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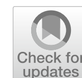
ORIGINAL ARTICLE



Sirtuin2 correlates with lymph node metastasis, increased FIGO stage, worse overall survival, and reduced chemosensitivity to cisplatin and paclitaxel in endometrial cancer

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Abstract

Background This study aimed to investigate the correlation of sirtuin2 (SIRT2) with clinical characteristics, prognosis in endometrial cancer (EC) patients, and its effect on chemosensitivity in EC cell lines.

Methods A total of 137 EC patients who underwent surgical resection were retrospectively enrolled. SIRT2 expression in tumor tissues ($n = 137$) and adjacent tissues ($n = 61$) was detected by immunohistochemistry (IHC) staining and evaluated by a semiquantitative scoring method. EC patients' clinical characteristics and survival data were collected. Besides, SIRT2 was modulated by plasmid transfection in EC cells, then their chemosensitivity to cisplatin and paclitaxel was evaluated.

Results SIRT2 was increased in tumor tissues compared with adjacent tissues (reflected by both IHC score and high-expression ratio, both $P < 0.001$). Meanwhile, tumor SIRT2 was positively correlated with lymph node metastasis ($P = 0.037$) and the International Federation of Gynecology and Obstetrics (FIGO) stage ($P = 0.044$), but not other clinical characteristics. Moreover, tumor SIRT2 high expression was correlated with worse overall survival (OS) ($P = 0.023$), while it could not independently predict OS ($P = 0.090$, hazard ratio $= 2.782$). Besides, both mRNA and protein levels of SIRT2 were increased in Ishikawa ($P = 0.035$) and KLE ($P < 0.001$) cells compared with human endometrial epithelial cells. SIRT2 overexpression decreased chemosensitivity to cisplatin and paclitaxel in Ishikawa cells, while SIRT2 knockdown increased chemosensitivity to cisplatin and paclitaxel in KLE cells (all $P < 0.05$).

Conclusion SIRT2 correlates with lymph node metastasis, increased FIGO stage, worse OS, and reduced chemosensitivity to cisplatin and paclitaxel in EC.

Keywords Chemosensitivity · Clinical characteristics · Endometrial cancer · Overall survival · Sirtuin2

Introduction

Endometrial cancer (EC) is one of the most common gynecological cancer which causes around 320,000 new cases annually worldwide [1]. Notably, the incidence of EC is increasing not only in developing countries but also in developed countries (estimated to increase from 19.1/100,000 in 2012 to 42.1/100,000 in 2030 in the USA) [2, 3]. Therefore, EC is a critical public health issue currently and it also will be a heavy burden in the near future. In terms of treatment, the adjuvant/neoadjuvant therapy for EC patients is largely guided by the risk factors including the International Federation of Gynecology and Obstetrics (FIGO) stage, age, and histological subtypes [4, 5]. However, these factors are not enough for guiding the personalized treatment, and searching for novel prognostic biomarkers might improve the personalized treatment, thus ameliorating the prognosis of EC patients [5].

The sirtuin (SIRT) family members are a group of NAD^+-dependent deacetylase that take part in various biological processes [6]. Among the SIRT family members, SIRT2 exerts crucial physiological functions in several diseases including gynecological cancers [6, 7]. One previous study suggests that SIRT2 overexpression is found in tumor tissues of cervical cancer patients and cervical

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cancer cell lines HeLa and SiHa; besides, suppressing SIRT2 impairs proliferation of HeLa and SiHa [8]. Another study reports that SIRT2 promotes cell proliferation in cervical cancer cells by deacetylating the N-terminal domain of RhoGDIα [9]. Moreover, it is also suggested that SIRT2 is dysregulated in ovarian cancer patients, and its dysregulation promotes proliferation through increasing cyclin-dependent kinase 4 expression in ovarian cancer cells [10, 11]. However, the clinical role of SIRT2 in EC patients remains largely unclear.

In this study, we detected SIRT2 expression in 137 surgical EC patients to explore its correlation with clinical characteristics and prognosis of EC patients, then assessed its effect on chemosensitivity in EC cell lines in vitro.

