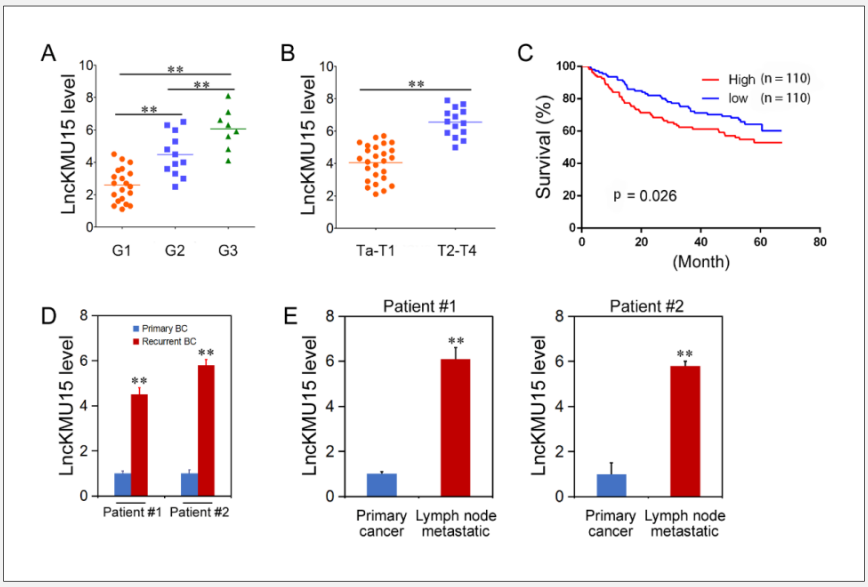

Figure 2. The expression of lncRNA KMU15 is closely related to various clinicopathological parameters of bladder cancer.

A. The expression of lncRNA KMU15 is higher in high grade bladder cancer tissues. ** p < 0.01; B. The expression of lncRNA KMU15 is higher in high stage bladder cancer tissues. ** p < 0.01; C. The survival rate of bladder cancer patients with lncRNA KMU15 low expression group was higher than that of lncRNA KMU15 overexpression group (p = 0.026); D. The expression level of lncRNA KMU15 in recurrent bladder cancer tumor tissues is significantly increased. ** p < 0.01; E. The expression level of lncRNA KMU15 in tumor tissues of patients with lymph node metastasis is significantly increased. ** p < 0.01.

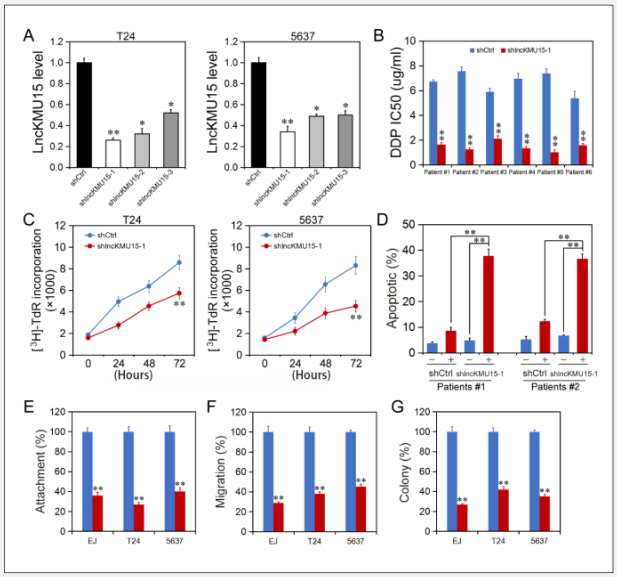

Figure 3. Knockdown of lncRNA KMU15 suppressed bladder cancer cell growth and enhances DDP chemosensitivity *in vitro*.

A. Expression of lncRNA KMU15 in T24 and 5637 bladder cancer cell lines after transfection of different shlncKMU15 vectors. * p < 0.05, ** p < 0.01; B. Inhibition of lncRNA KMU15 reduces chemoresistance of DDP in primary bladder cancer cells. ** p < 0.01; C. [^{3}H]-TdR incorporation assay was used to detect the proliferative capacity of T24 and 5637 bladder cancer cells after inhibition of lncRNA KMU15. ** p < 0.01; D. Annexin-FITC/PI assay detects DDP-induced apoptosis in primary bladder cancer cells after inhibition of lncRNA KMU15. ** p < 0.01; E. The cell adhesion assay detects the adhesion of EJ, T24, and 5637 bladder cancer cells after inhibition of lncRNA KMU15. ** p < 0.01; F. Wound healing assay detects migration of EJ, T24, and 5637 bladder cancer cells after inhibition of lncRNA KMU15. ** p < 0.01; G. Colony formation assays detect colony forming ability of EJ, T24, and 5637 bladder cancer cells following inhibition of lncRNA KMU15. ** p < 0.01.

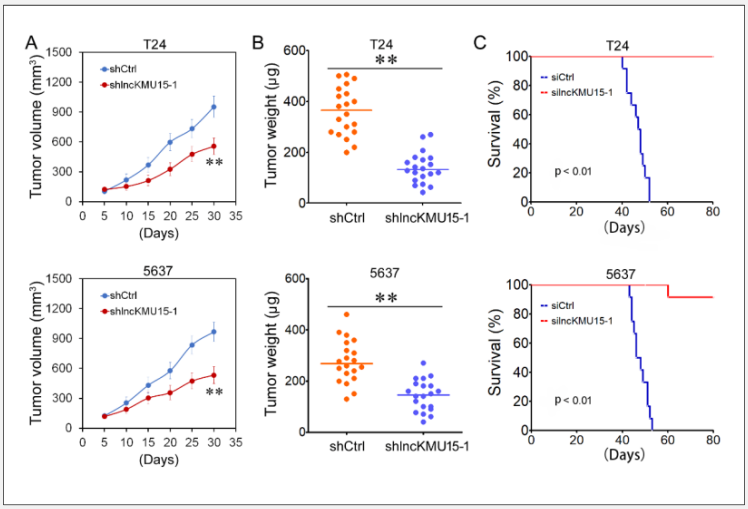

Figure 4. Knockdown of lncRNA KMU15 inhibits bladder cancer growth *in vivo* and improves survival rate of xenograft tumor mice treated with DDP.

A. Tumor volume reduction in T24 and 5637 bladder cancer xenograft mice after inhibition of lncRNA KMU15. ** p < 0.01; B. Tumor weight loss in T24 and 5637 bladder cancer xenograft mice after inhibition of lncRNA KMU15. ** p < 0.01; C. The survival rate of T24 and 5637 bladder cancer xenografts was increased after inhibition of lncRNA KMU15. ** p < 0.01.

RNA KMU15 could be a new therapeutic target or a prognostic biomarker for bladder cancer.

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Declaration of Interest:
The authors declare no conflict of interest.

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