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Research paper

Overexpression of lncRNA UCA1 promotes osteosarcoma progression and correlates with poor prognosis

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ABSTRACT

Long non-coding RNAs (lncRNAs) have been proved to play important roles in the tumorigenesis and development of several human malignancies. Our study aims to investigate the expression and function of lncRNA-UCA1 in osteosarcoma. lncRNA-UCA1 expression was detected in osteosarcoma tissues and cell lines by using qRT-PCR. Association between lncRNA-UCA1 levels and clinicopathological factors and patient's prognosis was analyzed. The roles of lncRNA-UCA1 in regulating osteosarcoma cell proliferation, apoptosis, migration, and invasion were evaluated in vitro. We found that lncRNA-UCA1 expression was upregulated in osteosarcoma tissues and cell lines. High lncRNA-UCA1 expression was significantly correlated with large tumor size, high tumor grade, positive distant metastasis, and advanced clinical stage. Multivariate regression analysis identified lncRNA-UCA1 overexpression as an independent unfavorable prognostic factor. lncRNA-UCA1 knockdown inhibited osteosarcoma cell proliferation, promoted cell apoptosis, and suppressed cell invasion and migration, whereas lncRNA-UCA1 overexpression showed opposite effects. These findings suggested that lncRNA-UCA1 may contribute to osteosarcoma initiation and progression, and would be not only a novel prognostic marker but also a potential therapeutic target for this disease.

1. Introduction

Osteosarcoma is one of the most common primary bone tumor and occurs predominantly in children and young adults [1]. With the development of multiple therapeutic strategies including wide tumor excision, neoadjuvant or adjuvant chemotherapy, and radiotherapy, the 5 year survival of the non-metastatic patients has increased to 65% [2]. However, osteosarcoma is very aggressive and approximately 40–50% of patients will eventually develop metastases, especially pulmonary metastases [3]. The prognosis of these patients is rather poor, and the long-term survival rate is only 10–30% [4]. The complex molecular mechanisms underlying osteosarcoma tumorigenesis and progression remain largely unclear. Identification of new candidate molecules that take part in these processes is crucial for developing new therapeutic approach for osteosarcoma and improving clinical outcomes of patients with this disease.

Long noncoding RNAs (lncRNAs) are defined as RNA transcripts of more than 200 nucleotides in length with no or little protein-coding capacity [5]. LncRNAs can regulate gene expression through diverse mechanisms including epigenetic silencing, mRNA splicing, lncRNA-miRNA interaction, lncRNA-protein interaction and lncRNA-mRNA interaction [6]. Recent studies showed that lncRNAs are involved in a wide range of biological processes, such as embryonic development, cell proliferation, apoptosis, invasion, metastasis and angiogenesis [7–9]. Furthermore, lncRNAs can act as oncogenes or tumor suppressors, and play important roles in carcinogenesis and cancer development [10,11]. Abnormal lncRNA expression and its association with various important clinicopathological parameters have been reported in many types of cancers. In terms of osteosarcoma, increased lncRNA FGFR3-AS1 expression correlated with large tumor size, advanced Enneking stage, and poor survival [12]. Plasma lncRNA TUG1 contributed to osteosarcoma detection and dynamic surveillance [13]. Silence of lncRNA TUSC7 promoted osteosarcoma cell proliferation and increased colony formation in vitro [14]. LncRNA ODRUL inhibition could inhibit osteosarcoma cell proliferation and migration, and partly reversed doxorubicin resistance [15]. Therefore, lncRNAs may be utilized for osteosarcoma diagnosis and prognosis, and serve as potential therapeutic targets.

Abbreviations: lncRNA, long noncoding RNA; UCA1, Urothelial carcinoma associated 1; RT-PCR, reverse transcription-polymerase chain reaction; DMSO, dimethyl sulfoxide; MTT, 3-(4,5-dimethylthiazol-2-yl)−2,5-diphenyltetrazolium bromide; DMEM, Dulbecco's modified Eagle's medium; TNM, tumor-node-metastasis

