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Original contribution

Elevated CTHRC1 expression is an indicator for poor prognosis and lymph node metastasis in cervical squamous cell carcinoma☆,☆☆

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Summary Collagen triple helix repeat containing 1 (CTHRC1) is overexpressed in different kinds of cancer tissues and may thus promote tumor formation. Thus, we aimed to explore whether CTHRC1 could be a predictor of clinical significance including survival in cervical squamous cell carcinoma (CSCC). Western blot analysis was conducted in 20 frozen tissue specimens of CSCC and 10 frozen tissue sections of normal cervix. Immunohistochemistry was performed in 130 tissues with CSCC. The relationships of CTHRC1 expression with clinicopathological variables, and prognosis of CSCCs were explored. Statistical analyses were carried out using χ^2 test, multivariate Cox proportional-hazard model, Kaplan-Meier method, and univariate and multivariate logistic regression. The expression of the CTHRC1 protein was significantly higher in tumors than in normal tissues ($P < .001$). CTHRC1 overexpression was strongly associated with the International Federation of Gynecology and Obstetrics stage ($P = .038$), histologic grade ($P < .001$), stromal infiltration depth ($P < .001$), lymphovascular space invasion ($P = .023$), lymph node metastasis ($P = .001$), and recurrence ($P = .021$). The multivariate proportional-hazard model revealed that CTHRC1 overexpression was an independent predictor of overall survival and disease-free survival ($P = .034$ and $P = .025$, respectively). Multivariate logistic regression analysis revealed that high CTHRC1 expression was positively correlated with lymph node metastasis (odds ratio: 2.658; 95% confidence interval: 1.120-6.305; $P = .020$). Therefore, CTHRC1 may be a valuable biomarker for predicting the prognosis and metastasis of CSCC and a potential therapeutic target for treatment of the disease.

1. Introduction

Cervical cancer is a major malignant disease among women and accounts for 444 500 new cases and 230 200 deaths in less developed countries worldwide each year [1]. The overall survival (OS) of patients with cervical cancer has increased because of the development of cervical screening, surgery, chemotherapy, and vaccines against human papillomavirus (HPV). However, most patients are still diagnosed

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at the late stage, and their OS rates remain poor. Furthermore, more than 99% of cervical cancer cases are associated with oncogenic HPV subtypes, and the predominant histological type of cervical cancer is cervical squamous cell carcinoma (CSCC) [2]. Thus, effective biomarkers should be identified for early detection and identification of therapeutic targets for CSCC.

Collagen triple helix repeat containing 1 (CTHRC1) is a secreted glycosylated protein that consists of a short, collagen-like motif with 12 Gly-x-y repeats [3]. CTHRC1 is highly conserved from lower chordates to mammals and widely expressed in injured arteries and skin wounds and in developing skeleton, kidney, and heart. CTHRC1 is a cell type–specific inhibitor of transforming growth factor-β, which influences collagen types I and III deposition, neointimal formation, and smooth muscle cell dedifferentiation. Previous studies reported that CTHRC1 was aberrantly expressed in malignant melanoma and cancers of the lung, gastrointestinal tract, breast, esophagus, cervix, ovary, pancreas, and liver; this protein was also found to be correlated with tumor metastasis and invasion [4-16]. However, the status of CTHRC1 expression and its clinical role in CSCC remain unclear. Thus, the present study aimed to examine CTHRC1 expression in CSCC tissues and explore the possible relationships between CTHRC1 expression and various clinicopathological factors including lymph node metastasis.

2. Materials and methods

2.1. Patients and samples

Paraffin-embedded specimens were obtained from 130 patients with CSCC who received surgery at the Department of Obstetrics and Gynecology, Daqing Oilfield General Hospital, Daqing, China, between May 2010 and May 2012. All patients with CSCC underwent radical hysterectomy and pelvic lymphadenectomy. No patient had received chemotherapy, radiotherapy, or immunotherapy before surgery. The tumor stages were evaluated in line with the International Federation of Gynecology and Obstetrics (FIGO) staging system. Among 130 patients, 74 were classified as FIGO stage I and 56 as FIGO stage II. In the light of histologic grade, 35 cases were well differentiation, 57 were moderate differentiation, and 38 were poor differentiation. Thirty-three cases were confirmed lymph node metastasis by histologic review. Patients with high-risk factors, such as poor histologic grade, parametrial involvement, deep stromal infiltration, lymphovascular space invasion (LVSI), and lymph node metastasis, underwent postoperative radiotherapy. Details of patients' characteristics were provided in Table 1.

