Abstract. The aim of the present study was to analyze the differences in zinc finger of the cerebellum 1 (ZIC1) expression between cervical cancer tissue, precancer tissue and normal cervical tissue to determine its clinicopathological and prognostic value in cervical squamous cell carcinoma (CSCC). Reverse transcription-quantitative PCR was used to determine the mRNA expression levels of ZIC1 in 569 fresh-frozen biopsy tissues, and immunohistochemistry was performed to detect ZIC1 protein expression in 80 CSCC tissues and 320 cervical intraepithelial neoplasia (CIN) grade III samples. The association of ZIC1 expression with the clinicopathological characteristics of CSCC was then analyzed using Cox regression analysis, and Kaplan-Meier curves were used to analyze the prognostic value. The level of ZIC1 mRNA expression in CSCC was significantly lower compared with normal cervical tissues and CIN I-III tissues (P<0.001). There was a negative correlation between ZIC1 immunoreactivity score (IRS) in CSCC tissue and adjacent noncancerous tissue (R=-0.279; P=0.012); the mean IRS of ZIC1 in CSCC tissue was 5.36±3.48, which was significantly lower compared with the corresponding adjacent noncancerous tissues (11.31±5.68; P<0.001) and CIN III samples (10.42±1.54; P<0.001). In addition, expression of ZIC1 was negatively associated with International Federation of Gynecology and Obstetrics (FIGO) stage (P=0.027) and lymph node metastasis (P<0.001). In Cox regression analysis, ZIC1 expression [hazard ratio (HR), 0.61; 95% confidence interval (CI), 0.40-0.92; P=0.018), FIGO staging (HR, 3.55; 95% CI, 2.35-5.37; P<0.001) and lymph node metastasis (HR, 2.50; 95% CI, 1.62-3.86; P<0.001) were three independent prognostic factors of overall survival. Furthermore, ZIC1 expression was also associated with disease-free survival (P=0.003). These results suggest that ZIC1 expression in CSCC may be lower than in normal cervical tissues or CIN tissues, and high expression of ZIC1 may be negatively associated with FIGO stage and lymph node metastasis. Therefore, ZIC1 may be a promising biomarker for the prognosis of CSCC.

Introduction

Human papillomavirus (HPV) infection is the primary cause of the majority of cases of cervical cancer (CC) worldwide, and CC has become one of the leading causes of cancer-associated death among females in 2018 (1). The most common type of CC is cervical squamous cell carcinoma (CSCC) (1). The prognostic of cervical cancer remains poor as it has a high rate of metastasis and recurrence (2). Cervical intraepithelial neoplasia (CIN) are types of precancerous lesions closely associated with cervical carcinoma, including CIN I-III which reflect the continuous development of cervical cancer (3). Therefore, it is crucial to identify novel prognostic markers for auxiliary assessment of CIN grading and prognosis of patients with CSCC.

Zinc finger of the cerebellum 1 (ZIC1) was first identified in cerebellum tissues in 1994 (4). A previous study has shown that ZIC1 serves an important role in the growth and development of the brain nervous system, muscle cell production and bone development (5). In addition, methylation of ZIC1 is associated with the development and progression of cervical cancer (6). Ectopic ZIC1 expression was found to suppress the growth of colorectal cancer cells by reducing phosphorylation of Akt and

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Contribution equally

Abbreviations: HPV, human papillomavirus; CC, cervical cancer; CSCC, cervical squamous cell carcinoma; CIN, cervical intraepithelial neoplasia; ZIC, zinc finger of the cerebellum; IHC, immunohistochemistry; IRS, immunoreactivity score; OS, overall survival; DFS, disease-free survival; RT-qPCR, reverse transcription-quantitative PCR; Leep, loop electrosurgical excision procedure; FIGO, International Federation of Gynecology and Obstetrics