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Urothelial carcinoma associated 1 (UCA1) is an lncRNA originally identified in human bladder carcinoma [16]. Overexpression of UCA1 significantly enhanced bladder cancer cell proliferation and migration and confered drug resistance. Recently, UCA1 has been reported to be upregulated and exert its oncogenic activity in several cancers such as esophageal squamous cell carcinoma [17], breast cancer [18], non-small cell lung cancer [19], gastric cancer [20], colorectal cancer[21], hepatocellular carcinoma [22], renal cell carcinoma [23], ovarian cancer [24], and prostate cancer [25]. However, the significance of UCA1 in osteosarcoma is still unclear. In the present study, we investigated the expression level of UCA1 in osteosarcoma samples and cell lines. We also investigated the correlation between UCA1 expression and clinicopathological characteristics and patient's survival. Moreover, we explored the role of UCA1 in the regulation of biological behaviors of osteosarcoma cells.

2. Materials and methods

2.1. Patients and clinical specimens

Matched fresh osteosarcoma specimens and adjacent non-tumorous tissues were acquired from 135 patients at Hanzhong Municipal Central Hospital between January 2006 and December 2010. None of the patients received chemotherapy or radiotherapy before sample collection. All specimens were frozen in liquid nitrogen immediately after collection and stored at −80 °C until use. Table 1 showed the details of clinical and pathological characteristics of the patients. The follow-up data were available and complete for each patient. Overall survival was calculated from the day of primary surgery to death or last follow-up. This project was approved by the Clinical Research Ethics Committee of our hospital and all patients provided written informed consent.

2.2. Cell culture

The normal osteoblast cell line hFOB1.19 and human osteosarcoma cell lines (HOS, Saos-2, MG-63, U2OS) were purchased from the Chinese Academy of Medical Sciences and cultured in Dulbecco's modified Eagle's medium (DMEM, USA) supplemented with 10% fetal bovine serum (FBS, USA), penicillin (100 U/ml), and streptomycin (100 μg/ml). All cells were incubated at 37 °C in 5% CO_2.

2.3. RNA extraction and real-time PCR

Total RNA was extracted by Trizol reagent (Invitrogen, Carlsbad, CA, USA). The first-strand cDNA was synthesized from 1 μg of total RNA using the Reverse Transcription System Kit (Takara, Dalian, China). The real-time PCR was carried out using SYBR Premix Ex Taq kit (Takara, Dalian, China) on an ABI 7500 Real-Time PCR System (Applied Biosystems, CA, USA). Each assay was performed in triplicate, and GAPDH was used as the endogenous control gene. The primer sequences used were as follows: UCA1, 5′-TTCCTTATTATCTCTTCTG-3′ (forward) and 5′-TCCATCATACGAATAGTA-3′ (reverse); GAPDH, 5′-CTCGCTTTGGCAGCA CA-3′ (forward) and 5′-AACGCTTCACGAATTTGCGT-3′ (reverse). The relative amount of UCA1 to GAPDH was calculated using the $2^{-\Delta Ct}$ method, where $\Delta CT = (CT_{UCA1} - CT_{GAPDH})$.

2.4. UCA1 knockdown and overexpression

The cDNA encoding UCA1 was PCR-amplified and subcloned into the pCDNA3.1 vector (Invitrogen, Shanghai, China). The empty pcDNA3.1 vector was used as the control. UCA1 small interfering RNA (si-UCA1) and negative control siRNA (si-NC) were synthesized by GenePharma (Shanghai, China). Transfections were performed using Lipofectamine 2000 according to the manufacturer's instructions (Invitrogen, CA, USA).

Table 1
Association of lncRNA-UCA1 expression with clinicopathological factors in osteosarcoma.

Clinicopathological features	Number of cases	lncRNA-UCA1 expression		P
		Low n (%)	High n (%)	
Age				
< 20 years	98	46(46.9%)	52(53.1%)	0.339
≥ 20 years	37	21(56.8%)	16(43.2%)	
Gender				
Male	95	49(51.6%)	46(48.4%)	0.573
Female	40	18(45.0%)	22(55.0%)	
Tumor size				
> 8 cm	57	20(35.1%)	37(64.9%)	0.005
≤ 8 cm	78	47(60.3%)	31(39.7%)	
Anatomic location				
Tibia/femur	93	48(51.6%)	45(48.4%)	0.512
Elsewhere	42	19(45.2%)	23(54.8%)	
Tumor grade				
Low	45	30(66.7%)	15(33.3%)	0.004
High	90	37(41.1%)	53(58.9%)	
Histological type				
Osteoblastic	52	28(53.8%)	24(46.2%)	0.774
Fibroblastic	26	11(42.3%)	15(57.7%)	
Chondroblastic	20	9(45.0%)	11(55.0%)	
Telangiectatic	21	12(57.1%)	9(42.9%)	
Others	16	7(43.8%)	9(56.2%)	
Enneking stage				
I	35	27(77.1%)	8(22.9%)	< 0.001
II	66	32(48.5%)	34(51.5%)	
III	34	8(23.5%)	26(76.5%)	
Distant metastasis				
Absent	101	58(57.4%)	43(42.6%)	0.002
Present	34	9(26.5%)	25(73.5%)	