Methods

Patients

A total of 137 formalin-fixed paraffin-embedded (FFPE) EC tissue specimens and 61 FFPE adjacent tissue specimens were retrospectively collected from 137 EC patients who underwent surgical resection in our hospital between July 2014 and March 2019. The medical documents of patients were checked, and all 137 EC patients met the following criteria: (i) confirmed diagnosis of EC by pathological examination, (ii) age older than 18 years, (iii) no preoperative neoadjuvant therapy, (iv) had retained EC tissue specimen that was available for immunohistochemical (IHC) detection, (v) clinical feature and outcome data were available, and (vi) no other concurrent tumors. The written informed consents were collected from patients or their legal representatives. This study was conducted with approval from the Institutional Review Board of our hospital.

Data extraction

Medical documents of each patient were reviewed, and main clinical feature data were extracted, including patients' age, menopausal status, diabetes mellitus (DM), hypertension, histological subtype, myometrial invasion extent, cervical invasion status, lymph node metastasis status, and FIGO stage (according to 2009 FIGO staging system [12]). The surgical date and last visit date (including death date) of patients were abstracted from follow-up records. The follow-up deadline was 2019/09/30. The median follow-up time was 34 months with the minimum and maximum follow-up time of 6 and 61 months, respectively. The overall survival (OS) was calculated from the surgical date to the patients' death date or last follow-up date. Patients who lost follow-up were treated as censored data.

IHC assay and SIRT2 expression evaluation

IHC assay was performed for the detection of SIRT2 expression in the 137 FFPE EC tissue specimens and 61 FFPE adjacent tissue specimens. Rabbit Anti-SIRT2 antibody (Abcam, USA) was used as the primary antibody in a 1:8000 dilution, and Goat Anti-Rabbit IgG H&L (HRP) (Abcam, USA) was served as secondary antibody in 1:1000 dilution. IHC staining procedure was performed in strict accordance with the immunohistochemistry protocol available on https://www.abcam.cn/protocols/immunostaining-paraffin-frozen-free-floating-protocol. Based on the IHC staining intensity and density of positive-stained cells, a semiquantitative scoring method was applied for SIRT2 expression evaluation, which was carried out as described in previous studies [13, 14]. Finally, an IHC score ranging from 0 to 12 for each tissue was obtained, and the SIRT2 expression was classified as follows: IHC score 0 to 3, SIRT2 low expression; IHC score 4 to 12, and SIRT2 high expression.

In vitro experiment

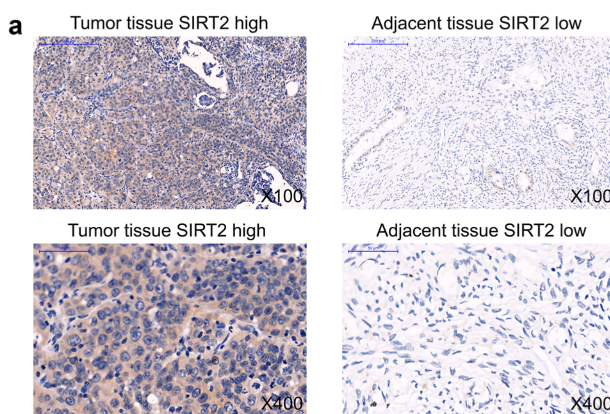
Human EC cells Ishikawa (BCRJ, Brazil) were cultured in DMEM medium (Gibco, USA) supplemented with 10% fetal bovine serum (FBS) (Gibco, USA). Human EC cells KLE (ATCC, USA) were cultured in DMEM/F12 medium (Gibco, USA) supplemented with 10% FBS (Gibco, USA). Normal human endometrial (uterine) epithelial cells (HEEC) (Lifeline® Cell Technology, USA) were cultured in Lifeline® ReproLife™ Medium (Lifeline® Cell Technology, USA). All cells were cultured in a humidified atmosphere with 5% CO_2 at 37 °C. The SIRT2 expressions in the Ishikawa cells and KLE cells were determined by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and western blot (WB) assays, with HEEC cells severed as control. RT-qPCR and WB were performed as described in a previous study [15]. The pcDNA3.1 vector was used to structure SIRT2 overexpression plasmid (pcDNA-SIRT2) and corresponding negative control plasmid (pcDNA-NC). The pGPH1 vector was used to structure SIRT2 knock-down plasmid (pGPH1-SIRT2) and corresponding NC plasmids (pGPH1-NC). Using Lipofectamine 2000 (Thermo Fisher Scientific, USA), the pcDNA-SIRT2 and pcDNA-NC were transfected into Ishikawa cells, and the pGPH1-SIRT2 and pGPH1-NC were transfected into KLE cells, respectively. The normal Ishikawa cells and KLE cells

