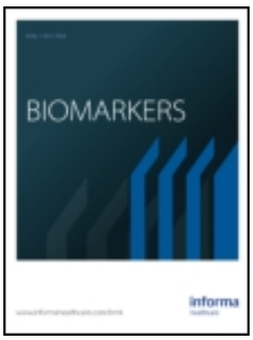

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RESEARCH ARTICLE

Downregulation of ERp57 expression is associated with poor prognosis in early-stage cervical cancer

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Abstract

Objective: We investigated the clinical significance of ERp57 in the progression of cervical cancer.
Methods: mRNA and protein expression of ERp57 in cervical neoplasias were examined.
Results: ERp57 mRNA expression was significantly decreased in cervical cancers. Immunohistochemistry revealed that ERp57 expression in 123 cervical cancers was downregulated compared to cervical intraepithelial neoplasias or normal tissues ($p < 0.001$). Low ERp57 expression was significantly associated with worse overall survival (HR = 12.19, $p = 0.018$).
Conclusions: Low ERp57 expression independently predicts a poor outcome for patients with cervical cancer, supporting the notion that ERp57 may be a promising novel cancer target.

Keywords

Cervical cancer, ERp57, immunohistochemistry, survival, tissue microarray

History

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Introduction

Cervical cancer is one of the most common gynecologic tumors worldwide and is a leading cause of female cancer-related death in developing countries (Moody et al., 2010). According to official statistics, more than 50% of all cases and deaths from the disease worldwide were reported in the Asia Oceania region, with the highest incidence and mortality rates in South Central and Southeast Asia (Garland et al., 2012). The high mortality is ascribed to disease recurrence after cervix resection and lack of effective treatment for advanced stage disease (Chun, 2009). Although many clinicopathological factors have been described as prognostic tools, a limited number of these parameters have been incorporated and used in the clinic. Furthermore, molecular markers that accurately predict response to therapy are limited because of their low sensitivity and specificity. Therefore, it is necessary to identify reliable molecular markers predictive of the clinical outcome of patients with cervical cancer.

ERp57, the protein encoded by the *PDIA3* on chromosome 15, is a glycoprotein-specific thiol-oxidoreductase and a component of the protein disulfide isomerase (PDI) family that is involved in the major histocompatibility complex (MHC) I antigen processing molecules (Lindquist et al., 1998). The role of the MHC class I molecule is to present small peptides to cytotoxic T lymphocytes (Radcliffe et al., 2002), which can potentially trigger a cascade of immune responses. Defective component expression of the MHC class I antigen processing complex is hypothesized to be an important mechanism of MHC class I downregulation and can lead to immune evasion by tumor cells. Defects in MHC class I expression have been found in many tumor types and are associated with advanced stage and poor survival in patients with cancer (Atkins et al., 2004; Mehta et al., 2008; Ogino et al., 2003).

Because ERp57 has an important role in antigen processing, the regulation of ERp57 protein expression may be associated with human diseases including cancer. Tumor cells utilize impaired antigen presentation as one immune escape mechanism that results in the progression of tumorigenesis (Igney et al., 2002). For example, downregulation or loss of MHC class I antigens has been found in many types of tumors and is associated with an adverse prognosis (Atkins et al., 2004; Ogino et al., 2003; Seliger et al., 2000). Furthermore, loss of ERp57 protein expression has been reported to be associated with poor prognosis in gastric cancer and head and neck cancer (Leys et al., 2007; Ogino et al., 2003). Despite evidence supporting ERp57 involvement in tumorigenesis, the relationship between ERp57 expression and clinicopathological factors in various human cancers, including cervical cancer, remains unclear.

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In this study, we investigated the mRNA level of ERp57 in cervical cancer cells, cancer tissues and normal cervical epithelial tissues. Additionally, we studied the subcellular localization of ERp57 in CaSki cells by Western blotting combined with subcellular fractionation. To evaluate the potential relationship between ERp57 and various clinicopathological parameters, we analyzed ERp57 protein expression in a large series of cervical cancer, precursor and corresponding normal tissues, and demonstrated that ERp57 expression levels are altered during cervical carcinogenesis and down-regulation of ERp57 is correlated with poor prognosis.

Materials and methods

Patients and specimens

After gaining institutional review board approval, 123 paraffin-embedded cervical cancer, 187 cervical intraepithelial neoplasia (CIN) and 310 matched normal cervix tissues that had been resected at Gangnam Severance Hospital, Yonsei University College of Medicine between 1996 and 2010 were retrieved. Some of the paraffin blocks were provided by the Korea Gynecologic Cancer Bank through the Bio & Medical Technology Development Program of the Korea Ministry of Education, Science and Technology. All tumor tissues were histologically revised and only specimens with sufficient tumor cells were included in the tissue microarray (TMA) construction. Tumor staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) classification system.