2.5. Cell proliferation assay

Osteosarcoma cells were seeded into 96-well plates after transfection. Cell density was adjusted to 5×10^3/well, and the final volume was 150 μl/well. Cell proliferation was determined every 24 h for 4 days. At the indicated time point, 20 μl of MTT (Sigma, USA) was added into each well and the cells were cultured for another 4 h at 37 °C. Then the supernatants were removed and 150 μl of DMSO was added. Optical density was detected at a wavelength of 490 nm and each assay was repeated three times.

2.6. Detection of apoptosis by flow cytometry

Cell apoptosis was measured by using an Annexin V-FITC Apoptosis Detection kit (BD Biosciences, San Diego, CA) according to the manufacturer's instructions. After transfection, osteosarcoma cells were harvested and washed twice with cold phosphate-buffered saline. Then, the cells were treated with Annexin V/

propidium iodide (PI) for 15 min in the dark at room temperature, and analyzed by flow cytometry assay.

2.7. Transwell invasion and migration assays

Cell invasion and migration assays were performed using the 24-well transwell chambers (8 μm pore size; BD Biosciences, San Jose, CA, USA). For the migration assay, about 1×10^5 osteosarcoma cells were resuspended in 200 μl serum-free medium and placed in the top chambers. DMEM (600 μl) containing 10% FBS was filled into the bottom chambers. After 24 h of incubation at 37 °C, the cells that did not migrate through the pores were removed by a cotton swab, and cells on the lower surface of the membrane were stained with crystal violet and counted. The invasion assay protocol was similar to that of the migration assay except that t the cell culture insert surface was first coated with Matrigel.

2.8. Statistics

All statistical analyses were performed using the SPSS 17.0 software package (SPSS, Chicago, IL, USA). The significance of differences between groups was estimated by Student's *t*-test and Chi-square test. Survival curves were constructed with the Kaplan-Meier method and compared by log-rank test. The significance of survival variables was evaluated using a multivariate Cox proportional hazards regression analysis. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Increased UCA1 expression in osteosarcoma tissues and cell lines

UCA1 expression in osteosarcoma tissues and cell lines was measured by qRT-PCR. We found that UCA1 expression in osteosarcoma samples was significantly higher than in adjacent nontumorous tissues (Fig. 1(A), $P < 0.001$). In addition, UCA1 expression was significantly increased in four osteosarcoma cell lines compared to hFOB cells (Fig. 1(B), $P < 0.001$). Since MG-63 cells exhibited the highest UCA1 expression while HOS cells expressed relatively low UCA1 levels among the four osteosarcoma cell lines, these two cell lines were selected for the transfection of si-UCA1 or pcDNA-UCA1.

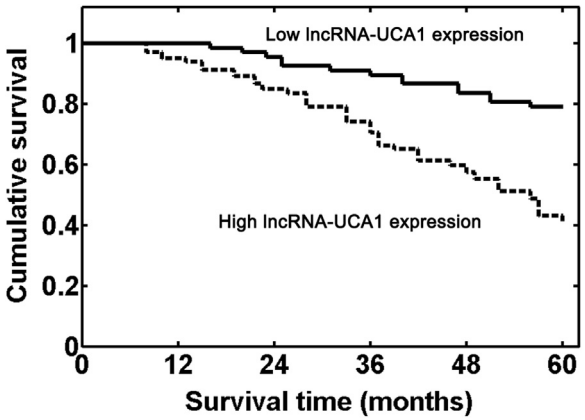

Fig. 2. Kaplan-Meier survival curves of osteosarcoma patients based on lncRNA-UCA1 expression levels. Patients in the high UCA1 expression group had significantly poorer prognosis than those in low UCA1 expression group ($P < 0.001$, log-rank test).