Key words: zinc finger of the cerebellum 1, cervical squamous cell carcinoma, prognosis, clinicopathological features, cervical intraepithelial neoplasia
Erk (7). Furthermore, ZIC1 downregulation has been associated with metastasis and a poor prognosis in patients with breast carcinoma or gastric cancer (8,9). However, a previous study reported that ZIC1 was upregulated in endometrial cancer in Hong Kong Chinese women (10). Our previous study also revealed that ZIC1 was upregulated in endometrial cancer compared with corresponding normal tissue, and was positively correlated with endometrial carcinogenesis (11). Although ZIC1 exhibits different functions in neoplasms compared with normal physiological tissue, ZIC1 is thought to be essential for carcinogenesis, and may thus serve as a novel target for treating patients with cervical cancer (10,11).

Based on the reported effects of ZIC1 on cervical carcinoma, the aim of the present study was to determine the mRNA expression levels of ZIC1 in normal cervical tissue, CIN samples and CSCC tissues by using reverse transcription-quantitative PCR (RT-qPCR), and to compare ZIC1 expression between the three tissue types. In addition, the protein expression levels of ZIC1 in 80 cases of CSCC with radical hysterectomy were determined using immunohistochemistry (IHC) to examine the clinicopathological and prognostic value of ZIC1 in patients with CSCC.

Materials and methods

Tissue samples. The present study was approved by The Ethics Committee of Kunshan First People's Hospital (Jiangsu, China), and written informed consent was obtained from each patient for the use of their tissues for research and publication. A total of 569 fresh-frozen biopsy tissues comprised of normal cervical tissues (n=400), CIN I (n=50), CIN II (n=36), CIN III (n=38) and CSCC (n=45) were obtained from Kunshan First People's Hospital and the mRNA was extracted. These patients were recruited between January 2010 and December 2018, and the mean age of the patients was 53.26±11.08 years. Additionally, 80 patients (the mean age was 57.39±8.64 years) with CSCC at International Federation of Gynecology and Obstetrics (FIGO) stage IA, IB or IIA underwent radical hysterectomy at Kunshan First People's Hospital between January 2009 and January 2013 (12). The patients included in the study had not received chemotherapy or radiotherapy prior to surgery. The tumor specimens (mean size, 2.73±1.06 cm) and the corresponding adjacent noncancerous tissues were fixed in 10% formalin at 20˚C for 8 h and then embedded in paraffin blocks. Complete clinical and pathological data were available for all the patients. All patients received carboplatin + paclitaxel treatment regimen following surgery. The mean age of the patients was 53.10±12.76 years, and the follow-up duration ranged from 3-60 months, with a mean follow-up duration of 46.33±2.317 months. In addition, the pathological tissues of 320 patients with CIN III (the mean age was 47.21±9.07 years and recruited between January 2010 and December 2018) who underwent a loop electrosurgical excision procedure (LEEP) at Kunshan First People's Hospital were also stored in paraffin blocks for IHC analysis. The 569 cohort of patients, the 80 patients with CSCC and the 320 patients with CIN III were all proven to exhibit high-risk HPV infection using the Digene Hybrid Capture (r) (HC2) High-Risk HPV DNA Test (Qiagen GmbH), as previously described (13).

RT-qPCR. After pathological confirmation, total RNA was extracted using TRIzol® reagent (Thermo Fisher Scientific, Inc.), and 2 μg RNA was reverse transcribed using the miScript II RT kit (Thermo Fisher Scientific, Inc.) at 50˚C for 15 min then 85˚C for 2 min. qPCR was performed using an q5 real-time PCR detection system (Bio-Rad Laboratories, Inc.) using SYBR Premix Ex Taq™ kit (Takara Bio, Inc.). The sequences of the primers were as follows: ZIC1 forward, 5'-GGCTCCTTTTGTGGAATTAA-3' and reverse, 5'-AGT AATCATCTCCTTCTGGG-3'; and GAPDH forward, 5'-GAAGGTGAAGTGGTGTG-3' and reverse, 5'-GAAGAGT GGTAGGGGATTTC-3'. The PCR thermocycling conditions consisted of 94˚C for 4 min; followed by 40 cycles of 95˚C for 1 min, 60˚C for 1 min and 72˚C for 1 min. The relative mRNA expression levels were calculated using the 2^(-ΔΔCq) method and the formula of ΔΔCq was (Cq_Human(ZIC1)-Cq_Human(GAPDH))-(Cq_Normal ZIC1-Cq_Normal(GAPDH)) (14).