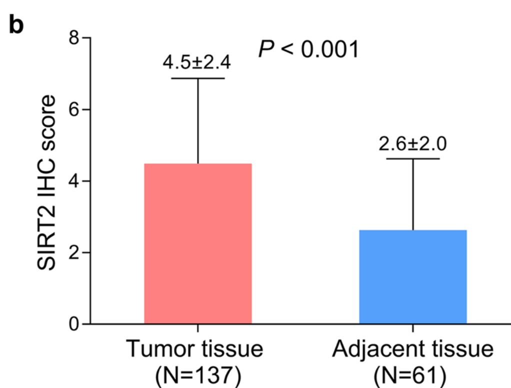
Table 1 Patients' characteristics

Items	EC patients (*N* = 137)
Age (years), mean ± SD	63.3 ± 9.5
Menopausal status, No. (%)	
Pre-menopause	22 (16.1)
Post-menopause	115 (83.9)
DM, No. (%)	
No	96 (70.1)
Yes	41 (29.9)
Hypertension, No. (%)	
No	60 (43.8)
Yes	77 (56.2)
Histological subtype, No. (%)	
Endometrioid carcinoma G1/G2	92 (67.2)
Endometrioid carcinoma G3	15 (10.9)
Serous carcinoma	20 (14.6)
Clear cell carcinoma	10 (7.3)
Myometrial invasion, No. (%)	
< 50%	87 (63.5)
≥ 50%	50 (36.5)
Cervical invasion, No. (%)	
None or epithelial	108 (78.8)
Stromal	29 (21.2)
Lymph node metastasis, No. (%)	
No	108 (78.8)
Yes	29 (21.2)
FIGO stage, No. (%)	
I	91 (66.4)
II	17 (12.4)
III	22 (16.1)
IV	7 (5.1)

EC endometrial cancer, *SD* standard deviation, *DM* diabetes mellitus, *FIGO* International Federation of Gynecology and Obstetrics

(without plasmid transfection) were served as controls. Forty-eight hours after transfection, the cells were treated with different concentrations of cisplatin (Sigma, USA) or paclitaxel (Sigma, USA) for another 48 h. The cisplatin concentration was prepared as follows: for Ishikawa cells: 0, 2, 4, 8, 16, and 32 μM; for KLE cells: 0, 5, 10, 20, 40, and 80 μM. The paclitaxel concentration was prepared as follows: for Ishikawa cells: 0, 0.5, 1, 2, 4, and 8 μM; for KLE cells: 0, 5, 10, 20, 40, and 80 μM. After 48-h treatment, the cell viability at different concentrations of cisplatin and paclitaxel was assessed using Cell Counting Kit-8 (Dojindo, Japan) according to the kit's instruction, and the absorbance at 450 nm was measured by Microplate Reader (BIO-TEK, USA). The relative cell viability was calculated using absorbance value at each concentration divided by absorbance value at 0 concentration.





c

Tissues	SIRT2 expression		*P* value
	Low	High	
Tumor tissue	66 (48.2)	71 (51.8)	<0.001
Adjacent tissue	44 (72.1)	17 (27.9)	

Fig. 1 SIRT2 expression in tumor and adjacent tissues of EC patients. **a** Representative images of IHC staining for SIRT2 detection. **b** Comparison of SIRT2 IHC score between tumor tissues and adjacent tissues. **c** Comparison of SIRT2 high expression ratio between tumor tissues and adjacent tissues. SIRT2 sirtuin 2, EC endometrial cancer, IHC immunohistochemistry

Statistical analysis

Data were shown as number with percentage or mean with standard deviation (SD) as appropriate. Difference analysis was determined by the chi-square test, Dunnett's *t* test, or independent sample *t* test. Correlation analysis was determined by chi-square test or Mantel–Haenszel test. OS was displayed using the Kaplan–Meier curve and determined by the Log-rank test between groups. Multivariable Cox's proportional hazard regression model analysis was performed to assess the OS-related factors. GraphPad Prism 6.01 (GraphPad Software Inc., USA) and SPSS 24.0 software (IBM, USA) were applied for data processing and analysis. $P < 0.05$ was defined as statistically significant.