Primary treatment for stage I/II consisted of type II or III radical hysterectomy with pelvic lymph node (LN) dissection. In cases of increased risk of relapse including positive resection margins, parametrial invasion, or positive LN metastasis, platinum-based concurrent chemoradiation was added as adjuvant therapy. Patients with inoperable disease were treated with radiotherapy (both external radiotherapy and brachytherapy) or both cisplatin-based chemotherapy and radiotherapy.

Data collected by reviewing the medical records of patients with cervical cancer included age, diagnoses of prior or current malignancies, Hybrid Capture® 2 (HC2) results, SCC (squamous cell carcinoma) antigen levels, surgical procedure and survival status. SCC antigen levels were recorded at primary diagnosis up to one week prior to operation or chemoradiation therapy. Pathological data included tumor grade, cell type, tumor size and LN metastases. Fresh cervical tissue samples including normal cervix ($n = 2$) and cervical cancer ($n = 10$) were also collected for mRNA detection. In addition, five cervical cancer cell lines were used for mRNA detection.

SYBR green real-time PCR

The HeLa, CaSki, SiHa and ME180 cell lines were purchased from the American Type Culture Collection (ATCC, Manassas, VA) and the SNU17 cell line was purchased from the Korean Cell Line Bank (KCLB, Seoul, Korea). Cells were maintained in DMEM/F12 supplemented with 10% FBS in the presence of 5% CO_2 at 37 °C in a humidified incubator. Total RNA was extracted from 2 normal cervical epithelial tissues, 5 cervical cancer cell lines and 10 cervical cancer tissues using the RNeasy Mini kit (Qiagen, Valencia, CA). Next, cDNA was generated from 2 μg of total RNA extracted from each sample using the SuperScript™ III first-strand synthesis system (Invitrogen, Carlsbad, CA) according to the manufacturer's protocol. SYBR Green real-time PCR was performed using an ABI 7300 instrument (Applied Biosystems, Foster City, CA). Primers specific for *ERp57* were used (forward: 5′-GTCGAAGGGCCTTTC TTG-3′, reverse: 5′-AGCTGCGTGGCAAGGATAAA-3′). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a house-keeping gene, was used as an internal control. Amplification was performed under the following conditions: pre-incubation for 2 min at 50 °C, then denaturation for 10 min at 95 °C followed by 40 cycles of denaturation for 15 sec at 95 °C and annealing/extension for 1 min at 60 °C. The comparative $2^{-\Delta\Delta Ct}$ method was used for relative quantification of gene expression as described previously (Livak et al., 2001).

Western blotting

CaSki cells were cultured, harvested and fractionated with the NE-PER Nuclear and Cytoplasmic extraction kit according to the manufacturer's protocol (NE-PER Reagents, Thermo Scientific, Rockford, IL). Ten micrograms of the cellular fractionations were separated by 4–12% SDS-PAGE and transferred to a nitrocellulose membrane. After blocking for one hour with 5% nonfat milk in TBST (50 mM Tris, 150 mM NaCl, 0.05% Tween 20, pH 7.5), the membrane was rinsed with TBST and then incubated overnight at 4 °C with polyclonal rabbit anti-ERp57 (1:500; Santa Cruz Biotechnology, Santa Cruz, CA) in TBST containing 5% BSA. For validation of the cellular fractionation process, the membrane was also blotted with antibodies against calnexin (BD Transduction Lab, San Jose, CA) and Lamin B1 (Santa Cruz Biotechnology). Subsequently, the membrane was washed with TBST and incubated with anti-mouse or rabbit conjugated to horseradish peroxidase (1:5000; Millipore, Billerica, MA) for two hours. The signal was detected using a SuperSignal Chemiluminescence kit (Thermo Scientific).

Tissue microarray (TMA) construction and immunohistochemical staining

TMAs were constructed from archival formalin-fixed, paraffin-embedded tissue blocks, as previously described (Noh et al., 2012). Briefly, for each tumor and matched normal epithelial tissue, a representative area was carefully selected from a hematoxylin and eosin (H&E) stained section of the donor block, cored and placed into the recipient array block using a 1.0-mm needle.