Table 2
Univariate and multivariate analysis of overall survival in 135 osteosarcoma patients.

Variable	Univariate analysis		Multivariate analysis	
	HR	p-value	HR	p-value
Age	1.528	0.225	–	–
Gender	1.120	0.773	–	–
Anatomic location	1.685	0.179	–	–
Tumor grade	3.562	0.012	2.872	0.026
Tumor size	3.101	0.028	1.153	0.089
Clinical stage	5.969	< 0.001	5.116	0.001
Distant metastasis	4.383	0.003	4.989	0.002
lncRNA-UCA1 level	5.746	< 0.001	3.141	0.015

3.2. Correlation between UCA1 expression and clinical features and patient's prognosis

To assess the correlation of UCA1 expression with clinicopathologic characteristics, the osteosarcoma samples were classified into high UCA1 expression group (n=68) and low UCA1 expression group (n=67) according to the median UCA1 expression level of all samples. Table 1 showed that high expression of UCA1 was significantly correlated with large tumor size ($P = 0.005$), high tumor grade ($P = 0.004$), positive distant metastasis

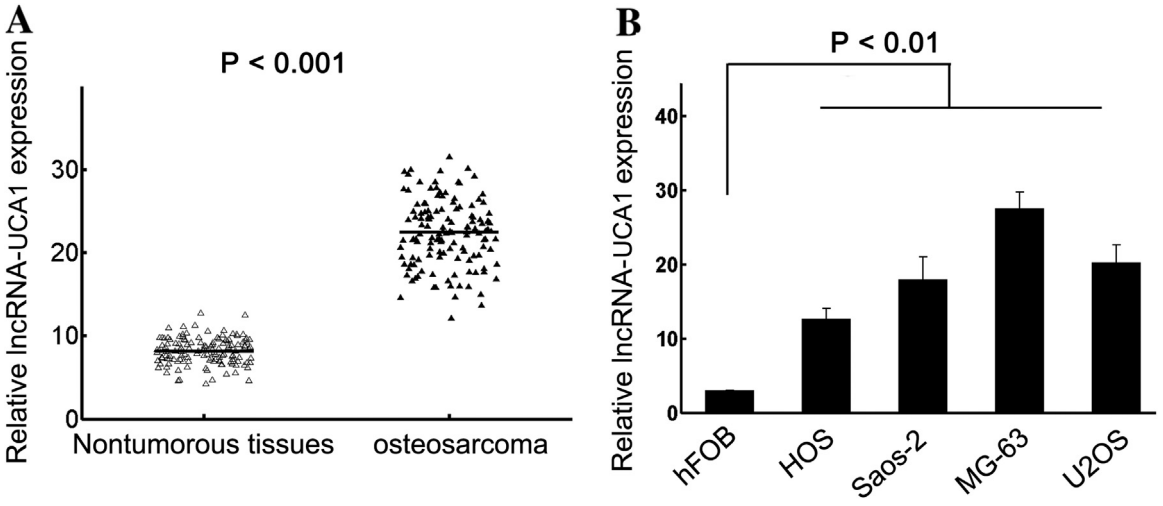

Fig. 1. Expression of lncRNA-UCA1 in osteosarcoma tissues and cell lines. (A) UCA1 expression was significantly higher in osteosarcoma samples than in adjacent nontumorous tissues. (B) Increased UCA1 expression in four osteosarcoma cell lines compared to normal osteoblast cells.

