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ORIGINAL ARTICLE

Clinical Application of Long Non-Coding RNA-UCA1 as a Candidate Gene in Progression of Esophageal Cancer

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Abstract

Esophageal cancer (EC) is known as one of the most prevalent gastrointestinal cancers, and results in the seventh highest number of cancer-relevant deaths. Long non-coding RNAs (lncRNAs) have substantial roles in several biological processes. LncRNA human urothelial carcinoma associated 1 (UCA1) is announced to be enhanced in multiple types of human cancers. This survey was carried out to identify the potential role of the lncRNA-UCA1 in the progression of EC. A case-control investigation was performed on 140 FFPE tissues of EC patients consisting of 70 cancerous tissues and 70 marginal tissues samples. To determine the lncRNA-UCA1 gene expression changes, quantitative reverse-transcription polymerase chain reaction (qRT-PCR) method was utilized. In addition, the associations between the lncRNA-UCA1 gene expression and clinicopathological parameters were assessed. Our findings revealed that the lncRNA-UCA1 was notably up-regulated in EC tissues compared to adjacent normal tissues ($P < 0.05$). LncRNA-UCA1 expression was substantially correlated to alcohol drinking ($P = 0.008$) and socioeconomic status ($P = 0.001$), while shared no correlation with age, hot drinking status and stage ($P > 0.05$). Our data indicated that the lncRNA-UCA1 play an important role in the progression of EC and may be considered as a candidate gene in the pathogenesis of EC patients.

Keywords *LncRNA-UCA1* · Candidate gene · Esophageal Cancer · LncRNAs

Introduction

EC is death-dealing cancer and is organized in the category of prevalent causes of cancer-related deaths worldwide [1]. It embraces two main subunits, esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (AC). An increasing body of evidence recommends that over 90% of all EC cases are squamous cell carcinomas, which are reported with an advanced outbreak of esophageal carcinoma in China [2]. The risk factors for both EC types are smoking, high alcohol drinks, hot drinks, obesity, and long-term gastroesophageal reflux illness [3]. However, the therapy of EC have enhanced, the prognosis is still poor [4]. The cure for EC comprises surgery, chemotherapy and radiation therapy. Most of the patients are diagnosed when they reach the advanced stage [5], and curative results are depressing in a way that five-year survival level of patients with stage 0, I, II and III is about 95%, 50 to 80%, 10 to 40% and 10 to 15%, respectively [6].

Non-coding regions in DNA play pivotal functions in the modification of varied biological operations, encompassing cell growth and proliferation, migration, metabolism, and apoptosis [7]. LncRNAs (long non-coding RNAs) were initially thought to be counterfeit transcriptional noise, while they are determined as newfound modifiers in the progression of various cancers. Roughly, 70–80% of the human genome is identified as the non-protein coding areas and is transcribed as non-coding RNAs (ncRNAs) [8].

The considerable segment of this "unclassified genetic material" is long non-coding RNA (lncRNA) with a length of 200 nucleotides [9]. Histone adjustment and canonical spliceosome machinery can modify the transcription of lncRNAs [10]. LncRNAs might play the role of amplifiers by regulating chromatin or sponges to attach proteins and microRNAs (miRNAs) [11, 12]. The well-defined role of lncRNAs is the enlistment of modulating complexes of chromatin to particular genomic regions utilizing chromosomal looping [13].

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Some investigations have highlighted the oncogenic or tumor suppressor functions of lncRNAs in advancement and progressions of many cancer types including hepatocellular, lung, pancreatic, osteosarcoma, and colon cancers [14]. Many investigations indicate that transcriptional complexes adjust the expression of lncRNAs typically through attaching to their promoters [15].

Urothelial carcinoma associated 1 (UCA1) as a newfound lncRNA, which contains three exons and two introns, settled in the chromosome 19p13.12 [16–18]. According to recent studies, the transcription factor, hypoxia-inducible transcription, transcriptional complex factor, and microRNA can modulate the expression level of lncRNA-UCA1 (Fig. 1). Up-regulation of lncRNA-UCA1 was initially detected in the oncogenesis of bladder cancer [15]. Previous investigations showed that the lncRNA-UCA1 possibly acts the crucial role as an oncogene in human cancers including hepatocellular, breast, colorectal and gastric [19].