For immunohistochemical staining, 5 μm paraffin sections were incubated at 60 °C for two hours, deparaffinized in xylene and hydrated in serial alcohol solutions to distilled water for five minutes each. Heat antigen retrieval was performed by submerging slides in pH 6 citrate buffer at 121 °C for 15 minutes using a pressure cooker (DAKO, Carpinteria, CA) and blocking in 1% skim milk for 30 minutes. Endogenous enzyme activity was inhibited with 3% hydrogen peroxide containing sodium azide for an additional

30 minutes. After rinsing, the sections were incubated at room temperature for one hour with antibodies against ERp57 (1:200, Santa Cruz Biotech., rabbit polyclonal IgG, Cat.# sc-32761, epitope corresponding to amino acids 108-207 mapping within an internal region of ERp57 of human origin). The remainder of the procedure, including labeling and visualization, was completed using an automated immunostaining system with a NovoLink Polymer Detection System (Leica Biosystems, Newcastle, UK). Stained sections were lightly counterstained with hematoxylin, dehydrated in graded alcohol solutions, cleared in xylene, mounted and cover-slipped. For validation of the immunohistochemical staining on tissue microarray slides, we selected five conventional whole section slides from five cases included in this study, performed immunohistochemical staining for ERp57 and compared the staining pattern of the tissue microarray slides and matched conventional slides from the same case. In addition, stromal cells in whole sections of cervical cancer tissue were used as an internal positive control. The primary antibody was omitted from the negative control.

Interpretation of ERp57 expression

Protein expression was measured using a semi-quantitative method (Kirkegaard et al., 2006). A histoscore was generated based on (a) intensity [categorized as 0 (absent), 1 (weak), 2 (moderate) or 3 (strong)] and (b) the percentage of positively stained epithelial cells [scored as 0 (0–5% positive), 1 (6–25%), 2 (26–50%), 3 (51–75%) or 4 (>76%)]. The overall protein expression score was calculated by multiplying the intensity and positivity scores (overall score range, 0–12). The histoscore was then dichotomized into loss of expression (histoscore, 0–6) and intact expression (histoscore, 7–12). We arbitrarily selected a histoscore of 7 as the cut-off point for intact expression because a histoscore of 7 or more corresponded to cases with diffuse (>51%) and strong or moderate intensity. We did not compare other cut-off values in this study.

Statistical analysis

The Mann–Whitney test or the Kruskal–Wallis test for continuous variables was used when variance homogeneity was not assumed. Otherwise one-way analysis of variance (ANOVA) was used when appropriate. Survival curves were generated by the Kaplan–Meier method, and statistical significance was calculated by the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model to determine the independent significance of relevant clinical covariates. Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL). Statistical significance was set at $p<0.05$ and all p values were determined from two-sided tests.

Results

Clinicopathological characteristics of cases

Patients ranged in age from 21 to 79 years (mean, 42.6 years). The mean ages were 39.3 ± 10.3 years for low-grade CIN, 38.4 ± 11.0 years for high-grade CIN and 48.8 ± 11.4 years for cervical cancer. There was a significant age difference between low- or high-grade CIN and cancer patients ($p<0.001$, respectively). However, ERp57 expression did not correlate with patient age, but was similar in all age groups (Spearman's $rho = -0.068$, $p = 0.233$). Patient clinical characteristics are detailed in Table 1. Tumor grade data was available for 119 cases, and 4 cases (3.4%) were well, 80 cases were moderate (67.2%), and 35 cases were poor (29.4%). FIGO staging was available for all 123 cases: 89 cases were stage I (72.3%) and 34 cases were stage II (27.7%). There were 96 squamous cell carcinomas (78.0%), 22 adenocarcinomas/adenosquamous carcinomas (17.9%), 4 small cell carcinomas (3.3%) and 1 clear cell carcinoma (0.8%). Follow-up duration ranged from 5 to 60 months, with a mean of 37.8 months. The HC2-based HPV infection rate was 76.5% (26/34) in low-grade CIN, 88.9% (96/108) in high-grade CIN and 95.3% (61/64) in cervical cancer.

Table 1. Expression of ERp57 on IHC analysis in relation to clinicopathological characteristics.