The median age of the patients was 43 years (27-70 years). All tissue slides were assessed by 3 experienced pathologists. The patients were followed up for survival analysis until May 2017 (median, 65 months; range, 15-86 months). *OS* was defined as the period from the date of surgery until death or to the time of the most recent follow-up. *Disease-free survival* (DFS) was defined as the time interval (in months) between completion of therapy and recurrence. Recurrence was either radiologically or histologically confirmed. The study was approved by the Medical Ethics Committee of Daqing Oilfield General Hospital, and patient consent was obtained for the purpose of research.

Table 1 Relationship of CTHRC1 protein overexpression with clinicopathologic characteristics in patients with CSCC

Variables	No.	CTHRC1 expression status		*P*
		Low (%)	High (%)	
Age (y)				.935
<45	83	43 (51.8)	40 (48.2)	
≥45	47	24 (51.1)	23 (48.9)	
FIGO stage				.038
I	74	44 (59.5)	30 (40.5)	
II	56	23 (41.1)	33 (58.9)	
Histologic grade				<.001
Well	35	18 (51.4)	17 (48.6)	
Moderate	57	33 (57.9)	24 (42.1)	
Poor	38	16 (42.1)	22 (57.9)	
Tumor size (diameter)				.057
<4 cm	73	43 (58.9)	30 (41.1)	
≥4 cm	57	24 (42.1)	33 (57.9)	
Depth of stromal infiltration				<.001
<1/2	76	50 (65.8)	26 (34.2)	
≥1/2	54	17 (31.5)	37 (68.5)	
LVSI				.023
No	100	57 (57.0)	43 (43.0)	
Yes	30	10 (33.3)	20 (66.7)	
Parametrial involvement				.483
No	122	64 (52.5)	58 (47.5)	
Yes	8	3 (37.5)	5 (62.5)	
Lymph node metastasis				.001
No	97	58 (59.8)	39 (40.2)	
Yes	33	9 (27.3)	24 (72.7)	
Recurrence				.021
No	109	61 (55.0)	48 (45.0)	
Yes	21	6 (33.3)	15 (66.7)	

2.2. Western blot analysis

Twenty frozen tissue specimens of CSCC and 10 frozen tissue sections of normal cervix were homogenized in radioimmunoprecipitation assay buffer containing 1% protease inhibitor mixture. The mixture was centrifuged at 12 000*g* and 4°C for 15 minutes, and the supernatant was obtained. The protein extract (60 μg) was separated by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred onto polyvinylidene difluoride filters (Millipore Company, Billerica, MA, USA). The membranes were blocked in a blocking buffer (pH 7.6) at 37°C for 1 hour and incubated with CTHRC1 protein rabbit anti-human polyclonal

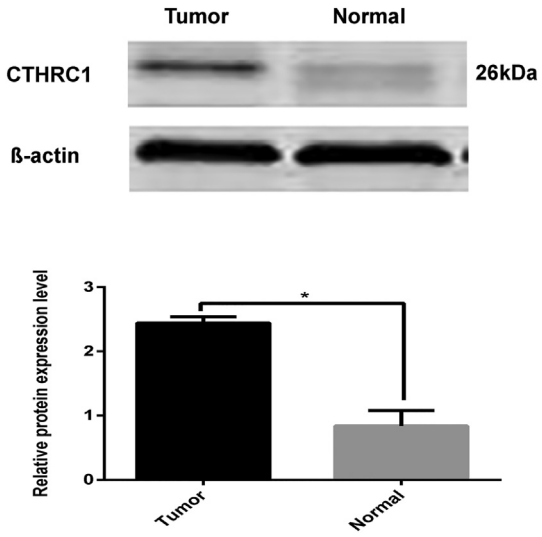

Fig. 1 Western blotting analysis of CTHRC1 protein expression in normal cervix and in CSCC tissues. The expression of CTHRC1 was elevated in CSCCs compared with normal cervical tissues ($P < .001$). Each protein sample was repeated in triplicate.

antibody (Abcam, diluted at 1:800, Cambridge, MA, USA) overnight at 4°C. The blots were stained using a chemiluminescence detection system. β-Actin was used as internal control.

