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Long non-coding RNA LINP1 promotes the malignant progression of prostate cancer by regulating p53

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Abstract. – OBJECTIVE: We aim to investigate the expression of long non-coding RNA-LINP1 (lncRNA LINP1) in prostate cancer (PCa) and its potential mechanism.

PATIENTS AND METHODS: The expression of lncRNA LINP1 in 74 pairs of PCa and normal tissues were detected by quantitative Real-time polymerase chain reaction (qRT-PC the relationship between its expression a pathological features and prognosis of PC also analyzed. The expression of lncRNA L in the PCa cell line was verified by qRT-P Knockdown of LINP1 was constr d by tra fection of small interfering RN) in tw PCa cell lines (Lncap and P logica function of LINP1 was eva d by c ounting kit-8 (CCK-8) assay, colo at gration and invasion assay , the potential mech of L as explored by Western blot RT-PCR.

RESULTS: R results sh d higher expression PCa than th of normal tissues. re PCa patients with a lower e sion o those with higher expre had a hig r stage, lymphatic stasis and dista etastasis rate, and l over survival rate. Proliferation, inva- an tastasis in cells transfected with ere re kably decreased than those t ed wi gative control (si-NC). Moreove ions of the key proteins in the p53 s athway, including p53, PTEN, Akt and CD ere remarkably decreased in cells after knockdown of LINP1. In addition, a negrrelation between LINP1 and p53 was med by rescue experiments.

CONCLUSIONS: Up-regulated LINP1 in PCa was correlated with a higher PCa stage, lymphatic metastasis, distant metastasis, and worse prognosis. Furthermore, LINP1 could promote the proliferative, migratory and invasive abilities of PCa by regulating the p53-signaling pathway.

Key Wor
Lo ding RNA, LINP1, 53, Prostate cancer.

oduction

Prosta er (PCa) is one of the most common nant tumors of the urinary system. PCa is the of cancer death in the United States, fol- ung cancer and colorectal cancer[1]. In China, e incidence of PCa has been rising year by year, which has become one of the most severe tumors that seriously affects the life and health of men[2]. The development and progression of PCa are comprehensively regulated by multiple factors, including the environmental, dietetic and genetic factors[3,4]. So far, unclarified pathogenesis of PCa makes difficult the diagnosis and treatment[5]. The detection of serum prostate specific antigen (PSA) is a common clinical method for the diagnosis of PCa, but unfortunately its specificity is low[6]. Although the prostate biopsy is the gold standard for the diagnosis of PCa, its invasive trauma restrains its application in PCa patients[7]. Therefore, it is of great significance to elucidate the underlying mechanism of PCa for further prediction and diagnosis of PCa patients.

With the rapid development of molecular biology and gene diagnosis technology, the long-term interactions between genetic and environmental factors are considered to result in irreversible genetic changes and malignant transformation of cells. It is mainly characterized by the activated oncogenes and the inactivated tumor suppressor genes[8]. These changes eventually lead to the dysfunctional signal transduction involving cell proliferation, apoptosis and differentiation[9].

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So far, researchers[10] have found that non-coding RNAs (nc-RNAs) were greatly involved in the development and progression of tumors. It is well recognized now that 98% of the human genomes were non-encoding RNAs, of which long non-encoding RNAs (lncRNA) were a class of RNAs with more than 200 nucleotide (nt) in length. It was well recognized in modulating gene expressions at the transcriptional, post-transcriptional and epigenetic level. It was also widely involved in the physiological and pathological processes of organisms[11, 12]. Recent studies have shown that the expression of lncRNA was unbalanced in multiple tumors, which showed certain tissue specificity. Moreover, lncRNA might promote the proliferative and invasive abilities of tumor cells through a variety of mechanisms, thereby exerting an essential regulatory role in the tumor development[13]. Differentially expressed lncRNAs have been found in many tumor tissues, such as PCa, hepatocellular carcinoma, breast cancer and non-small cell lung cancer[14]. However, the molecular mechanism of lncRNA in tumors was still unclear, especially in PCa. In general, lncRNAs might be involved in multiple aspects of gene regulation, including proliferation, cell cycle, apop differentiation, metastasis and other biologica cesses[15,16]. Several researches[17,18] have demonst that lncRNA PCAT1 and lncRNA PCAT7 co promote PCa, whereas lncRNA p2 d lncRN GAS5 might inhibit the devel PCa[19,2 Additionally, it was also i ed ncRNA was involved in the Wnt y, F activation, TGF-β inhibitio ithelial mesenchyma sitio pathogenesis of PCa[21], Howeve her supp tudies are still needed for stration. In th nt study, the expressi in 74 pairs of tumor and paracancer tissu Ca was detected. We also e ed the biolo fect of LINP1of PCa cell evious investigati have suggested that l cou hibit the differentiation and metas- of r cells, which eventually controlled elopm We aimed to investigate the ro NP1 e prognosis and progression of in P