	No.	%	Mean scores (95% CI)	Range	p Value
All study subjects	620	100	8.96 (8.68–9.23)	0–12	
Diagnostic category					$p<0.001$
Normal	310	53.4	10.79 (10.56–11.02)	0–12	
Low-grade CIN	37	5.4	10.81 (10.01–11.61)	4–12	
High-grade CIN	150	21.7	6.81 (6.20–7.43)	0–12	
Cancer	123	17.8	5.75 (5.18–6.32)	0–12	
FIGO stage					$p=0.879$
I	89	72.3	5.78 (5.08–6.47)	0–12	
II	34	27.7	5.68 (4.65–6.70)	0–12	
Tumor grade					$p<0.001$
Well/moderate	84	70.5	6.44 (5.75–7.13)	0–12	
Poor	35	29.5	4.09 (3.18–4.99)	0–12	
Cell type					$p=0.004$
SCC	96	78.0	5.31 (4.71–5.92)	0–12	
Others	27	22.0	7.30 (5.94–8.65)	0–12	
Tumor size					$p=0.520$
≤4 cm	85	69.1	5.62 (4.91–6.33)	0–12	
>4 cm	38	30.9	6.03 (5.05–7.00)	0–12	
LN metastasis					$p=0.601$
No	80	78.4	5.78 (5.06–6.49)	0–12	
Yes	22	21.6	6.18 (4.73–7.63)	0–12	
SCC antigen					$p=0.297$
Negative	63	68.4	5.38 (4.60–6.16)	0–12	
Positive	29	31.6	6.10 (4.96–7.25)	2–12	
HPV test in CIN					$p=0.391$
Negative	20	14.1	8.70 (6.90–10.50)	NA	
Positive	122	85.9	7.89 (7.18–8.59)	NA	

SCC, squamous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous carcinoma; NA, not applicable.

mRNA expression and subcellular localization of ERp57

The *ERp57* expression levels were significantly lower in cancer cell lines (mean $2^{-\Delta\Delta Ct} = 0.36$, $p = 0.014$) and tumor-bearing cancer tissues (mean $2^{-\Delta\Delta Ct} = 0.89$, $p = 0.013$) compared with normal cervical epithelial tissues (mean $2^{-\Delta\Delta Ct} = 8.89$), reflecting low *ERp57* mRNA expression in cancer cell lines (24.7-fold) and tissues (9.9-fold) (Figure 1a). To examine the specificity and capability of anti-ERp57 antibodies, we subsequently investigated the level of ERp57 protein in CaSki cells by Western blotting. Western blot analysis of the cultured cervical cancer cultured cells revealed a clear single band around 60 kDa corresponding

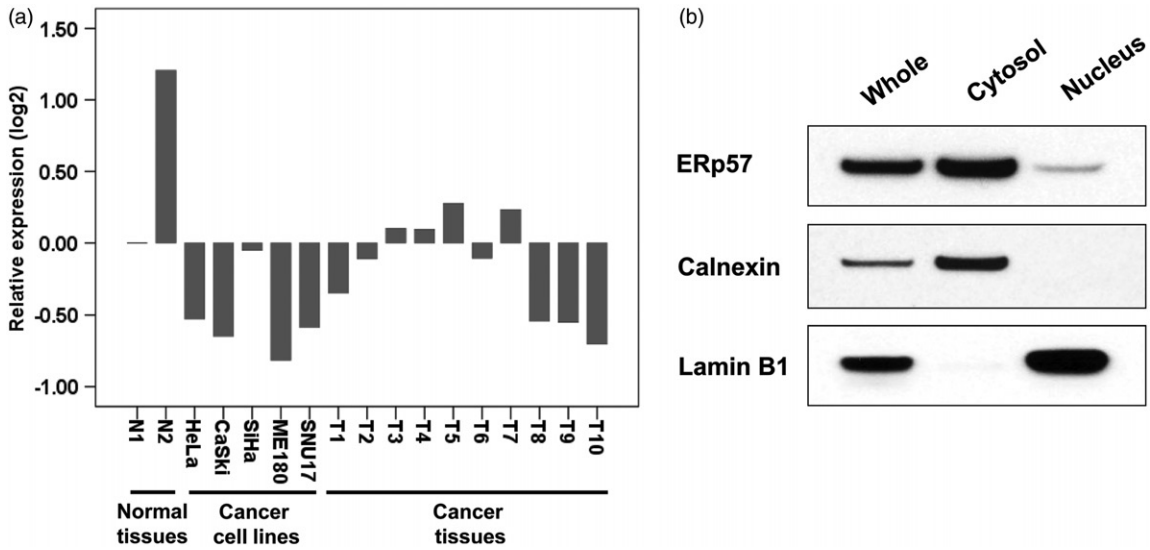

Figure 1. Relative quantitation and subcellular localization of ERp57. (a) Based on the $\Delta\Delta C_T$ relative to the normal cervical epithelial tissue, the relative expression of ERp57 mRNA in cervical cancer cells and tissues was calculated. The reference tissue, N1, was considered to have a value of 1. N, normal cervical epithelial tissue; T, cervical cancer tissue. (b) Western blot analysis characterized the expression of ERp57 in CaSki cells. Nuclear and cytoplasmic fractions from CaSki cells were analyzed by Western blot analysis using an anti-ERp57 antibody. Calnexin and Lamin B were used as an index for each nuclear or cytosolic fraction.