2.3. Immunohistochemical staining of CTHRC1

Paraffin-embedded samples were sectioned at 4 μm and stained with hematoxylin and eosin for tumor confirmation. Using the Two-Step IHC Detection Reagent Kit (Zhong Shan Golden Bridge Biological Technology Inc, Beijing, China) following standard procedures, the sections were dewaxed in xylene and rehydrated through graded alcohol concentrations. The slides were incubated in 3% H_2O_2 for 10 minutes and then immersed in 10 mmol/L citrate buffer (pH 6.0) in a pressure cooker for 3 minutes for antigen restoration. After washing with phosphate-buffered saline, the sections were incubated with CTHRC1 antibody (Abcam, diluted at 1:200) overnight at 4°C and a secondary antibody for 20 minutes at room temperature followed by incubation with dispensed diaminobenzidine solution. The negative ones were stained with phosphate-buffered saline instead of primary antibodies.

2.4. Immunohistochemical staining evaluation

The levels of CTHRC1 protein expression were assessed semiquantitatively based on the combined scores of the staining intensity and percentage of positive-staining tumor cells. The staining intensity was scored as follows: 0 (no staining), 1 (weak staining), 2 (moderate staining), and 3 (strong

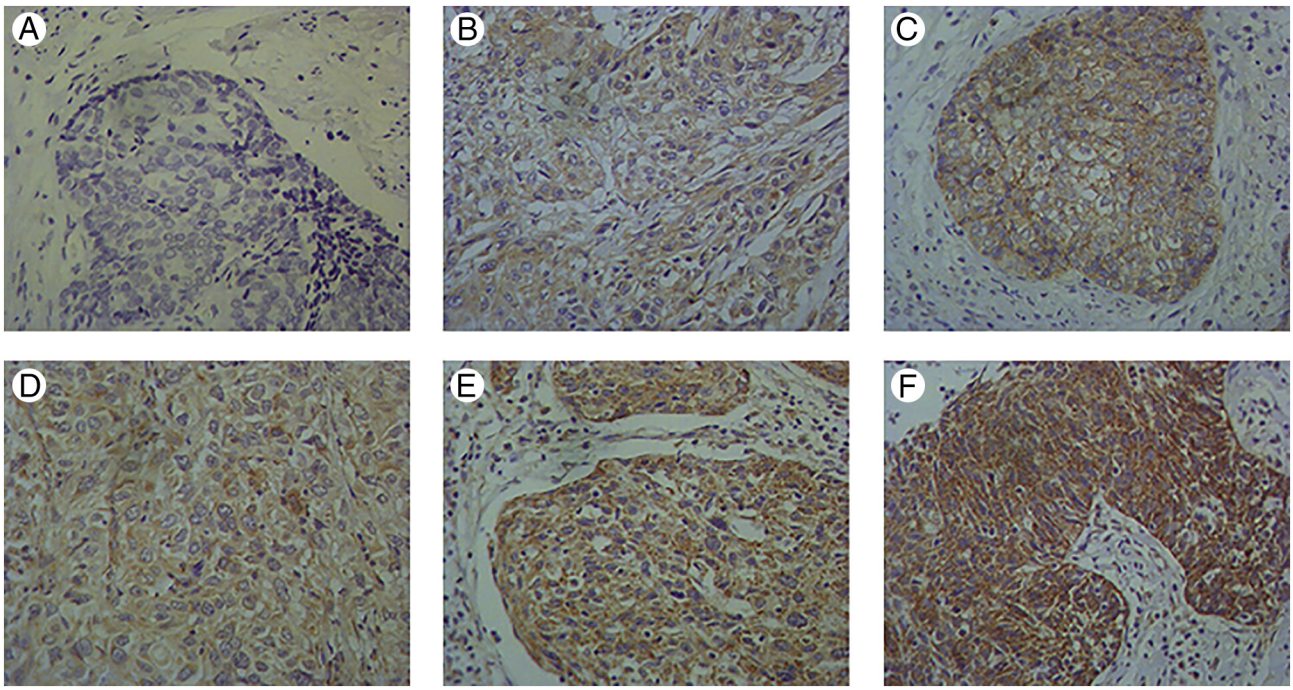

Fig. 2 Immunohistochemical staining of CTHRC1 in cervical tissues: (A) negative control of CTHRC1 expression in a CSCC (original magnification ×200); (B) low expression of CTHRC1 in CSCC (×400); (C) low expression of CTHRC1 in CSCC (×200); (D) high expression of CTHRC1 in CSCC without lymph node metastasis (×400); (E) high expression of CTHRC1 in CSCC without lymph node metastasis (×200); (F) high expression of CTHRC1 in CSCC with lymph node metastasis (×200).

staining). The percentage of positive cells, measured as the extent of immunostaining, was scored as follows: 0 (<25%), 1 (5%-50%), and 2 (>50%). The sum of staining intensity score and percentage of positive staining was used to determine expression levels: 0-2, low expression and 3-5, high expression. The independent scores were carried out by 2 pathologists who were blinded of the clinicopathologic information. Cases with significant disagreement were re-reviewed by discussion between the original 2 pathologists.