Patients and Methods

Patients and PCa Samples

74 pairs of tumor and paracancerous tissues surgically resected from PCa patients were collected. Based on the 8th Edition of UICC/AJCC Prostate Cancer TNM Staging Standard, all the enrolled patients were pathologically diagnosed as PCa. All PCa patients did not receive any preoperative radiotherapy or chemotherapy. The experiment was approved by the Ethical Co mittee, and patients signed the consent infor

Cell Lines and Reagents

Four human PCa cell lines (P DU-1 22RV1, Lncap) and the human r l prostatic matrix immortalized cell lin PMV were obtained from ATCC (M USA). The F-12k medium, 1640 me fetal l vine serum (FBS) w urch om Technologies (Carl CA, US ells were cultured in ted F-12k m and/ or 1640 medi g 10% feta bovine serum (FBS) (Clone Logan, UT, USA). Cells were cultured in an or with 5% CO_2 and s humidity at 3

Cell Transfecti

negative ol (si-NC) and siRNA with LI terfere sequence (si-LINP1) were purch a (Shanghai, China). Cells in the loga growth phase were seeded into well plates until the cell confluence was up ll transfection was performed based on uctions of Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Transfected cells were harvested for quantitative Real-time polymerase chain reaction (qRT-PCR) and other functional experiments.

Cell Proliferation Assay

Transfected cells were harvested and seeded in 96-well plates at a density of 2×10^3/mL. Cell counting kit-8 (CCK-8) solution (Dojindo Laboratories, Kumamoto, Japan) was added into each well after cell culture for 6 h, 24 h, 48 h and 72 h, respectively. Cells were incubated at 37°C for 2 h in the dark. Absorbance (OD) values at the wavelength of 490 nm were detected by the microplate reader.

Colony Formation Assay

Transfected cells were collected and seeded in 6-well plates at a density of 200/mL for 2-week culture in complete medium. The medium was replaced 1 week later, and then replaced twice in the second week. 2 mL of paraformaldehyde were applied to fix the colonies for 20 min and 0.1% crystal violet solution was added for staining for another 20 min. After washed with phosphate-buffered saline (PBS) for 3 times, colonies were pictured in a light environment.

Cell Migration and Invasion Assay

48 h after transfection, cells were digested with trypsin and re-suspended in serum-free medium. The cell density was diluted to 2.0×10^5/mL. Transwell chambers with or without matrigel were placed in the 24-well plates, respectively. 200 μL of cell suspension were added to the upper compartment, and 500 μL of 1640 medium containing 10% FBS were added to the lower one. After 48 h inoculation, cells were fixed with 4% polyoxymethylene for 30 min at room temperature. After fixation, colonies were stained with crystal violet for 15 min and washed with PBS twice. The inner surface of the basement membrane was carefully cleaned. The membranes were then dried, inverted, and mounted on microscope slides for analysis. The cells were counted from five randomly chosen fields per well.

Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

We used TRIzol kit (Invitrogen, Carlsbad, CA, USA) to extract total RNA of the PCa cell lines and tissues. The extracted total RNA was reversely transcribed to complementary Deoxyribose Nucleic Acid (cDNA) by using the PrimeScript RT Reagent (TaKaRa, Otsu, Shiga, Japan). qRT-PCR was performed following the instructions of the SYBR® Premix Ex Taq™ (TaKaRa, Otsu, Shiga, Japan) and StepOnePlus Real-time PCR system (Applied Biosystems, Foster City, CA, USA). Primers used in the study were as follows: LINP1: forward: 5'-AGAAGAAC-3', reverse: 5'-CACAGAG-GAGCTACCCA-3'; β-actin: forward: 5'-CCT-GGCACCCAG-AT-3', reverse: 5'-GCT-GATCCAC-GAA-3'. The ABI Step One software was used for data analysis and the relative expression was presented by $2^{-\Delta\Delta Ct}$.

Western Blot

The transfected cells were lysed with lysate on ice for 30 min. After centrifuged at 14,000 rpm, 4°C for 15 min, the total concentration of the protein was determined by a bicinchoninic acid (BCA) kit (Pierce, Rockford, IL, USA). Total proteins were extracted and separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). Membranes were blocked with 5% skimmed milk for 1 h, followed by the incubation of primary antibody overnight. Membranes were then incubated with the secondary antibody at room temperature for 1 h. Immunoreactive bands were exposed by enhanced chemiluminescence method. Primary antibodies used in this research were β-catenin, c-myc, cyclin D1 and Tublinin. In addition, the corresponding secondary antibodies used in the study were anti-mouse and anti-rabbit. All the antibodies were purchased from Cell Signaling Technology (CST, Danvers, MA, USA).