to ERp57 (Figure 1b). Although ERp57 was detected in both cytosolic and nuclear fractions, high expression was restricted to cytosolic fractions (Figure 1b). The purities of the cytosolic and nuclear fractions were respectively confirmed with Calnexin and Lamin B1.

Association between ERp57 expression and clinicopathological characteristics

As shown in Figure 2, positive staining for ERp57 protein was located primarily in the cytoplasm of tumor and normal epithelial cells. Expression was higher in normal cervical epithelial tissue and low-grade CIN specimens than in high-grade CIN and cancer tissues ($p < 0.001$) (Table 1). This trend of progressively lower ERp57 protein expression corresponding to the phases of cervical cancer progression was significant by Spearman's rank correlation (p value of -0.589, $p < 0.001$). In addition, ERp57 immunoreactivity significantly correlated with tumor grade ($p < 0.001$) and cell type ($p = 0.004$) (Figure 3).

Prognostic significance of ERp57 expression

The mean follow-up period was 37.89 months (95% CI, 34.16–41.63). By the end of follow-up, 16 patients (13.0%) had died of cervical cancer, and recurrence or persistent disease was reported in 15 patients (12.2%). Kaplan–Meier plots demonstrated that patients with FIGO stage II and low ERp57 expression (histoscore ≤ 6) had significantly worse disease-free survival ($p < 0.001$ and $p = 0.029$, respectively) (data not shown), and patients with low ERp57 expression also showed significantly worse overall survival ($p = 0.019$) (Figure 4). Cox multivariate proportional hazards analysis showed that low ERp57 expression [hazard ratio = 2.87 (95% CI, 1.03–8.07), $p = 0.044$], LN metastasis [hazard ratio = 2.79 (95% CI, 1.21–6.42), $p = 0.016$], and large tumor size [hazard ratio = 2.78 (95% CI, 1.17–6.60), $p = 0.020$] were related to poor disease-free survival (Table 2). Furthermore, low ERp57 expression [hazard ratio = 12.19 (95% CI, 1.75–36.10), $p = 0.018$] and non-SCC cell type [hazard ratio = 4.33 (95% CI, 1.57–11.91), $p = 0.005$] were independent prognostic factors for overall survival.

Discussion

ERp57 has been found in many different subcellular locations and it is involved in a remarkable variety of processes. One of the widely studied functions of ERp57 is its role in the assembly of MHC class I antigen processing (Lindquist et al., 2001). The glycosylated heavy chain of MHC class I binds to both calnexin and ERp57, and this complex oxidizes the heavy chain through disulfide bond formation. The oxidized heavy chain allows assembly of soluble subunit β_2-microglobulin and subsequently contributes to the formation of the MHC class I peptide-loading complex (Garbi et al., 2006). This complex is composed of heavy chain class I protein, β_2-microglobulin, calreticulin, ERp57, tapasin and the transporters associated with antigen presentation (TAPs). It has recently been reported that the level of *ERp57* gene promoter methylation was significantly higher in CIN and cervical cancer cases in comparison to normal tissues. In addition, the high level of *ERp57* methylation was correlated with human papillomavirus 16 positivity in human cervical cancer cases (Hasim et al., 2012). Therefore, ERp57 may be linked to cancer progression by an unknown mechanism.

To gain some insight into the timing of ERp57 down-regulation during tumor development, we studied ERp57 expression in low- and high-grade CIN, both of which are considered premalignant lesions, and in invasive cervical cancer. IHC analysis revealed a drastic reduction in ERp57 protein expression in high-grade CIN (mean histoscore = 6.81) and invasive cervical carcinoma (mean = 5.75) specimens compared to normal tissues (mean = 10.79). This finding suggests that ERp57 may play an important role in cervical carcinogenesis.