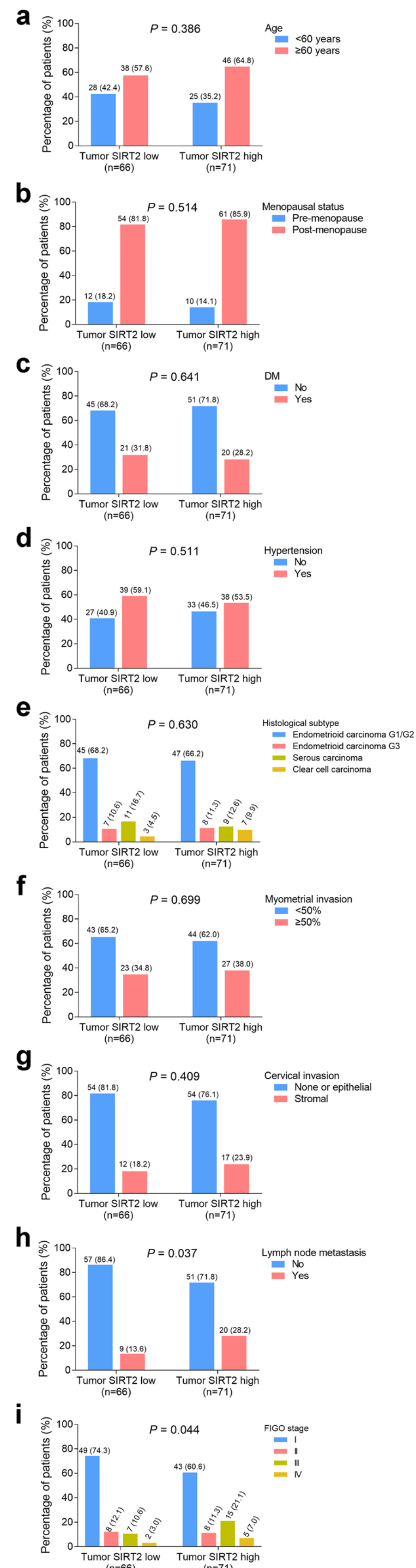


Fig. 2 Correlation of tumor SIRT2 with EC patients' clinical characteristics. Comparison of age (**a**), menopausal status (**b**), DM (**c**), hypertension (**d**), histological subtype (**e**), myometrial invasion (**f**), cervical invasion (**g**), lymph node metastasis (**h**), and FIGO stage (**i**) between patients with tumor SIRT2 low expression and patients with tumor SIRT2 high expression. SIRT2 sirtuin 2, EC endometrial cancer, DM diabetes mellitus, FIGO International Federation of Gynecology and Obstetrics

Results

Patients' clinical characteristics

A total of 137 EC patients with a mean age of 63.3 ± 9.5 years were retrospectively enrolled, of which detailed clinical characteristics were shown in Table 1. Briefly, there were 92 (67.2%) patients with G1/G2 endometrioid carcinoma, 15 (10.9%) patients with G3 endometrioid carcinoma, 20 (14.6%) patients with serous carcinoma, and 10 (7.3%) patients with clear cell carcinoma. Meanwhile, 87 (63.5%) patients had superficial myometrial invasion (< 50%) and 50 (36.55%) patients had deep myometrial invasion (≥ 50%); 108 (78.8%) patients had no cervical invasion or epithelial invasion, and 29 (21.2%) patients had stromal invasion; 29 (21.2%) patients presented lymph node metastasis while 108 (78.8%) did not. Besides, 91 (66.4%) patients were of FIGO stage I, 17 (12.4%) patients were of FIGO stage II, 22 (16.1%) patients were of FIGO stage III, and 7 (5.1%) patients were of FIGO stage IV (Table 1).

SIRT2 expression in EC patients

SIRT2 expression in tumor tissues ($n = 173$) and adjacent tissues ($n = 61$) was detected by IHC staining (Fig. 1a) and further evaluated by a semiquantitative scoring method. Both SIRT2 IHC score ($P < 0.001$) (Fig. 1b) and SIRT2 high expression ratio ($P < 0.001$) (Fig. 1c) were increased in tumor tissues compared with adjacent tissues.