Statistical Analysis

We used Statistical Product and Service Solutions (SPSS, IBM, Armonk, NY, USA) Software for all statistical analysis. Armonk, NY, USA) quantitative data were represented as mean±SD. *t*-test was used for continuous variables. The χ^2-test or the Fisher's exact method was applied for categorical variables. The survival time of PCa patients was evaluated by the Kaplan-Meier method, and the difference between curves was compared by the Log-rank test. $p<0.05$ was considered statistically significant ($\alpha=0.05$).

Results

LINP1 was Overexpressed in PCa Tissues and Cell Lines

LINP1 expressions in 74 pairs of PCa and paracancerous tissues and PCa cell lines were detected by qRT-PCR. Results showed that LINP1 expressions in PCa tissues were remarkably increased compared with those of paracancerous tissues (Figure 1A, B). Moreover, LINP1 was up-regulated in PCa cells in comparison with the human normal prostatic matrix immortalized cell line (WPMY-1), and the difference was statistically significant (Figure 1C). Particularly, the expression of LINP1 was the highest in PC-3 and Lncap cells, which were selected for the following *in vitro* experiments.

LINP1 Expression was Correlated with Clinical Stage, Lymphatic Metastasis, Distance Metastasis and Overall Survival of PCa Patients

According to the expression level of LINP1 in 74 pairs of PCa and paracancerous tissues, PCa patients were assigned into the high LINP1 expression group and the low LINP1 expression group. The χ^2-test was performed to analyze the relationship between LINP1 expression and age, sex, clinical stage, lymphatic metastasis and dis-

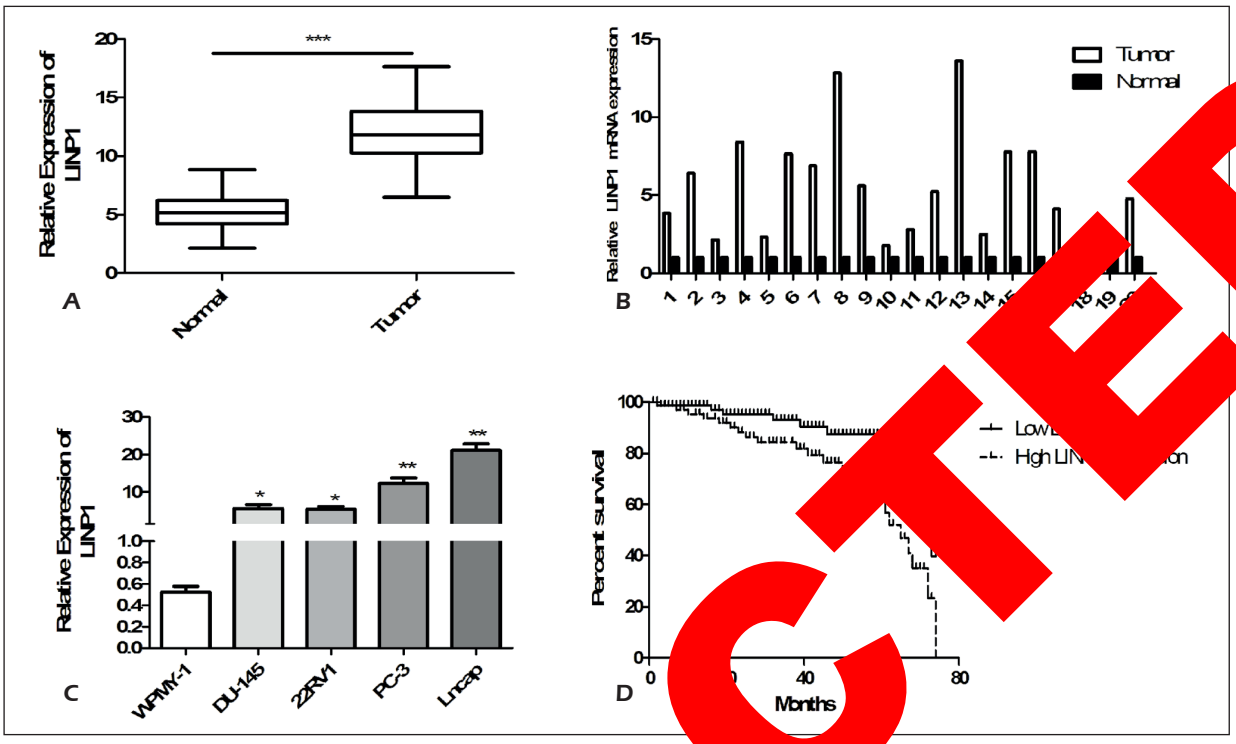


Figure 1. **A-B**, The expressions of LINP1in 74 pairs of tissues were significantly increased than those of the paracancerous tissues. **C**, Expression levels of LINP1 in 4 PCa cell lines (DU-145, 22RV1, Lncap) and normal prostate cell (WPMY-1). **D**, Kaplan-Meier survival curves of PCa patients based on LINP1. PCa patients with higher expression of LINP1 had a significantly worse prognosis. Representative data was expressed as mean ± SD (*p<0.05, **p<0.01).