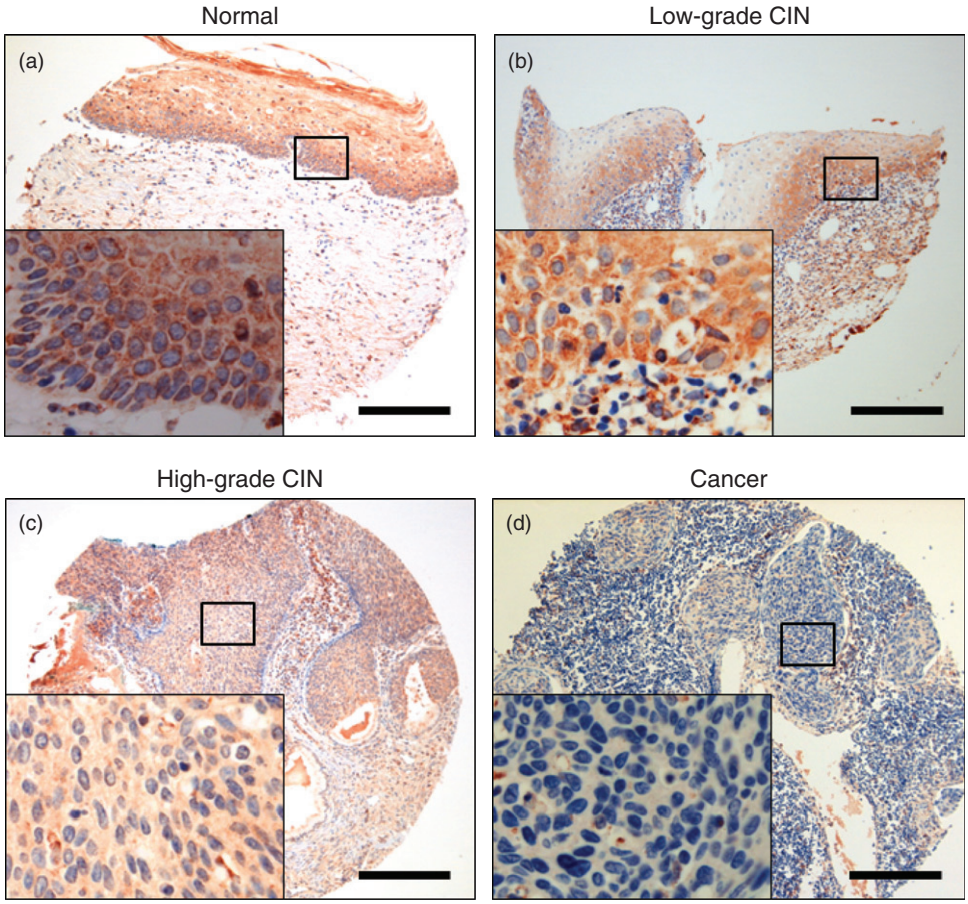

Figure 2. Representative ERp57 immunohistochemical staining images of formalin-fixed paraffin-embedded uterine cervix tissues on tissue microarrays show strong positive diffuse granular cytoplasmic staining in normal cervical epithelial tissue (a), weak to moderate cytoplasmic staining for low- (b) and high-grade (c) CIN and an absence of staining in cervical cancer specimens (d). The subcellular distribution is dominantly cytoplasmic and no definite nuclear staining pattern is noted. Bars: 200 μm.