Correlation of tumor SIRT2 expression with EC patients' clinical characteristics

The subsequent correlation analyses showed that tumor SIRT2 expression was positively correlated with lymph node metastasis ($P = 0.037$) (Fig. 2h) and FIGO stage ($P = 0.044$) (Fig. 2i). However, no correlation was found in tumor SIRT2 with age ($P = 0.386$) (Fig. 2a), menopausal status ($P = 0.514$) (Fig. 2b), DM ($P = 0.641$)

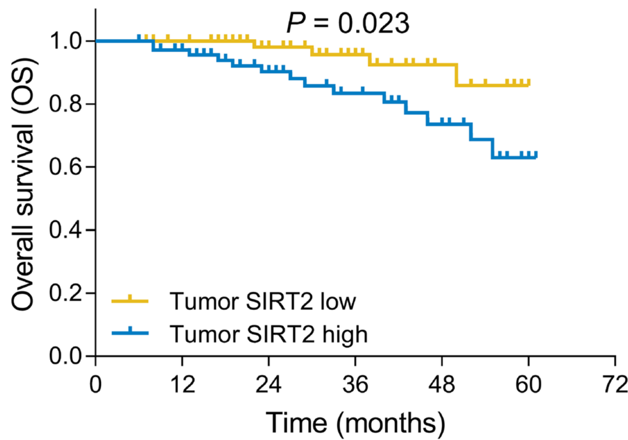


Fig. 3 Comparison of OS between EC patients with tumor SIRT2 low expression and EC patients with tumor SIRT2 high expression. SIRT2 sirtuin 2, OS overall survival, EC endometrial cancer

(Fig. 2c), hypertension ($P=0.511$) (Fig. 2d), histological subtype ($P=0.630$) (Fig. 2e), myometrial invasion ($P=0.699$) (Fig. 2f), or cervical invasion ($P=0.409$) (Fig. 2g).

Table 2 Multivariate Cox's proportional hazard regression analysis of OS-associated factors

Items	Cox's proportional hazard regression model			
	P value	HR	95%CI	
			Lower	Higher
Tumor SIRT2 high	0.090	2.782	0.852	9.077
Age ≥ 60 years	0.749	1.289	0.271	6.136
Post-menopause	0.904	0.882	0.113	6.895
DM	0.325	1.665	0.603	4.597
Hypertension	0.855	1.099	0.400	3.020
Histological subtype (serous carcinoma/clear cell carcinoma vs. endometrioid carcinoma)	0.008	4.578	1.487	14.094
FIGO stage (III/IV vs. I/II)	0.004	5.172	1.666	16.057

OS overall survival, *HR* hazard ratio, *CI* confidence interval, *DM* diabetes mellitus, *FIGO* International Federation of Gynecology and Obstetrics

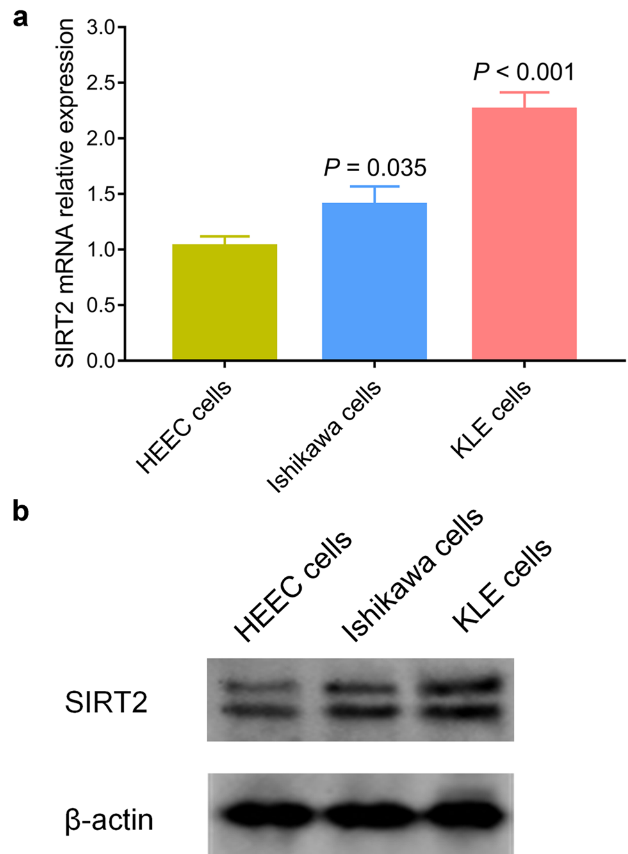


Fig. 4 SIRT2 expression in EC cells and HEEC cells. **a** Comparison of SIRT2 mRNA expression between Ishikawa cells and HEEC cells, as well as between KLE cells and HEEC cells. **b** Representative images of WB assay for SRIT2 expression in Ishikawa cells, KLE cells and HEEC cells. EC endometrial cancer, HEEC human endometrial (uterine) epithelial cells