tant metastasis of the PCa patients. As shown in Table I, up-regulated LINP1 was positively correlated with clinical stage, pathological T stage and distant metastasis, which indicated that ated with age, sex and tumor site in PCa patients. In addition, follow-up data were collected to indicate the relationship between the expression of LINP1 and the prognosis of PCa patients.

Table I. Association of lncRNALINP1 with clinicopathologic characteristics of prostate cancer.

Parameter	Number of cases	LINP1 expression		*p*-value
		Low (%)	High(%)	
Age (years)				0.343
≤60	31	20	11	
>60	43	23	20	
				0.146
	36	24	12	
	38	19	19	
T stage				0.008
T1-T2	42	30	12	
T3-T4	32	13	19	
Lymph node metastasis				0.033
No	44	30	14	
Yes	30	13	17	
Distance metastasis				0.029
No	59	38	21	
Yes	15	5	10	

The Kaplan-Meier survival curve indicated that up-regulated LINP1 was significantly related to the poor prognosis of PCa. The prognosis was worse in those patients with higher LINP1 expression ($p<0.05$, Figure 1D). Our data revealed that LINP1 might be a new biological marker for predicting the prognosis of PCa.

Knockdown of LINP1 Inhibited Proliferative Ability

To explore the function of LINP1 in the proliferative ability of PCa cells, we successfully constructed the LINP1 knockdown cell model (Figure 2A, 2B). Proliferative ability of cells transfected with si-NC and si-LINP1was detected by CCK-8 assay, respectively. Our data illustrated that the proliferative ability of cells transfected with si-LINP1 was significantly inhibited comparing to those transfected with si-NC (Figure 2C, 2D). Similar results were obtained from the colony formation assay (Figure 2E, 2F).

Knockdown of LINP1 Inhibited Migratory and Invasive Abilities

We then investigated if LINP1 could a the migratory and invasive ability of PCa Migration results demonstrated that the nu of PCa cells crossing the membrane of the T swell chamber was significantly ced af LINP1 knockdown (Figure 3 ggestin that LINP1 inhibited the mi ion y. Inva- sion results were in acc e wi ve findings (Figure 3C, 3D).

Knockdown o 1 Inhib the Activati 53 Signali Pathway

To eluc the l mechanism of LIN- P1in n oting cell p tion, migration and inv , we detected th tein expressions of TEN kt and CDK2 in the p53 signal- path after knockdown of LINP1. Lower level the PTEN, Akt and CDK2 pr were ved after LINP1 knockdown, exce igure 4A). Moreover, the mRNA and pro xpressions of p53 in 74 pairs of PCa and paracancerous tissues, as well as PCa cell re also detected by qRT-PCR and West- ot, respectively. The data showed that the p53 expressions in PCa tissues were remarkably lower than those of paracancerous tissues (Figure 4B). Lower LINP1 expression was found in PCa cells in comparison with WPMY-1 cells (Figure 4C). In addition, we observed that the mRNA and protein expressions of LINP1 were negatively correlated with p53 expression in PC-3 and Lncap cells (Figure 4D).

P53 Modulated LINP1 Expression in Human Prostate Cancer Cells

The above findings suggested th NP1 v remarkably upregulated after p5 ckdown i PCa cells. Therefore, we hypo zed t here might be an interaction bet INP d p53. In this study, 74 pairs of PCa t para cerous tissues were se d. Th ssi LINP1 and p53 in t Ca tissu nal tissues were det qRT-PCR. gative correlation bet nd p53 was observed (Figure 4D). A show ure 5, the p53 expression in PCa cells was ably lower than that o MY-1 cells. F rmore, we constru a small interference of p53 (si-p53), and th nsfection ency of si-p53 was detected by tern blot. restingly, the inhibited invas d met s of PC-3 cells by LINP1 knoc versed by si-p53.