The lncRNA-UCA1 function and mechanism in EC are enigmatic. However, in the present study, we aimed to assess the potential roles of lncRNA-UCA1 dysregulation in the pathogenesis of EC in an Iranian population.

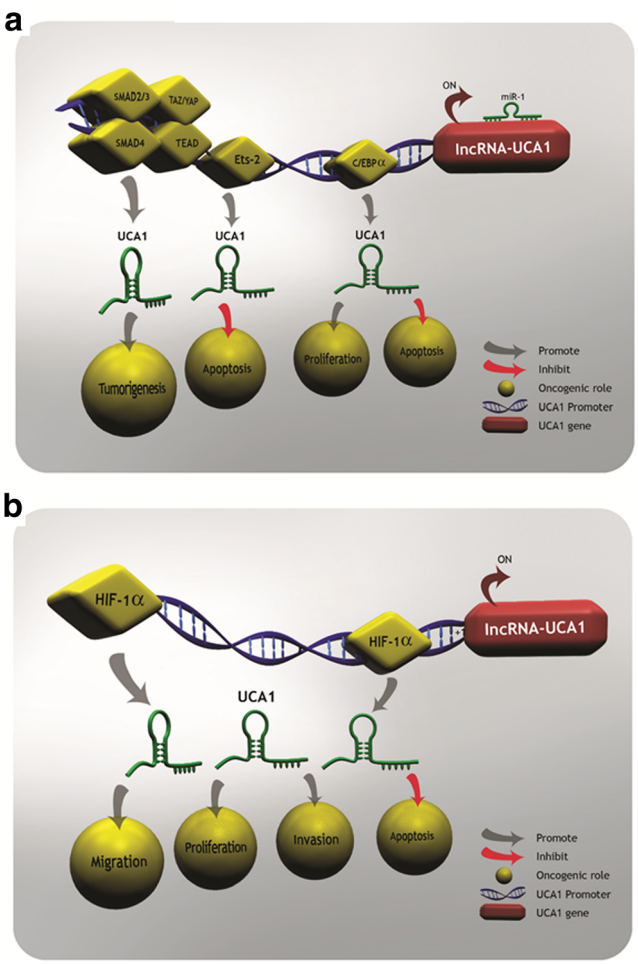

Fig. 1 A schematic explaining an intricate regulatory network between transcription factors SMAD4, SMAD2/3, TAZ/YAP, TEAD, Ets-2, C/EBPα (**a**) and HIF-1α (**b**) the *lncRNA-UCA1* gene expression in tumor microenvironment

Materials and Methods

Patients and Specimens

The present case-control study was performed on 140 formalin-fixed paraffin-embedded tissues (FFPE) samples (70 samples of cancerous tissues and 70 marginal tissues) in patients that were definitively diagnosed by the pathologists during 2015–2017 in the Affiliated the Tabriz International Hospital. In this survey, the patients were selected according to the definitive diagnosis of malignancy by pathologists who identified the stage of malignancy in stages (I-II-III-IV) of the EC. The patients that treated through surgery or those were under chemotherapy were excluded. The study was approved by the Ahar Branch Islamic Azad University of Iran and informed consent was obtained from all individual participants. 10 μm cuts were prepared from FFPE samples to the deparaffinization. All specimens have assessed the level of lncRNA-UCA1 gene expression changes.