Hematoxylin and eosin staining. After deparaffinization and rehydration, 5 μm longitudinal sections were stained with hematoxylin solution at 20˚C for 5 min followed by 5 dips in 1% acid ethanol and then rinsed in distilled water. Sections were stained with eosin solution at 20˚C for 3 min, followed by dehydration with graded alcohol and clearing in xylene. The mounted slides were then examined and photographed using an inverted light microscope (magnification x40, 100 and 400; Nikon Corporation).

IHC and evaluation of immunohistochemical staining. Immunostaining for ZIC1 was performed using a SP rabbit and mouse horseradish peroxidase (HRP) kit (CoWin Biosciences) on tissue sections cut from formalin-fixed paraffin-embedded CSCC tumor lesions or CIN III samples. The ZIC1 rabbit polyclonal antibody (1:200; cat. no. bs-11609R; BIOSS) was used as the primary antibody. In addition, PBS without primary antibodies was used as a negative control. The samples were incubated with the primary antibody at 4˚C overnight and subsequently, the biotinylated HRP secondary antibody (1:1,000; incubated at 20˚C for 15 min) and streptavidin-HRP conjugates (CoWin Biosciences) were used to detect ZIC1 expression. An immunoreactivity score (IRS) was calculated using a semi-quantitative assessment system for each case by two pathologists. The semi-quantitative assessment system was obtained by combining a score for staining intensity with a score for the staining percentage. The staining intensity score was defined as: 0, no staining; 1, mild staining; 2, moderate staining; and 3, strong staining. The staining percentage score was defined as: 0, 0%; 1, 1-10%; 2, 11-20%; 3, 21-30%; 4, 31-40%; 5, 41-50%; 6, 51-60%; 7, 61-70%; 8, 71-80%; 9, 81-90%; and 10, 91-100%. IRS was calculated by multiplying the staining intensity score with the staining percentage score. Any disagreement in the IRS score between the two pathologists was resolved by discussion. The mean IRS score from 80 patients with CSCC was calculated to be 5.36±3.48 and this was used as the cut-off value. Cases with an IRS score ≥5 were included in the high ZIC1 expression group, and cases with an IRS score <5 were included in the low ZIC1 expression group.

Statistical analysis. Continuous variables were expressed as the mean ± standard deviation and analyzed by using a
one-way ANOVA with a post-hoc Least Significant Difference test. Spearman’s rank correlation was performed to identify potential correlations in the IRS score between CSCC and the corresponding adjacent noncancerous tissues. A Pearson’s χ² test was used to analyze the association between ZIC1 expression and the clinicopathological characteristics of patients with CSCC. Cox regression analysis and Kaplan-Meier curves combined with a Log Rank test were used to analyze overall survival (OS) and disease-free survival (DFS). SPSS version 20.0 (IBM, Corp.) and GraphPad version 6.0 (GraphPad Software, Inc.) were used for statistical analyses. P<0.05 was considered to indicate a statistically significant difference.

Results

ZIC1 mRNA expression levels in biopsy tissues. The mRNA expression levels of ZIC1 in CSCC, CIN and normal cervical tissues were determined using RT-qPCR (Fig. 1). The level of ZIC1 mRNA expression in CSCC was significantly lower compared with normal cervical tissues or in CIN I-III (P<0.001; Fig. 1A). ZIC1 mRNA expression levels in CIN I-III were also significantly lower compared with normal cervical tissues (P<0.001; Fig. 1A). In addition, ZIC1 mRNA expression levels in CIN were associated with CIN grade, as lower expression was observed with increasing CIN grade (P<0.01; Fig. 1B). ZIC1 expression in any CIN grade was significantly lower compared with normal cervical tissues (P<0.01 or P<0.001; Fig. 1A).