Discussion

PCa is one of the most common malignant tumors worldwide. In recent years, the incidence and mortality of PCa have been increasing gradually in China, whereas its early diagnosis rate of PCa in our country was extremely low. Moreover, most of the PCa patients have already developed to the middle or late stage when they were first diagnosed[2,16]. Genetic factors, diet, risky lifestyle and precancerous lesions were closely related to the development of PCa. Over 50% of the clinical PCa patients have presented micro-metastasis before radical surgery, which was one of the direct cause of postoperative metastasis and recurrence[3,4]. The explorations of early diagnosis, metastasis, recurrence and adjuvant treatment of postoperative advanced PCa have been well recognized[6,7]. Researches have illustrated that lncRNAs exerted a crucial role in many diseases, including malignant tumor. There were many differentially expressed lncRNAs identified in PCa, which might be of great importance in the diagnosis, treatment and prognosis of PCa patients[22-24]. Therefore, exploration of the effect of these differentially expressed lncRNAs on PCa might help improve the prognosis of PCa patients.

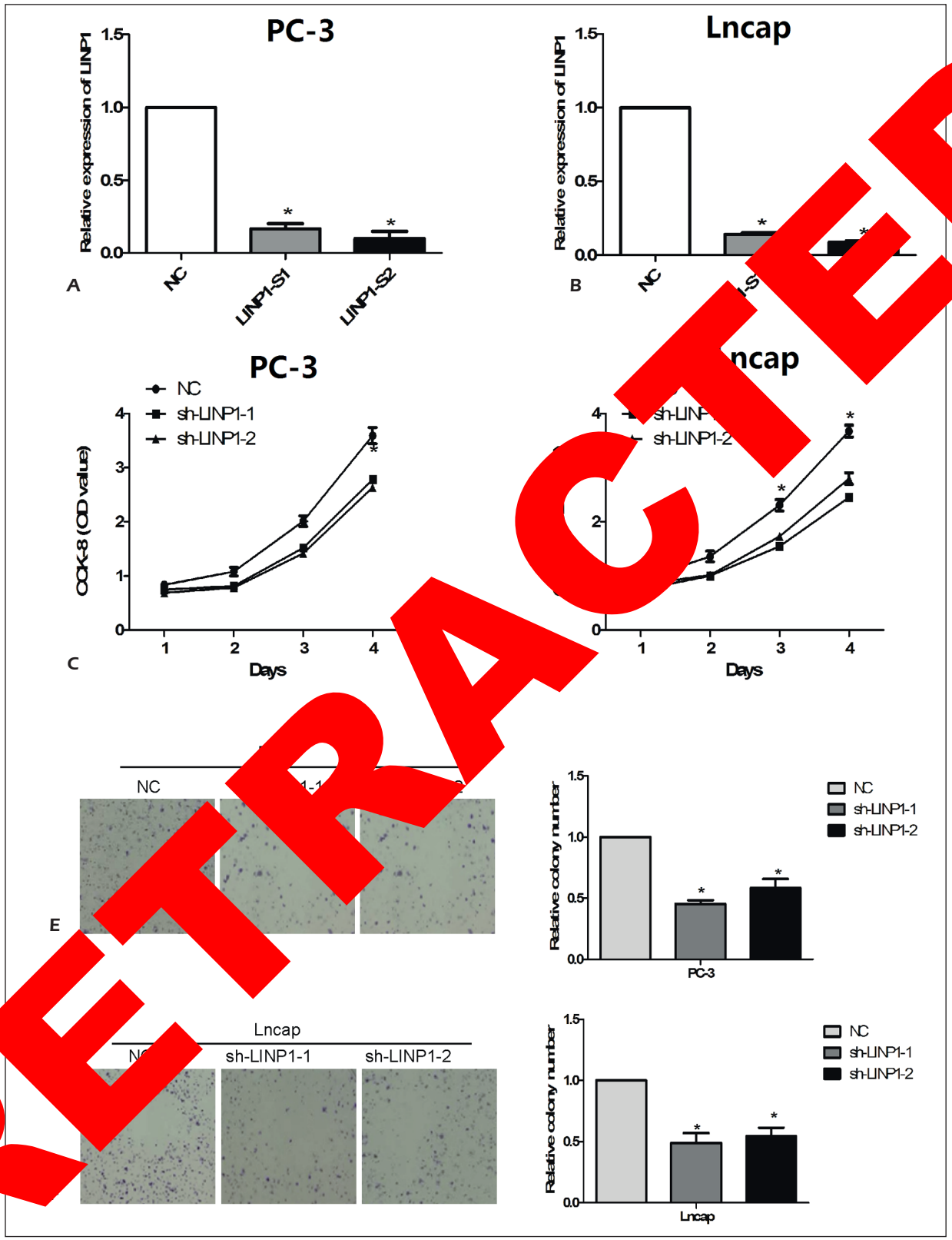


Figure 2. A-B, Transfection efficiency of LINP1 knockdown in PC-3 and Lncap cell lines was verified by qRT-PCR. **C-D**, Cell proliferation of PC-3 and Lncap cells after LINP1 knockdown. E, F, The cell colony formation in PC-3 and Lncap cells after LINP1 knockdown. Representative data was expressed as mean ± SD values (*p<0.05).