Correlation of tumor SIRT2 expression with EC patients' OS

The comparison of OS between patients with tumor SIRT2 high or low expression was conducted, and it was revealed that OS was decreased in patients with tumor SIRT2 high expression compared with patients with tumor SIRT2 low expression ($P=0.023$) (Fig. 3). Moreover, further multivariate Cox's proportional hazard regression analyses showed that histological subtype (serous carcinoma/clear cell carcinoma vs. endometrioid carcinoma) ($P=0.008$, HR = 4.578) and FIGO stage (III/IV vs. I/II) ($P=0.004$, HR = 5.172) were independent factors for worse OS; besides, tumor SIRT2 high expression was an important factor reflecting worse OS, but no statistical significance was found ($P=0.090$, HR = 2.782) (Table 2).

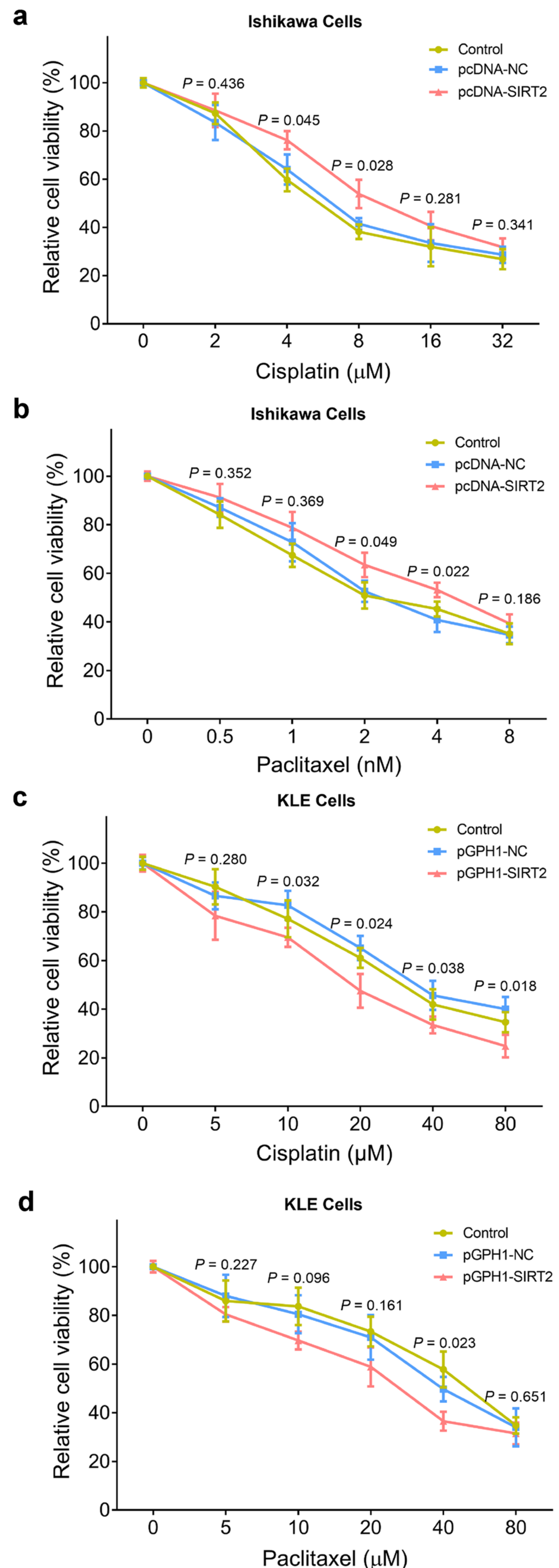


Fig. 5 Relative cell viability of Ishikawa cells and KLE cells under cisplatin or paclitaxel treatment after plasmid transfection. **a** Comparison of Ishikawa relative cell viability between the pcDNA-SIRT2 group and the pcDNA-NC group under 0, 2, 4, 8, 16, and 32 μM cisplatin treatment. **b** Comparison of Ishikawa relative cell viability between the pcDNA-SIRT2 group and the pcDNA-NC group under 0, 0.5, 1, 2, 4, and 8 nM paclitaxel treatment. **c** Comparison of KLE relative cell viability between the pGPH1-SIRT2 group and pGPH1-NC group under 0, 5, 10, 20, 40 and 80 μM cisplatin treatment. **d** Comparison of KLE relative cell viability between the pGPH1-SIRT2 group and pGPH1-NC group under 0, 5, 10, 20, 40, and 80 μM paclitaxel treatment. SIRT2 sirtuin 2, NC negative control