RNA Isolation

Total RNA was extracted from EC tissues using NucleoSpin® total RNA FFPE Kit according to the manufacturer's protocol (ACHEREY-NAGEL GmbH & Co. KG, Duren, Germany). Quality and quantity of the extracted RNA were evaluated by standard gel electrophoresis with 1% agarose and a NanoDrop spectrophotometer.

cDNA Synthesis

First strand cDNA was synthesized utilizing PrimeScript™ 1st strand cDNA Synthesis Kit (Takara, Japan) according to the manufacturer's protocols. The cDNA was synthesized from 2 μL of RNA in a 20 μL solution including 1 μL of dNTP mixture (10 mM each), 4 μL of 5X PrimeScript Buffer, 0.5 μL of RNase Inhibitor (20 units), 1 μL of Random 6 mers (50 μM) and 1.0 μl of PrimeScript RTase (200 U/μl). It was synthesized at 42 °C for 30 min and the reaction was inactivated at 95 °C for 5 min.

Quantitative Real-Time PCR (qRT-PCR)

Real-time PCR was performed utilizing TaqMan probe according to premix Ex Taq ™ (Perfect Real Time) kit protocol (Takara, Japan). The PCR amplifications were performed for dena¬turation at 95 °C for 5 min, qPCR was performed for 35 cycles consisting of 95 °C for 8 s, 59 °C for 12 s and 72 °C for 20 s, on the Applied Biosystems 7500. Real-time PCR

reactions were performed in duplicate. The housekeeping gene GAPDH was used for normalizing of gene expression. The correlative levels of lncRNA-UCA1 expression were computed by the $2^{-\Delta\Delta Ct}$ method (Table 1).

Statistical Analysis

Student's t test was used to determine the difference of lncRNA-UCA1 gene expression levels among EC specimens and marginal tissues. To analyze the correlations between lncRNA-UCA1 expression and clinicopathological properties Pearson's chi-square was utilized. A value of $p < 0.05$ was deliberated to demonstrate a statistically notable outcome. All statistical analyses were carried out by SPSS 21.0 software.

Results

A total of 70 patients with EC, 47 patients (63%) were male and 28 patients (37%) were female. The average age determined 63.51 ± 9.41 (ranging from 39 to 88) years. The lncRNA-UCA1 gene expression changes were assessed by Real-time PCR in 70 paired tissues of EC. The results of our research exhibited the lncRNA-UCA1 was up-regulated in cancerous tissues versus the marginal tissues ($P < 0.001$) Fig. 2. We divided the 140 specimens into two group's lncRNA-UCA1 with high expression and low expression levels according to the median cancerous/marginal tissue ratio. The relationship between lncRNA-UCA1 expression and clinical features of EC patients was displayed in Table 2. The result demonstrated that up-regulation of lncRNA-UCA1 was remarkably connected with alcohol drinking ($P = 0.008$) and socioeconomic status ($P = 0.001$), whereas it had no relationship with age, hot drinking and stage (all $P > 0.05$) Table 2.

Discussion

Multiple announcements have demonstrated that various lncRNAs were substantially expressed in cancers and may play oncogenic or tumor suppressor genes roles. Multiple investigators have displayed that lncRNAs are correlated with

Table 1 The primers sequence was used in the *LncRNA-UCA1* gene expression analysis

Gene	Primers Sequence
LncRNA-UCA1	F 5'-ACGCTTAGGCTGGCAACCAT-3'
	R 5'-TGGCCCCATATGCGTGTACT-3'
TaqMan PROBE	5′- TGCCCATGGTGTCCTCAAGCC-3'
GAPDH	F 5′-GCCGTCTAGAAAAACCTGCC-3′
	R 5′-ACCACCTGGTGCTCAGTGTA-3′