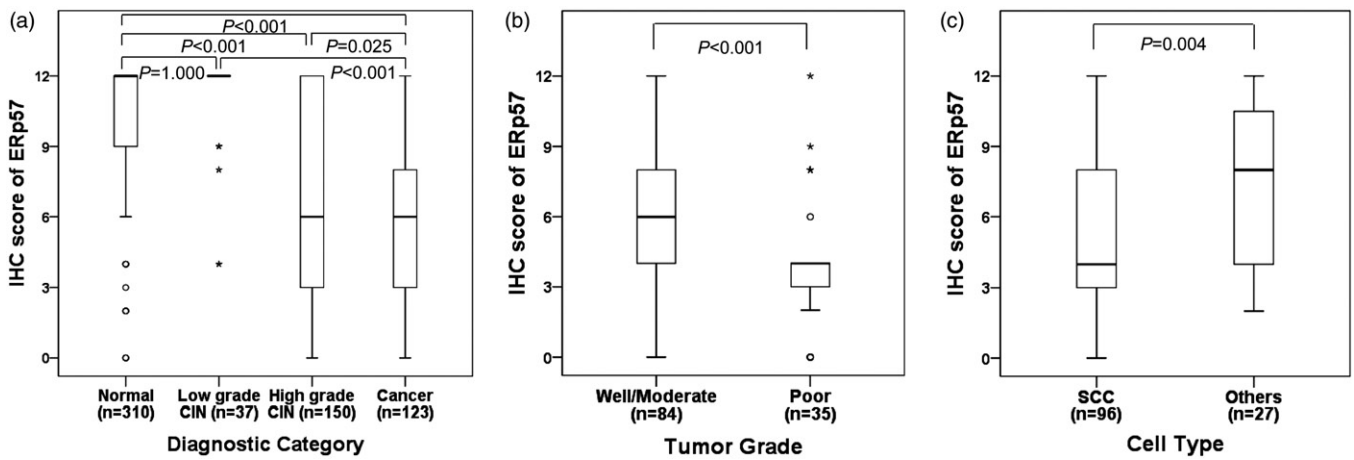

Figure 3. IHC staining scores for ERp57 in cervical neoplasm samples. IHC staining scores for ERp57 in high-grade CIN, cervical cancer and metastasis specimens were significantly lower than that in normal controls (a). ERp57 expression was significantly decreased in poorly differentiated (b) and squamous cell carcinomas (c).

As an MHC class I peptide-loading complex component, ERp57 is important for T-cell-mediated anti-tumor or antiviral immunity. Few studies have investigated the expression and distribution of ERp57 in tumors in addition to its clinical significance. Mehta et al. previously reported a 28–60% loss of ERp57 expression depending on histological type. They suggested that downregulation of ERp57 was significantly associated with HLA class I downregulation, a potential contributor to tumor progression (Mehta et al., 2008). Recently, Hasim and colleagues analyzed the association of cervical carcinogenesis with the aberrant regulation of HLA class I and expression of antigen processing machinery components including ERp57 (Hasim et al., 2012). They immunohistochemically examined the expression

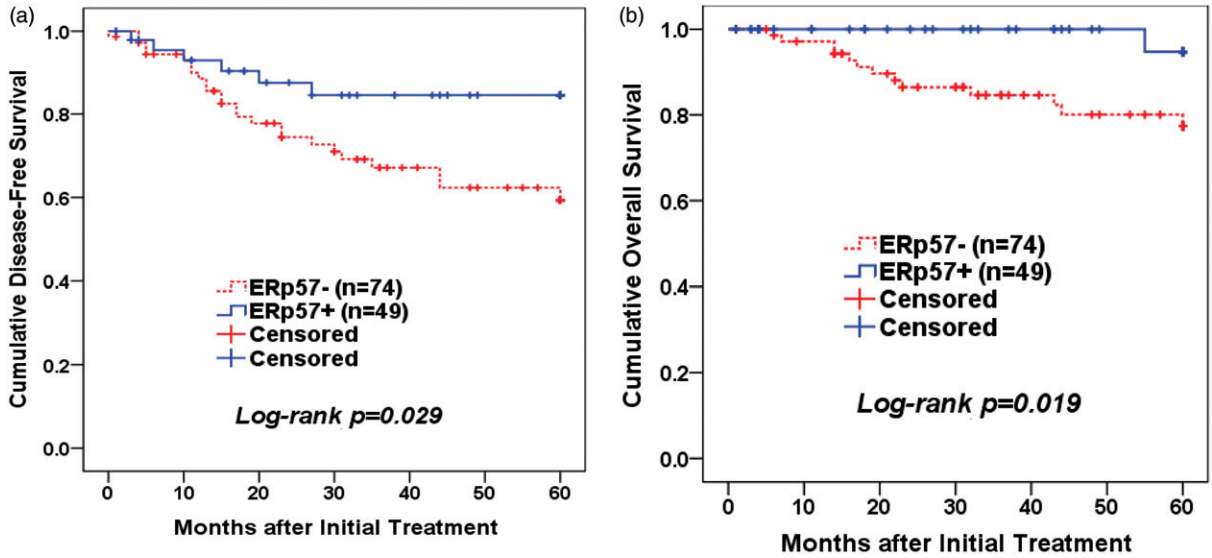

Figure 4. Kaplan–Meier plots for disease-free survival (a) and overall survival (b) for patients categorized by ERp57 expression. ERp57-, low ERp57 expression (histoscore, 0–6); ERp57+, ERp57 high expression (histoscore, 7–12).

Table 2. Univariate and multivariate analyses of the associations between prognostic variables and overall and disease-free survival in 123 cervical cancer cases.