SIRT2 expression in EC cell lines

Since chemoresistance is a critical issue that affects the prognosis of EC patients, we further evaluate the role of SIRT2 in the chemosensitivity of EC cells, and two EC cell lines (Ishikawa cells and KLE cells) as well as HEEC cells were cultured. The RT-qPCR assay showed that SIRT2 mRNA expression was elevated in both Ishikawa cells ($P = 0.035$) and KLE cells ($P < 0.001$) compared with HEEC cells (Fig. 4a); meanwhile, the WB assay showed that SIRT2 protein expression presented similar trends (Fig. 4b).

Effect of SIRT2 on chemosensitivity in EC cell lines

Subsequently, Ishikawa cells were transfected with SIRT2 overexpression plasmid (as the pcDNA-SIRT2 group) and negative control plasmid (as the pcDNA-NC group); meanwhile, KLE cells were transfected with SIRT2 knock-down plasmid (as pGPH1-SIRT2group) and corresponding negative control plasmids (as pGPH1-NC group). Besides, Ishikawa cells and KLE cells without plasmid transfection were respectively set as the corresponding control group. In Ishikawa cells, relative cell viability was increased in the pcDNA-SIRT2 group compared with the pcDNA-NC group under 4 and 8 μM of cisplatin treatment (both $P < 0.05$) (Fig. 5a) as well as 2 and 4 nM of paclitaxel treatment (both $P < 0.05$) (Fig. 5b). Additionally, in KLE cells, relative cell viability was reduced in the pGH1-SIRT2 group compared with the pGPH1-NC group under 10, 20, 40, and 80 μM of cisplatin treatment (all $P < 0.05$) (Fig. 5c) as well as 40 μM of paclitaxel treatment ($P = 0.023$) (Fig. 5d). These data suggested that SIRT2 could largely reduce chemosensitivity to cisplatin and minorly decrease that to paclitaxel in EC cell lines.

Discussion

Searching for novel prognostic biomarkers in EC patients might guide personalized treatment to promote their outcome [1, 4]. In the present study, we found that SIRT2 level was increased in tumor tissues compared with adjacent tissues. Meanwhile, tumor SIRT2 high expression was correlated with lymph node metastasis, increased FIGO stage, and worse prognosis. Besides, SIRT2 mRNA and protein levels were elevated in EC cell lines compared with HEEC cells. Moreover, SIRT2 overexpression largely decreased chemosensitivity to cisplatin and faintly reduced that to paclitaxel in EC cell lines, while SIRT2 knockdown had the opposite effect. To the best of our knowledge, this study was the first to specifically explore the prognostic effect of SIRT2 in EC patients and the role of SIRT2 in chemosensitivity of EC cell lines.

SIRT2 is reported to participate in the progression of several cancers through regulating multiple signaling pathways. For instance, in gastric cancer cell lines, SIRT2 overexpression promotes proliferation, migration, and invasion through modulating phosphoenolpyruvate carboxykinase 1 (PEPCK1)/Ras/extracellular signal-regulated kinases (ERK)/c-Jun N-terminal kinases (JNK)/ matrix metalloproteinase-9 (MMP-9) signaling [16]. In colorectal cancer cell lines, SIRT2 knockdown suppresses angiogenesis via inhibiting the phosphorylation of signal transducer and activator of transcription3 (STAT3) and further reducing the secretion of vascular endothelial growth factor (VEGF) [17]. Besides, the dysregulation of SIRT2 in tumor tissues of cancer patients is also reported. In cervical cancer patients, SIRT2 expression is enhanced in tumor tissues compared with adjacent tissues [18], and similar trends are also found in patients with esophageal squamous cell carcinoma [19]. However, SIRT2 expression in EC patients remains largely unknown; only one previous study suggests that SIRT2 mRNA level is dysregulated in EC tissues compared with noncancerous endometria [20]. In the present study, we retrospectively analyzed SIRT2 expression in 137 EC patients and found that SIRT2 expression was increased in EC tissues compared with adjacent tissues. Possible explanations could be that SIRT2 high expression might activate several tumorigenesis-associated pathways such as Ras/ERK pathway (as in gastric cancer cells [16]) and the Wnt/β-catenin pathway (as in mouse embryonic fibroblasts [21]), as well as regulating some oncogenes including K147 and KRAS [22], which promoted the malignant transformation of endometrial epithelial cells; thus, it was elevated in tumor tissues of EC patients.