2.5. Statistical analysis

SPSS 13.0 software (SPSS, Chicago, IL) was used for statistical analysis. The χ^2 test was used to evaluate the relationship of CTHRC1 overexpression with clinicopathologic variables. Survival curves were plotted by the Kaplan-Meier method and estimated using log-rank test. A Cox regression model was used to identify factors that were independently related with the prognosis. Univariate and multivariate logistic regressions were performed to assess the effect of CTHRC1 elevated expression on lymph node metastasis. The experiment of Western blot was repeated in triplicate. A $P < .05$ (2-sided) was considered statistically significant.

3. Results

3.1. Elevated CTHRC1 protein expression in CSCC tissues

Western blot analysis revealed a specific band for CTHRC1 at 20 kDa (Fig. 1), indicating the low expression of the protein in normal cervical tissues. The CTHRC1 expression significantly increased in CSCC tissues compared with that in normal tissues (Fig. 1, $P < .001$).

The CTHRC1 expression was primarily localized in the cytoplasmic compartment of the tumor cells. The representative immunostaining images are presented in Fig. 2.

3.2. Association between CTHRC1 protein expression and clinicopathological variables

The relationship between CTHRC1 expression and clinicopathological variables in CSCCs is summarized in Table 1. The elevated CTHRC1 expression was associated with FIGO stage ($P = .038$), histologic grade ($P < .001$), stromal infiltration depth ($P < .001$), LVSI ($P = .023$), lymph node metastasis ($P = .001$), and recurrence ($P = .021$). By contrast, no

Table 2 Univariate survival analysis of OS and DFS in 130 patients with CSCC

Variables	OS			DFS		
	Mean ± SE	5 y (%)	*P*	Mean ± SE	5 y (%)	*P*
Age (y)			.416			.421
<45	75.6 ± 2.4	80.7		74.5 ± 2.6	78.7	
≥45	78.1 ± 2.5	87.2		76.9 ± 2.9	87.1	
FIGO stage			.003			.002
I	82.1 ± 1.4	91.9		81.5 ± 1.6	90.2	
II	67.6 ± 3.3	71.4		65.6 ± 3.7	70.1	
Histologic grade			.007			.004
Well	85.3 ± 0.5	84.4		85.3 ± 0.5	82.3	
Moderate	76.4 ± 2.6	78.9		75.6 ± 2.8	77.9	
Poor	67.4 ± 4.1	73.7		64.7 ± 4.7	70.3	
Tumor size (diameter)			.066			.061
<4 cm	79.5 ± 2.0	89.0		78.7 ± 2.2	87.3	
≥4 cm	71.0 ± 2.9	75.4		69.4 ± 3.3	74.3	
Depth of stromal infiltration			.002			.002
<1/2	81.8 ± 1.5	90.8		81.1 ± 1.7	90.1	
≥1/2	67.6 ± 3.5	72.2		66.1 ± 3.6	70.1	
LVSI			<.001			<.001
No	80.6 ± 1.5	90.0		79.9 ± 1.7	88.6	
Yes	57.0 ± 4.2	60.0		52.9 ± 4.5	58.2	
Parametrial involvement			.089			.090
No	77.5 ± 1.8	84.4		76.5 ± 1.9	82.9	
Yes	52.3 ± 6.8	62.5		50.0 ± 7.9	62.5	
Lymph node metastasis			<.001			<.001
No	80.6 ± 1.6	89.7		80.2 ± 1.7	89.1	
Yes	63.5 ± 4.4	63.6		60.7 ± 4.9	60.5	
CTHRC1 expression			<.001			<.001
Low	84.1 ± 0.9	95.5		83.9 ± 1.0	94.9	
High	66.9 ± 3.1	69.8		65.1 ± 3.4	68.0	