Expression of ZIC1 in CSCC and CIN III samples. Hematoxylin and eosin staining of (A) noncancerous tissues, (C) CIN III and (E) CSCC tissues (magnification x100). Immunohistochemistry staining for ZIC1 protein (B) in noncancerous tissues, (D) CIN III and (F) CSCC tissues (magnification x400). (G) There was a negative correlation between ZIC1 expression in CSCC tissues and expression in adjacent noncancerous tissues. (H) Statistical comparison of IRS of ZIC1 staining in CSCC, noncancerous tissues and CIN III samples. *P<0.05, ***P<0.001. CSCC, cervical squamous cell carcinoma; N, corresponding adjacent noncancerous tissues; CIN, cervical intraepithelial neoplasia; ZIC1, zinc finger of the cerebellum 1; IRS, immunoreactivity score.
with that in the corresponding adjacent noncancerous tissues (11.31±5.68; P<0.001) and the CIN III samples (10.42±1.54; P<0.001; Fig. 2H). In addition, the mean IRS of ZIC1 in noncancerous tissues was significantly higher compared with CIN III samples (P=0.014; Fig. 2H).

**Association between ZIC1 expression and clinicopathological features in patients with CSCC.** As the mean IRS of ZIC1 expression in CSCC was 5.36±3.48, an IRS of 5 was used as the cut-off value. Cases with an IRS ≥5 were included in the high ZIC1 expression group, and cases with IRS <5 were included in the low ZIC1 expression group. In Table I, high expression of ZIC1 was negatively associated with FIGO stage (P=0.027) and lymph node metastasis (P<0.001), but there were no significant associations with any of the other clinicopathological characteristics (age, tumor size, tumor grading and vascular invasion) between high and low ZIC1 expression (P>0.05).

**OS.** Kaplan-Meier analysis showed that the OS time of the low ZIC1 expression group (39.62±4.06 months) was significantly lower compared with the high ZIC1 expression group (51.26±2.44 months; P=0.019; Fig. 2H). In univariate Cox regression analysis (Table II), ZIC1 (P=0.027), tumor grading (P=0.020), lymph node metastasis (P=0.003) and FIGO stage (P<0.001) were associated with OS. In multivariate analysis, ZIC1 expression (HR, 0.61; 95% CI, 0.40-0.92; P=0.018), FIGO staging (HR, 3.55; 95% CI, 2.35-5.37; P<0.001) and lymph node metastasis (HR, 2.50; 95% CI, 1.62-3.86; P<0.001) were determined to be independent prognostic factors. Of the 320 patients with CIN grade III, there were no deaths in the 5 years following LEEP treatment.

**DFS.** In Fig. 3B, the DFS time of the low ZIC1 expression group (33.88±3.77 months; P=0.002) was significantly lower compared with the high ZIC1 expression group (48.65±2.53 months). In Cox regression analysis (Table III), ZIC1 expression (P=0.003), tumor grading (P=0.022), FIGO stage (P<0.001) and lymph node metastasis (P=0.006) were four independent factors of DFS. Of the 320 patients with CIN grade III, there were no incidences of recurrence in the 5 years following LEEP treatment.