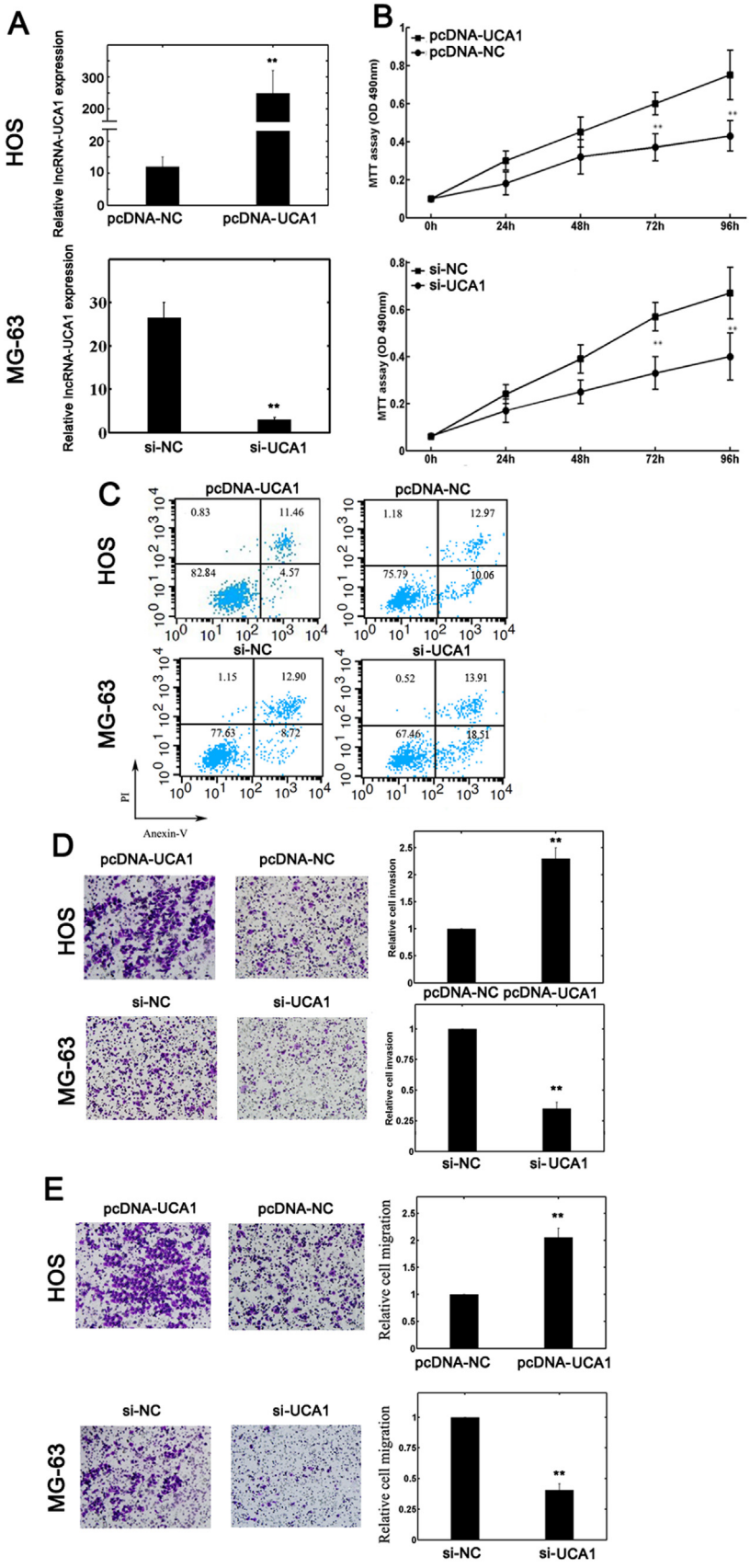

Fig. 3. Effects of lncRNA-UCA1 on the biological behaviors of osteosarcoma cells. (A) qRT-PCR analysis confirmed increased UCA1 expression in HOS cells transfected with pcDNA-UCA1, and decreased UCA1 expression in MG-63 cells transfected with si-UCA1. $^{**}P < 0.01$. (B) MTT assay showed that lncRNA-UCA1 promoted cell proliferation. $^{**}P < 0.01$. (C) Flow cytometric analysis indicated that lncRNA-UCA1 reduced cell apoptosis. (D, E) Down-regulation of lncRNA-UCA1 impeded the invasion/migration of MG-63 cells, while up-regulation of lncRNA-UCA1 promoted cell invasion/migration ability in HOS cells. $^{**}p < 0.01$.

(P=0.002), and advanced Enneking stage (P < 0.001). Kaplan-Meier survival curves indicated that patients in low UCA1 expression group had better 5-year overall survival than those in high UCA1 expression group (P < 0.001, Fig. 2). Univariate Cox proportional hazards analysis revealed that UCA1 expression, tumor size, tumor grade, metastasis status, and clinical stage were prognostic indicators (Table 2). Multivariate analysis confirmed UCA1 expression (P=0.015) as an independent prognostic indicator for overall survival of osteosarcoma patients in addition to tumor grade (P=0.026), tumor stage (P=0.001), and distant metastasis (P=0.002; Table 2).