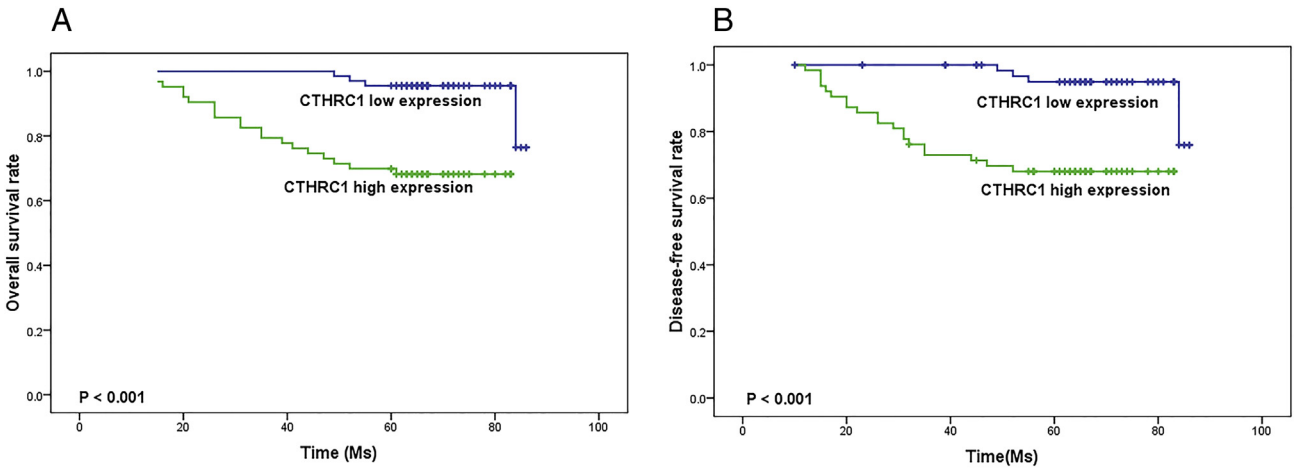

Fig. 3 Kaplan-Meier analysis for survival of prognosis in 130 patients with CSCC according to CTHRC1 expression: (A) OS and (B) DFS.

Table 3 Multivariate Cox regression analysis of OS and DFS in 130 patients with CSCC

Variables	OS			DFS		
	HR	95% CI	*P*	HR	95% CI	*P*
FIGO stage			.014			.007
I						
II	3.347	1.282-8.736		3.870	1.450-10.328	
Histologic grade						.036
Well			.032			
Moderate	16.049	1.953-131.908		13.095	1.609-106.605	.016
Poor	14.554	1.812-116.919	.010	15.165	1.880-122.359	.011
LVSI			.012			.002
No			.004			
Yes	3.904	1.550-9.831		4.837	1.818-12.870	
Lymph node metastasis						.026
No			.047			
Yes	2.538	1.012-6.360		2.755	1.126-6.740	
CTHRC1 expression						.024
Low			.032			
High	4.247	1.136-15.875		4.465	1.222-16.312	

Table 4 Multivariate analysis of the association between lymph node metastasis and CTHRC1 expression in CSCC

Variables	*B*	SE	*P*	OR	95% CI
Depth of stromal infiltration					
<1/2					
≥1/2	−0.355	0.465	.040	0.701	0.282-1.744
Parametrial involvement					
No					
Yes	1.575	0.503	.033	4.831	1.802-12.955
CTHRC1 expression					
Low					
High	0.977	0.441	.020	2.658	1.120-6.305

Abbreviations: *B*, parameter estimator of association coefficient; SE, standard error.

significant correlation was found between CTHRC1 immunoreactivity and clinicopathological parameters, including age, tumor size, and parametrial involvement ($P > .05$).

3.3. Effect of CTHRC1 overexpression on survival

The univariate logistic regression analysis indicated that elevated CTHRC1 expression in CSCC tissues was associated with reduced OS and DFS of the patients (Table 2; both $P < .001$; Fig. 3). The multivariate logistic regression analysis revealed that CTHRC1 overexpression was an independent prognostic factor for OS and DFS of patients with CSCC (Table 3; $P = .032$ and $P = .024$, respectively).

3.4. Association between CTHRC1 overexpression and lymph node metastasis in CSCC

The univariate logistic regression analysis of the clinicopathological parameters indicated that lymph node metastasis was strongly correlated with histologic grade ($P = .019$), parametrial involvement ($P = .013$), stromal infiltration depth ($P = .003$), and CTHRC1 overexpression ($P = .027$). In the evaluation of the independent prediction of CTHRC1 expression, the multivariate logistic regression analysis (Table 4) demonstrated that lymph node metastasis was associated with CTHRC1 overexpression ($P = .020$; odds ratio [OR]: 2.658; 95% confidence interval [CI]: 1.120-6.305), stromal infiltration depth ($P = .040$; OR: 0.701; 95% CI: 0.282-1.744), and parametrial involvement ($P = .033$; OR: 4.831; 95% CI: 1.802-12.955).