**Discussion**

In developing countries, cervical cancer is one of the most common types of cancer in females, which has significant repercussions for the medical and academic fields (1). Although the 9-valent HPV vaccine has the potential to prevent HPV infection and the occurrence of high-risk HPV cervical cancer, widespread use of the vaccine has not been adopted due to
Table II. Prognostic value of ZIC1 expression and clinicopathological factors for overall survival of patients with cervical squamous cell carcinoma.

| Variable                                | Univariate analysis | Multivariate analysis |
|-----------------------------------------|---------------------|-----------------------|
|                                         | HR  | 95% CI  | P-value | HR  | 95% CI  | P-value |
| ZIC1 expression, high vs. low           | 0.42 | 0.20-0.91 | 0.027  | 0.61 | 0.40-0.92 | 0.018*  |
| Age, >53 vs. ≤53 years                  | 1.07 | 0.80-1.44 | 0.652  |      |          |         |
| Tumor size, >2 vs. <2 cm                | 1.33 | 0.84-2.11 | 0.217  |      |          |         |
| Tumor grading, G3 vs. G1 and G2         | 1.27 | 1.04-1.56 | 0.020  |      |          |         |
| FIGO stage, IIA vs. I                   | 2.32 | 1.68-3.19 | <0.001 | 3.55 | 2.35-5.37 | <0.001  |
| Lymph node metastasis, yes vs. no       | 1.52 | 1.16-2.00 | 0.003  | 2.50 | 1.62-3.86 | <0.001  |
| Vascular invasion, yes vs. no           | 1.05 | 0.81-1.36 | 0.704  |      |          |         |

ZIC1, zinc finger of the cerebellum 1; HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; -, no results.

Figure 3. Kaplan-Meier survival curves of patients with cervical squamous cell carcinoma stratified by high or low expression of ZIC1. (A) Overall survival and (B) disease-free survival. Blue lines represent the low ZIC1 expression group and the green lines represent the high ZIC1 expression group. ZIC1, zinc finger of the cerebellum 1.

Table III. Prognostic value of ZIC1 expression and clinicopathological factors for disease-free survival of patients with cervical squamous cell carcinoma.

| Variable                                | Univariate analysis | Multivariate analysis |
|-----------------------------------------|---------------------|-----------------------|
|                                         | HR  | 95% CI  | P-value | HR  | 95% CI  | P-value |
| ZIC1 expression, high vs. low           | 0.41 | 0.22-0.76 | 0.005  | 0.69 | 0.55-0.88 | 0.003  |
| Age, >53 vs. ≤53 years                  | 1.38 | 0.89-2.13 | 0.146  |      |          |         |
| Tumor size, >2 vs. <2 cm                | 1.46 | 0.81-2.64 | 0.205  |      |          |         |
| Tumor grading, G3 vs. G1 and G2         | 1.86 | 1.25-2.75 | 0.002  | 1.59 | 1.07-2.35 | 0.022  |
| FIGO stage, IIA vs. I                   | 2.02 | 1.36-2.99 | <0.001 | 2.89 | 1.95-4.29 | <0.001 |
| Lymph node metastasis, yes vs. no       | 1.68 | 1.13-2.49 | 0.010  | 2.23 | 1.26-3.94 | 0.006  |
| Vascular invasion, yes vs. no           | 1.12 | 0.73-1.73 | 0.597  |      |          |         |

ZIC1, zinc finger of the cerebellum 1; HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics.
methylation of the ZIC1 promoter (19). Ectopic expression of that in normal thyroid cells, and was typically associated with significantly reduced in malignant thyroid cells compared with normal tissues and CIN samples. In addition, ZIC1 expression was found to be significantly reduced with normal cervical tissues, and with CIN samples. In addition, ZIC1 expression in CIN samples was significantly lower compared with normal cervical tissues, and with CIN samples. In addition, ZIC1 expression was found to be significantly reduced with normal cervical tissues, and with CIN samples. In addition, ZIC1 expression was found to be significantly reduced with normal cervical tissues, and with CIN samples. In addition, ZIC1 expression was found to be significantly reduced with normal cervical tissues, and with CIN samples. In addition, ZIC1 expression was found to be significantly reduced with normal cervical tissues, and with CIN samples. In addition, ZIC1 expression was found to be significantly reduced with normal cervical tissues, and with CIN samples.
Competing interests

The authors declare that they have no competing interests.

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