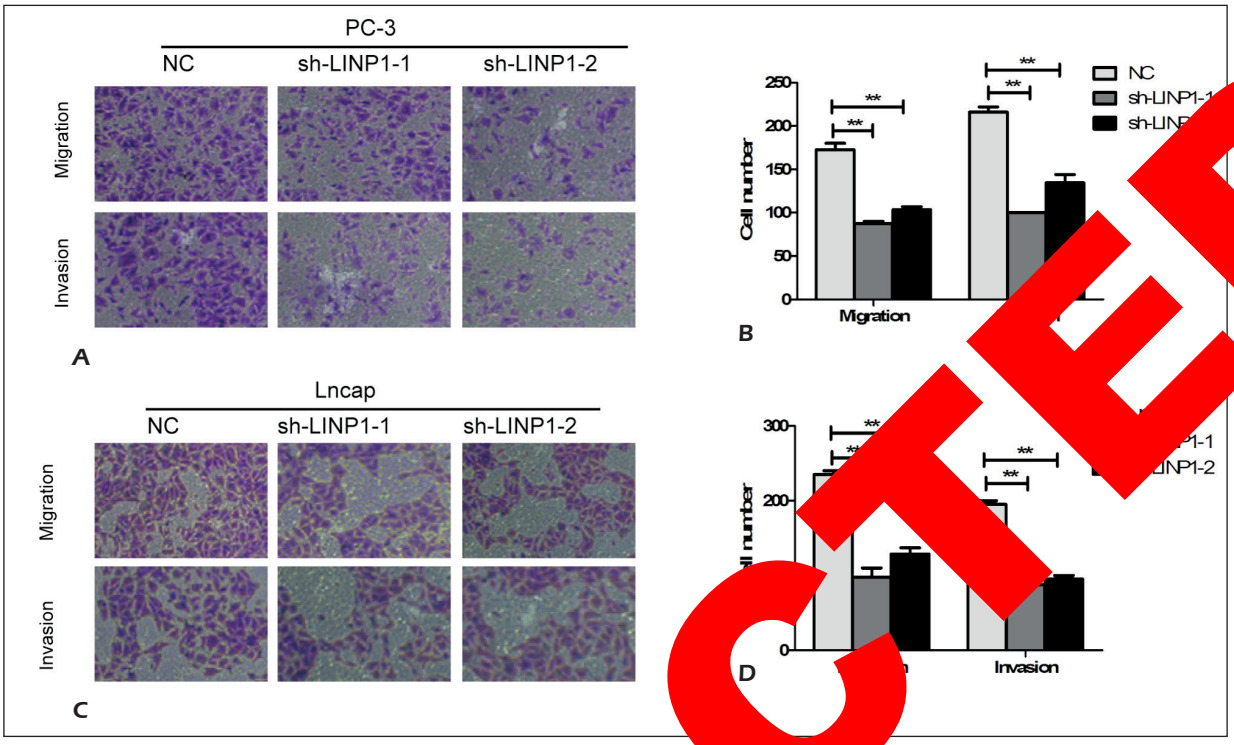


Figure 3. *A-B*, PC-3 cells transfected with si-LINP1 di... a significant... ...ution and invasion capacity. *C-D*, Lncap cells transfected with si-LINP1 displayed a significant... ...on and invasion capacity. Representative data was expressed as mean ± SD values (**$p<0.01$).

We explored the expressio... in PC... and its potential mechanis... irst, ...validated the expression of LI... 74 ...PCa and paracancerous tissues... that up-regulated L... was ...ely correlated with the tum... ge, lymp... etastasis, distant metast... poor prognc... PCa patients, sugg... NP1 might play an oncogenic role ...ca. ... clarify the biological functi... of LINP1 i... ve constructed the si-L... for the follow... *vitro* assays. CCK-8 ...ay, c... y formation assay, migration and ...sion ...ay all suggested that LINP1 could ...e dev... ent and progression of PCa c... ...eve... specific molecular mechanism was ...