4. Discussion

In this study, CTHRC1 expression was strongly increased in CSCC compared with that in normal tissues. Hence, CTHRC1 may have an oncogenic effect on CSCC. We also explored the relationship between CTHRC1 expression and clinicopathological characteristics in detail. CTHRC1 was found to be associated with lymph node metastasis and poor clinical prognosis. Therefore, CTHRC1 may be an independent predictor of the prognosis of CSCC.

CTHRC1 plays an important role in vascular remodeling in response to injuries by promoting cell migration, limiting collagen matrix deposition, and inhibiting collagen I synthesis. In melanoma, CTHRC1 can facilitate cell metastasis by enhancing cell adhesion and modifying action organization and cell morphology variation. A high level of CTHRC1 expression can influence the sensitivity of temozolomide in melanoma cells [5]. CTHRC1 can also contribute to promoter demethylation and tumor cell invasion and metastasis. Moreover, the high CTHRC1 expression was significantly associated with pTNM stage, tumor differentiation, tumor invasion depth, lymph node metastasis, recurrence, vascular/lymphatic invasion, tumor size, and peritoneal seeding in gastric cancer [17]. Moreover, CTHRC1 overexpression could be a useful biomarker for early detection of non–small cell lung cancer and could be related to poor prognosis [18]. CTHRC1 can promote the characterization of the tumor microenvironment, lymph node, and bone metastasis in breast cancer [9,19]. In hepatocellular carcinoma, CTHRC1 increases the adhesion of cancer cells to the extracellular matrix (ECM) by activating focal adhesion kinase and promoting the migration capability of tumor cells, thereby inducing the expression of integrin β1 expression, an independent predictor of prognosis [5]. Our results are consistent with previous reports on the roles of CTHRC1 in tumor progression. Overall, the present study reported that CTHRC1 overexpression could be related to the FIGO stage, tumor differentiation, recurrence, metastasis, and poor treatment outcome. Therefore, CTHRC1 could be an independent prognostic factor.

A high level of CTHRC1 expression could contribute to lymph node metastasis and tumor progression by degrading ECM protein and inducing changes in the structural composition of stromal ECM in the tumor microenvironment [16]. The Wnt/PCP signaling pathway and the tumor microenvironment play an important role in cancer progression. Tissue polarity and cell movement are controlled by the Wnt/PCP signaling pathway and mainly involved in tumor propagation and metastasis. CTHRC1 plays a considerable role in proliferation, invasion, and metastasis of esophageal squamous cell carcinoma by upgrading cyclin D1, snail1, and MMP14 through the Raf/MEK/ERK/FRA-1 pathway [15]. CTHRC1 is a Wnt cofactor that selectively activates the Wnt/PCR pathway by stabilizing ligand-receptor interactions; this protein also induces tissue matrix remodeling and repair by limiting collagen deposition and promoting of cell migration [20,21].

In renal cell carcinoma cells, CTHRC1 downregulation positively suppresses the epithelial-mesenchymal transition process; inhibits renal cell carcinoma cell migration and invasion; and restrains the expression of β-catenin, c-Myc, and cyclin D1 [22]. In silencing CTHRC1 U-87 MG cells, E-cadherin is upregulated, whereas N-cadherin, SNAIL, and Slug are downregulated. Therefore, CTHRC1 plays a major role in the growth of glioblastoma through epithelial-mesenchymal transition and could be a candidate molecular target for glioblastoma prevention and therapy [14].

CTHRC1 could be an important potential marker for assessing tumor metastasis and survival of patients with CSCC. However, our study has some limitations. We did not detect CTHRC1 staining in benign cervical mucosa or in CIN. And the sample size of different groups is small. As such, further randomized research should be conducted on a large sample size, which should include all pathological types, benign cervical mucosa, and cervical intraepithelial neoplasia, to verify the specificity and sensitivity of CTHRC1 and its prognostic role in CSCC.

Finally, CTHRC1 was overexpressed in a large proportion of patients with CSCC, and a high level of CTHRC1 expression was significantly correlated with tumor metastasis and

poor prognosis. Therefore, CTHRC1 may be a novel prognostic target marker for CSCC. Further research should investigate the effect of CTHRC1 on the migration and metastasis of CSCC cell lines by using siRNA to elucidate the underlying mechanisms of CTHRC1 activation. Moreover, our subsequent study will determine the effect of HPV status associated with CTHRC1 on CSCC metastasis and migration.

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