3.3. *Effects of UCA1 on the biological behaviors of osteosarcoma cells*

Fig. 3(A) confirmed increased UCA1 expression in HOS cells after pcDNA-UCA1 transfection, and decreased UCA1 expression in MG-63 cells following si-UCA1 transfection. MTT assay showed that cell proliferation was significantly impaired in MG-63 cells transfected with si-UCA1, while proliferation of HOS cells was increased after pcDNA-UCA1 transfection (Fig. 3(B)). Flow cytometry demonstrated promoted cell apoptosis after si-UCA1 transfection and reduced cell apoptosis after pcDNA-UCA1 transfection (Fig. 3(C)). As shown in Fig. 3(D) and (E), down-regulation of UCA1 impeded MG-63 cell invasion and migration, while transfection of HOS cells with pcDNA-UCA1 promoted cell invasion/migration ability.

4. Discussion

It is urgent to develop novel targets for the diagnosis, treatment, and prognosis of osteosarcoma. Increasing evidence has demonstrated that lncRNAs play important roles in almost every aspects of physiological and pathological processes in the human body [6]. Changes of lncRNA expression are involved in cancer formation and progression, which may provide a new but promising way to deal with cancer [26,27]. In the present study, we observed high UCA1 expression in osteosarcoma tissues and cell lines, providing the first evidence that UCA1 upregulation was closely associated with osteosarcoma initiation. Then we confirmed the correlation between increased UCA1 levels and aggressive clinicopathological features of osteosarcoma samples. UCA1 overexpression enhanced HOS cell proliferation, invasion and migration, and inhibited cell apoptosis, whereas UCA1 silencing in MG-63 cells showed opposite effects. These findings revealed that UCA1 might contribute to osteosarcoma progression and serve as a potential therapeutic target. Furthermore, osteosarcoma patients with high UCA1 levels tended to have shorter overall survival compared to patients with low UCA1 levels, and multivariate Cox hazard regression analysis identified UCA1 expression as an independent prognostic indicator. To our knowledge, this is the first study to analyze the expression and clinical significance of UCA1 in osteosarcoma.

Our results are consistent with previous findings in other malignancies. Functional assays revealed that ectopic expression of UCA1 promoted cell proliferation and/or reduced cell apoptosis in non-small cell lung cancer [19], breast cancer [18], colorectal cancer [28], and renal cell carcinoma [23]. Knockdown of UCA1 impaired cell invasion or migration ability in breast cancer [29], esophageal squamous cell carcinoma [17], hepatocellular carcinoma[22], ovarian cancer [30], and melanoma [31]. UCA1 also decreased chemosensitivity in colorectal cancer[28], ovarian cancer [24], and bladder cancer [32]. Clinical investigation demonstrated that UCA1 overexpression was related to lymph node metastasis and advanced FIGO stage in ovarian cancer [24]. Increased UCA1 expression correlated with worse differentiation, large tumor size, deep local invasion, and advanced TNM stage in gastric cancer [33]. Further, high UCA1 expression was an unfavorable prognostic factor for overall survival of patients with esophageal squamous cell carcinoma [17], gastric cancer [33], colorectal cancer [21], hepatocellular carcinoma [22], and epithelial ovarian cancer [34]. Taken together, these research indicated the oncogenic functions of UCA1 in human cancers and suggested a potential application for UCA1 in molecular targeted therapy.

We are aware of some limitations in our work. First, the clinical part was a retrospective study, and the tumor sample size was relatively small. Second, although we revealed the oncogene function of UCA1 in osteosarcoma, its probable downstream mediators are still unclear, and the underlying mechanisms by which UCA1 promotes cancer development and progression remain to be thoroughly clarified.

In summary, our study showed increased UCA1 expression in osteosarcoma and its association with aggressive clinicopathological features and poor patient's prognosis. Regulation of UCA1 expression influenced biological behaviors of osteosarcoma cells. These findings indicate that UCA1 might be an important molecular marker for prognostic evaluation of osteosarcoma and serve as a potential therapeutic target for this disease.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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