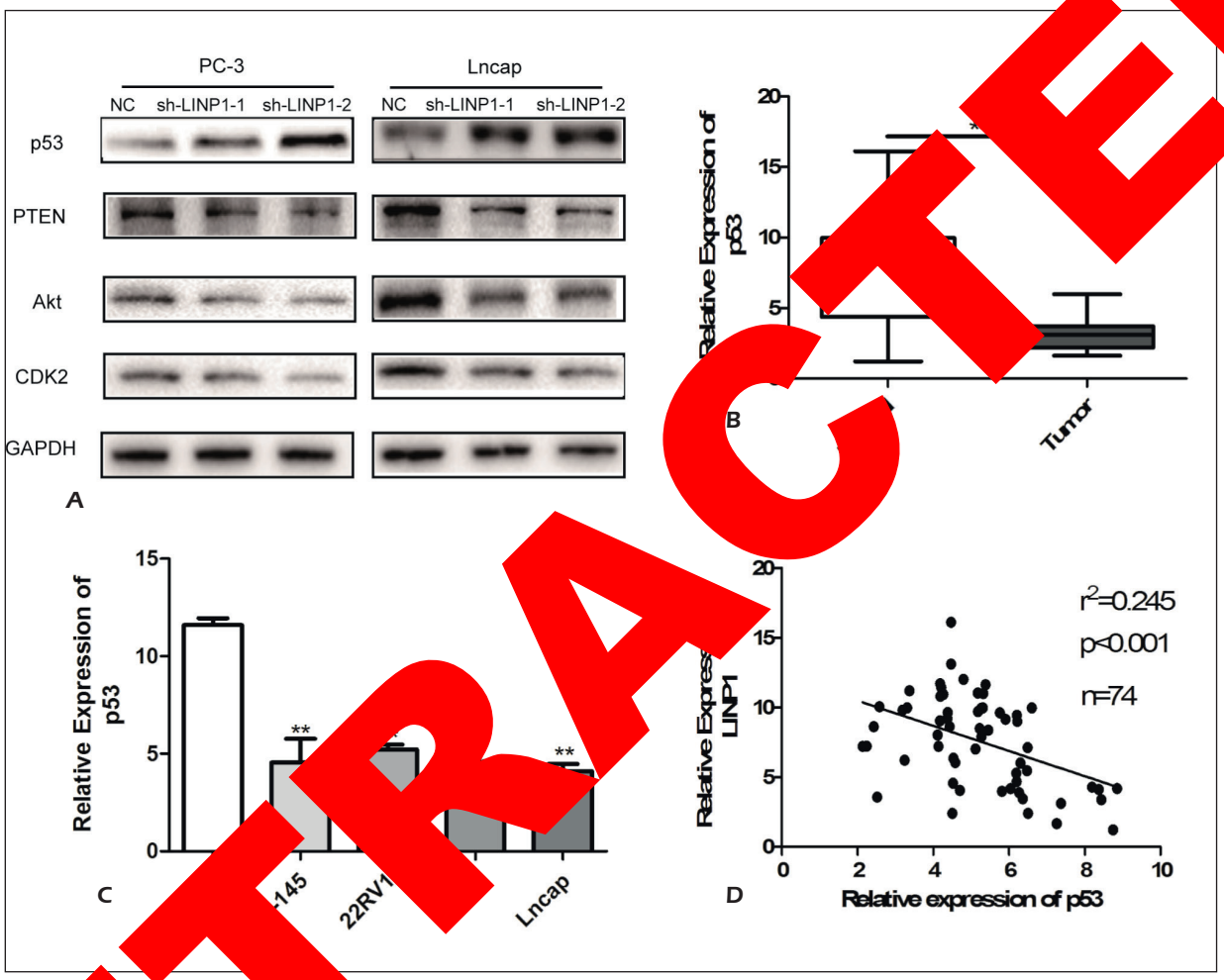
p53 ...ing pathway is a crucial signaling pathway related to tumorigenesis[25], and p53 ... has been found to be associated with u... 50% of human tumors. At present, p53 target therapy combined with radiotherapy has been applied in the treatment of nasopharyngeal carcinoma, head and neck squamous cell carcinoma and cervical cancer[26], indicating that p53 is expected to serve as a therapeutic biomarker[27].

In the present study, the *in vitro* experiments have proved that there was a negative interaction between LINP1 and p53. Further in-depth explorations in the biological function of p53 were still urgently needed for precisely diagnosing tumors.