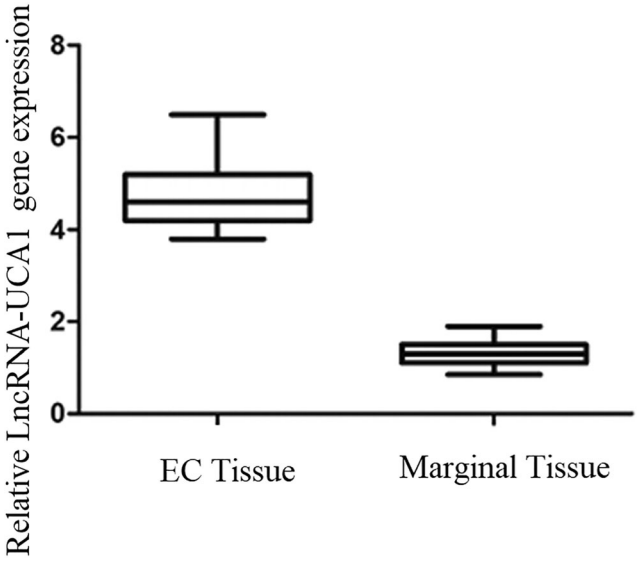

Fig. 2 The relative *lncRNA-UCA1* gene expression changes in cancerous tissues versus the marginal tissues ($P < 0.001$)

the development of ESCC [20, 21]. Considering the previous assessments, the oncogenic role of lncRNA-UCA1 was perceived in different cancers (Table 3).

The information revealed in our research showed that lncRNA-UCA1 was up-regulated in EC tissues compared to paired adjacent normal tissues, which was consistent with the

Table 2 The relationship between the *lncRNA-UCA1* gene expression changes and the clinicopathologic characteristics

Clinical features	Gene Expression Levels		*P* value
	High	Low	
Age (Years)	62.8 ± 2.4	60.2 ± 1.53	0.410
Stage (n)			0.147
I and II	18.0	17.0	
III and IV	12.0	23.0	
Smoking status (n)			0.054
Yes	4.0	19.0	
No	19.0	19.0	
Alcohol drinking (n)			0.008
Yes	14.0	7.0	
No	16.0	33.0	
Hot drinking (n)			0.257
Yes	32.0	15.0	
No	16.0	13.0	
Socioeconomic levels (n)			0.001
Good	17.0	35.0	
Poor	15.0	3.0	
Metastasis status (n)			0.690
No distant metastasis	16.0	12.0	
Distant metastasis	26.0	16.0	

Table 3 Overview of the *lncRNA-UCA1* dysregulation in various cancer types

Cancer types	Up-regulation	Down regulation	Biological function	Application	References
Hypopharyngeal cancer	✓	–	Promotes cell proliferation, migration and invasion	Biomarker	[22]
Glioma cancer	✓	–	Promotes cell proliferation, migration and invasion	Biomarker	[23]
Pancreatic cancer	–	✓	Decreases cell proliferation, prompts cell apoptosis and leads to cell cycle arrest	Biomarker	[24]
Lung cancer	✓	–	Promotes cell proliferation, migration and invasion	Biomarker	[25]
Tongue squamous cell carcinoma cells	✓	–	Promotes cell proliferation, migration and invasion	Biomarker	[26]
Breast cancer	✓	–	Promotes cell proliferation, migration and invasion	Biomarker	[27]
Colorectal cancer	✓	–	Promotes cell proliferation, migration,invasion and inhibits apoptosis	Biomarker therapeutic target	[19, 28]
Gastric cancer	✓	–	–	Biomarker therapeutic target	[29]
Hepatocellular carcinoma	✓	–	Promotes cell proliferation, invasion and migration	Biomarker therapeutic target	[30]
Melanoma	✓	–	Promotes cell proliferation	Biomarker	[31]
Ovarian cancer	✓	–	Promotes cell proliferation, invasion and migration	Therapeutic target	[32]
Esophageal squamous cell carcinoma	✓	–	Promotes cell proliferation, invasion and migration	Biomarker therapeutic target	[33]

former investigations. These results displayed that lncRNA-UCA1 might have an oncogenic role in EC.

Up-regulation of lncRNA-UCA1 led to increased cell proliferation and invasion in hypopharyngeal cancer [22]. In addition, up-regulation of lncRNA-UCA1 contributed to the enhancement of cell proliferation and invasion in glioma cancer [23]. Down-regulation of lncRNA-UCA1 diminished cell proliferation, induced cell apoptosis and resulted in cell cycle arrest in pancreatic cancer [24]. Elevated lncRNA-UCA1 contributed to the development of lung cancer and correlated with clinical diagnosis as a predictive biomarker in the oncogenesis of plasma [25].