	Disease-free Survival hazard ratio [95% CI], *p* value		Overall Survival hazard ratio [95% CI], *p* value	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
FIGO stage II	6.22 [3.25–12.89], <0.001	NS	NS	NA
Cell type (non-SCC)	NS	NA	2.76 [1.02–7.43], 0.044	4.33 [1.57–11.91], 0.005
Tumor grade (poor)	NS	NA	NS	NA
Tumor size (>4 cm)	3.00 [1.59–5.67], 0.001	2.78 [1.17–6.60], 0.020	NS	NA
LN metastasis	3.54 [1.74–7.20], <0.001	2.79 [1.21–6.42], 0.016	NS	NA
Age	NS	NA	NS	NA
SCC positive	NS	NA	NS	NA
ERp57 low expression	2.69 [1.10–6.56], 0.030	2.87 [1.03–8.07], 0.044	7.80 [1.24–19.70], 0.037	12.19 [1.75–36.10], 0.018

CI, confidence interval; NS, not significant; NA, not applicable.

of ERp57 in cervical lesions (64 CINs and 63 SCCs) and detected a loss of ERp57 expression in both CIN (42%) and SCC (56%). They also reported that ERp57 protein expression was significantly lower in lower stage tumors than in higher stages and it was inversely correlated with tumor differentiation. Consistent with previous studies, we found that ERp57 expression decreased according to the progression of cervical tumorigenesis ($p<0.001$) and was significantly stronger in well and moderately differentiated tumors in comparison with poorly differentiated ones ($p<0.001$). However, in contrast to their study, there was no significant difference in ERp57 expression between FIGO stages I and II. This discrepancy may be explained by a lack of standardized immunohistochemical methods, different standards of interpretation, small number of examined cases and/or a different disease spectrum in the cases studied.

With regard to different cancer cell types, the fact that ERp57 expression was significantly lower in squamous cell carcinomas (mean histoscore = 5.31) compared with non-SCC types (mainly adenocarcinoma/adenosquamous carcinomas; 81.5%, 22 out of 27) (mean histoscore = 7.30) was a finding of interest, as it suggests that the two aforementioned carcinomas can be distinguished based on genetic alterations. Furthermore, this finding demonstrates that each histologic type of cervical cancer develops via a distinct molecular mechanism. Consistent with our findings, Mehta et al. reported a higher frequency of ERp57 expression loss in squamous cell carcinomas (60%, 45 out of 76) compared with adenocarcinomas (28%, 7 out of 25) in their IHC study HLA class I loss in cervical carcinomas (Mehta et al., 2008). These findings suggest that each histologic type of cervical cancer could develop independently, and further studies are needed to identify the molecular genetic changes and percentage of ERp57 downregulation according to cell type. We also included HPV infection status in our analysis and observed no statistical difference between the expression of ERp57 in HPV-positive and -negative patients. Whether ERp57 expression is directly regulated by high-risk HPV remains unclear.

Our most notable finding is that low expression of ERp57 in cervical cancer predicts a shorter disease-free and overall survival. To our knowledge, the negative influence of ERp57 expression on the prognosis of cervical carcinoma patients has not been described previously. Multivariate Cox hazard analysis indicated that low ERp57 expression, large tumor size and LN metastasis are significantly associated with poorer disease-free survival in cervical cancer patients. Moreover, low ERp57 expression and non-SCC cell type were independent prognostic factors for overall survival on

multivariate analysis. Consistent with our findings, Leys et al. demonstrated that a loss of ERp57 expression was associated with tumor invasion and poor survival in an IHC study of 164 gastric cancer patients (Leys et al., 2007). Thus, given the role of ERp57 in the assembly of the MHC class I antigen processing complex, these findings suggest that downregulation of ERp57 may contribute to more aggressive tumor behavior. Furthermore, this study supports the notion that low ERp57 expression could serve as a novel and independent predictor of recurrence and death in early-stage cervical cancer patients. Because downregulation of ERp57 was an independent predictor of poor survival in early-stage disease, one can therefore infer that evaluation of ERp57 in patients with early-stage disease might be of significant value in identifying individuals who would benefit from more aggressive post-operative adjuvant therapies.

In conclusion, this is the first study to find that ERp57 expression is associated with the progression of cervical carcinogenesis, with a gradual reduction in the order of progression from normal epithelium to CIN to cancer. We also discovered important correlations between the downregulation of ERp57 and clinicopathological parameters that might be potentially useful clinically. Moreover, we suggest that downregulation of ERp57 expression is an independent predictor of poor prognosis in early-stage cervical cancer.

Declaration of interest

No potential conflicts of interest were disclosed.

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