With regard to the correlation between SIRT2 and the clinical characteristics of cancer patients, one previous study reveals that tumor SIRT2 high expression is correlated with increased tumor size, lymph node metastasis, and elevated FIGO stage in cervical cancer patients [18]. Another previous study illustrates that tumor SIRT2 expression is positively correlated with clinical disease stage, tumor invasion, and lymph node metastasis, but not tumor size or differentiation in patients with esophageal squamous cell carcinoma [19]. However, the correlation of SIRT2 with EC patients' clinical characteristics has not been reported yet. In this study, we found that tumor SIRT2 high expression was correlated with lymph node metastasis and increased FIGO stage. These data could be explained by the following: (1) SIRT2 high expression might activate the protein kinase B/glycogen synthase kinase-3β/β-catenin signaling to promote the epithelial to mesenchymal transition; meanwhile, it might also increase PEPCK1 level to activate mitochondrial metabolism and E-cadherin signaling, thus elevating the metastatic potential of EC cells (as in hepatocellular carcinoma cells [23, 24]), which could enhance lymph node metastasis in EC patients [23]; (2) SIRT2 high expression in tumor tissues might activate the PEPCK1/Ras/ERK/JNK/MMP-9 signaling to increase the proliferation, migration, and invasion of EC cells (as in gastric cancer cells [16]), which led to increased malignant behavior and resulted in elevated locoregional or peripheral tissue invasion; thus, it was positively correlated with FIGO stage in EC patients; (3) SIRT2 high expression might suppress chemosensitivity of EC cells (which could be deduced from our in vitro experiment) to reduce the cytotoxicity of therapeutic agents, which promote the progression of EC.

Moreover, the prognostic value of SIRT2 in cancer patients is reported by previous studies [18, 19]. In this study, data showed that tumor SIRT2 high expression was correlated with worse OS in EC patients. Our data could be explained by the following: the positive correlation in SIRT2 expression with lymph node metastasis and FIGO stage might indirectly lead to worse OS in EC patients. Besides, our in vitro study could also explain the correlation between SIRT2 high expression and worse OS in EC patients: in our in vitro study, we found that SIRT2 was elevated in EC cell lines compared with HEEC cells; meanwhile, SIRT2 overexpression reduced the chemosensitivity to cisplatin largely and only decreased that to paclitaxel to some extent in EC cells, while SIRT2 knockdown had the opposite effect. Therefore, SIRT2 high expression might reduce the chemosensitivity of EC cells, thus leading to worse OS in EC patients. However, further studies were encouraged to explore the mechanism of SIRT2 in modulating the chemosensitivity of EC cells, as well as the effect of SIRT2 on chemosensitivity in EC patients.

There were several limitations in this study. First, since many of the EC patients were ecdemic, they returned to local hospitals for follow-up after surgical resection and a short

period of treatment in our hospital; therefore, the accurate data of disease recurrence could not be obtained, and the analysis between SIRT2 and disease-free survival could not be conducted (which was also critical for evaluating the prognostic effect of SIRT2 in EC patients). Second, the sample size of this study was relatively small, which might cause low statistical power, especially in the analysis of the correlation between tumor SIRT2 expression and histological subtypes of EC patients. Third, the underlying molecular mechanisms of SIRT2 in regulating the proliferation, migration, invasion, and chemosensitivity of EC cells were not investigated in this study, which could be conducted further.

To be conclusive, SIRT2 high expression correlates with lymph node metastasis, increased FIGO stage, worse OS in EC patients, and reduced chemosensitivity to cisplatin and paclitaxel in EC cell lines. SIRT2 might serve as a potential prognostic biomarker for improving the personalized treatment in EC patients, thus ameliorating their overall prognosis.

Declarations

Ethics approval and consent to participate The written informed consents were collected from patients or their legal representatives. This study was conducted with approval from the Institutional Review Board of North China University of Science and Technology Affiliated Hospital.

Competing interests The authors declare that they have no competing interests.

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