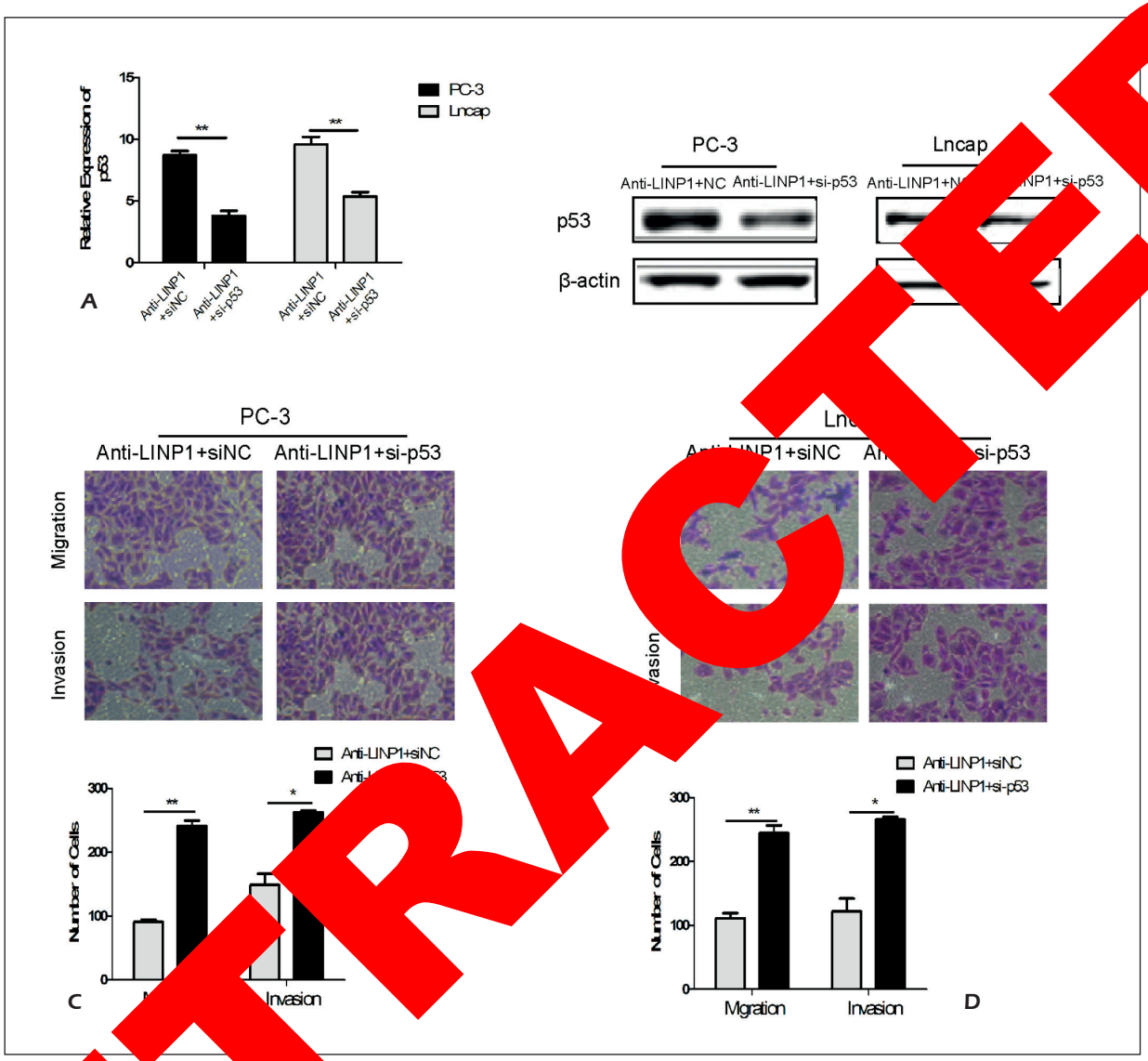
In summary, to investigate whether LINP1 promoted the development of PCa by regulating p53, we detected the expressions of key proteins in the p53 signaling pathway after knockdown of LINP1, including p53, PTEN, Akt and CDK2. We demonstrated that the expression levels of the above proteins were remarkably decreased after LINP1 knockdown, suggesting a negative regulatory relationship between LINP1 and p53.

Conclusions

We showed that up-regulated LINP1 in PCa was positively correlated with the tumor stage, lymphatic metastasis and distant metastasis and poor prognosis of PCa patients. In addition, LINP1 might promote the malignant progression of PCa by regulating the p53 signaling pathway.



Figur, Lnc- LINP1 kn e significantly changed the expressions of p53,PTEN, Akt and CDK2. **B-C**, The mRNA expre f p53 in human PCa tis and paracancerous tissues, and cell lines were detected by qRT-PCR. D, A negative correlation nd be LINP1 and p53 in tumor tissues. Representative data was expressed as mean ± SD values (**p<0.01).



Figu **A**, The expressio as verified by qRT-PCR in co-transfected cell lines. **B**, Western blot was used to verify the ex n of p53 in co-transfect ell lines. **C-D**, The roles of LINP1 and p53 in the regulation of PCa cell migration and invasion examin transwell assay. Representative data was expressed as mean ± SD values (*p<0.05, **p<0.01).

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Conflict of interest

The authors declared no conflict of interest.

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