Fang et al. revealed that lncRNA-UCA1 was considerably enhanced in tongue squamous cell carcinoma tissues and consistent with lymph node metastasis [26]. LncRNA-UCA1 was reported to be up-regulated in breast cancer tissues versus the adjacent normal tissues [27].

In addition, up-regulated of lncRNA-UCA1 was notably announced in colorectal cancer tissues and its expression was consistent with tumor size, type of histopathology, tumor depth and prognosis in patients of colon cancer [28].

Previously reported that the lncRNA-UCA1 was outstandingly enhanced in gastric cancer tissues and associated with the differentiation, invasion depth, TNM stage, tumor size and poor prognosis [29].

LncRNA-UCA1 was remarkably up-regulated in hepatocellular carcinoma tissues versus non-tumorous tissues, and clinicopathological assessments uncovered the correlation of increased lncRNA-UCA1 with developed TNM stage and cancer metastasis in hepatocellular carcinoma. Meantime, the lncRNA-UCA1 was detected as an autonomous prognostic factor to anticipate overall survival of hepatocellular carcinoma patient [30].

Up-regulation of lncRNA-UCA1 was reported in melanoma tissues compared with non-tumorous tissues. Furthermore, the lncRNA-UCA1 demonstrated an increased expression level in later stages (III and IV) of melanoma tissues versus prime stages (I, II) as well [31].

In addition, the findings revealed that the lncRNA-UCA1 was up-regulated in ovarian cancer. The microarray assay assessment displayed aberrant expressions and varied metastatic potentials of lncRNAs in ovarian cancer cells [32].

Li et al. showed the lncRNA-UCA1 was up-regulated in ESCC tissues and EC cell lines and it's associated with tumor differentiation, clinical stage, and lymph node metas¬tasis [33].

Wang et al. revealed that the lncRNA-UCA1 played the role of tumor suppressor genes in ESCC, and lncRNA-UCA1 was diminished in patients of EC tissues applying qRT-PCR as well as increased lncRNA-UCA1 may prohibit cell proliferation, migration, and invasion [34].

Jiao et al. reported that the lncRNA-UCA1 was remarkably over-expressed in esophageal cancer tissues versus adjacent non-tumorous tissues as and its expression is consistent with TNM stage, tumor differentiation and predicted poor prognosis [35].

Taken together, the multiple investigations displayed that, Wnt signaling pathway has an essential role in oncogenesis and progression of ESCC [34, 36].

Some studies recommended that the Wnt/β-catenin signaling pathway unsuitable activation might result in the progression of human cancers, for instance, ESCC [34]. While the upstream effectors of the Wnt/β-catenin signaling pathway and their modulation of oncogenesis and metastasis in ESCC is still vague and difficult to figure out utterly.

In addition, Deng et al. reported that the lncRNA-UCA1 up-regulation affected the Wnt signaling pathway through suppressing β-catenin function. Therefore, the obtained results propose that enhanced lncRNA-UCA1 lessened absolute and nuclear vital structures of β-catenin either. The correlation between lncRNA-UCA1 and Wnt signaling pathway has evidently not been formerly announced. Accordingly, it is recommended that lncRNA-UCA1 might modulate Wnt signaling to influence incidence and development in ESCC [36].

As described in above-mentioned studies, lncRNA-UCA1 could be lead to the development of EC. Consequently, the most interesting point in this study is that the lncRNA-UCA1 may be utilized as a candidate gene in the progression of EC. Though, the role and mechanism of lncRNA-UCA1 are still enigmatic in EC. However, future evaluations will be necessitated to confirm these mentioned assessments.

Conclusion

Generally, our data indicated that the lncRNA-UCA1 play an important role in the progression of EC and may be considered as a candidate gene in the pathogenesis of EC patients.

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Compliance with Ethical Standards

Conflict of Interest Authors declare no conflict of interest.

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