Sirtuin 2 in Endometrial Cancer: A Potential Regulator for Cell Proliferation, Apoptosis and RAS/ERK Pathway

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Abstract

Objective: The present study aimed to explore the function of sirtuin 2 (SIRT2) on cell proliferation, apoptosis, rat sarcoma virus (RAS)/extracellular signal-regulated kinase (ERK) pathway in endometrial cancer (EC).

Methods: SIRT2 expression in human EC cell lines and human endometrial (uterine) epithelial cell (HEEC) line was assessed by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and western blot. SIRT2 knock-down and control knock-down plasmids were transfected into HEC1A cells, respectively; SIRT2 overexpression and control overexpression plasmids were transfected into Ishikawa cells, respectively. After transfection, SIRT2, HRas proto-oncogene, GTPase (HRAS) expressions were evaluated by RT-qPCR and western blot. ERK and phosphorylated ERK (pERK) expressions were evaluated by western blot. Meanwhile, cell proliferation and cell apoptosis were measured.

Results: Compared to normal HEEC cell line, SIRT2 mRNA and protein expressions were increased in most human EC cell lines (including HEC1A, RL952 and AN3CA), while were similar in Ishikawa cell line. In HEC1A cells, SIRT2 knock-down decreased cell proliferation but increased apoptosis. In Ishikawa cells, SIRT2 overexpression induced cell proliferation but inhibited apoptosis. For RAS/ERK pathway, SIRT2 knock-down reduced HRAS and inactivated pERK in HEC1A cells, whereas SIRT2 overexpression increased HRAS and activated pERK in Ishikawa cells, suggesting that SIRT2 was implicated in the regulation of RAS/ERK pathway in EC cells.

Conclusion: SIRT2 contributes to the EC tumorigenesis, which appears as a potential therapeutic target.

Keywords
Sirtuin 2, endometrial cancer, cell proliferation, cell apoptosis, RAS/ERK pathway

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Introduction

Endometrial cancer (EC) is considered as the most common malignancy of the female genital tract in developed countries, which frequently occurs in post-menopausal women (accounting for nearly 75-85% of all EC cases).¹ For EC patients diagnosed at an early stage, surgical resection is optimum choice for curative outcomes, whereas for EC patients at advanced stage who involve in local or/and distance metastases, neoadjuvant/adjuvant treatment (including chemotherapy and chemoradiation therapy) is currently recommended to improve overall survival (OS) and disease-free survival (DFS).² Nonetheless, 5-year OS after exterention for pelvic recurrence still up to nearly 20% to 40%, and neoadjuvant/adjuvant treatment brings several adverse reactions (such as nausea, vomiting and alopecia), which result in poor quality of life in EC patients.² Hence, there is an urgent to explore molecular mechanism underlying EC to develop potential therapeutic targets, so as to improve prognosis in EC patients.

Sirtuins, belonging to the family of class III (nicotinamide adenine dinucleotide (NAD)-dependent) histone deacetylases (HDACs), are involved in aging and longevity, resulting from their regulation of genomic stability and metabolism.³ To date, 7 members of sirtuin family (sirtuin (SIRT) 1-7) have
been reported in mammals. As one of these members, SIRT2, an NAD\(^+\)-dependent deacetylase, participates in the processes of tumorigenesis and tumor progression.\(^4,5\) Recent evidences reveal that SIRT2 is upregulated in several carcinomas (such as cervical cancer, breast cancer and hepatocellular cancer).\(^6,8\) Meanwhile, its oncogenic role is also identified such as promoting cell growth, metastasis and invasion in various cancers (including gastric cancer and glioblastoma).\(^5,9\) Meanwhile, SIRT2 induces the cell proliferation, migration and invasion via rat sarcoma virus (RAS)/extracellular signal-regulated kinase (ERK)/ jun N-terminal kinase (JNK)/ matrix metalloproteinase-9 (MMP-9) pathway in cancers,\(^2\) and RAS/ERK pathway is identified as one of the major oncogenetic pathways in EC.\(^10\) As mentioned above, we hypothesized SIRT2 was implicated in the regulation of RAS/ERK pathway in EC; However, no related researches had been reported. Therefore, in the present study, we aimed to explore the function of SIRT2 on cell proliferation and apoptosis, also to investigate its regulatory effect on RAS/ERK pathway in EC.

**Methods**

**Cell Culture**

Human EC cell lines including HEC1A, RL952, AN3CA were bought from American Type Culture Collection (ATCC, USA), and human EC cell line Ishikawa was purchased from BANCO DE CÉLULAS DO RIO JANEIRO (BCRJ, Brazil). Normal human endometrial (uterine) epithelial cells (HEEC) were purchased from Lifeline\textsuperscript{®} Cell Technology (Lifeline\textsuperscript{®} Cell Technology, USA). Immortalized human endometrial stromal cell (CRL-4003) were purchased from American Type Culture Collection (ATCC, USA). The HECKA cells were cultured in medium containing 90\% McCoy’s 5A (modified) Medium (Gibco, USA) and 10\% fetal bovine serum (FBS) (Gibco, USA). The Ishikawa cells were cultured in medium containing 90\% Dulbecco’s Modified Eagle Medium (Gibco, USA) and 10\% FBS (Gibco, USA). The RL952 cells were cultured in medium containing 90\% Dulbecco’s Modified Eagle Medium/Nutrient Mixture F-12 Medium (Gibco, USA) and 10\% FBS (Gibco, USA). The AN3CA cells were cultured in medium containing 90\% Minimum Essential Medium (Gibco, USA) and 10\% FBS (Gibco, USA). The HEEC cells were cultured in medium containing 90\% Minimum Essential Medium (Gibco, USA) and 10\% FBS (Gibco, USA). The HEC cell lines were cultured in lifeline\textsuperscript{®} ReproLife\textsuperscript{TM} Medium (Lifeline\textsuperscript{®} Cell Technology, USA). All cells were cultured at 37\°C in a humidified incubator with 5\% CO\(_2\) atmosphere. The SIRT2 expression in human EC cells and HEEC cells were assessed by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and western blot.

**Plasmids Construction and Transfection**

SIRT2 shRNA sequence and nonsense shRNA sequence were designed, synthesized and cloned into pGPH1/RFP/Neo vector by GenePharma Biotech Company (Shanghai, China) to construct SIRT2 knock-down plasmid and control knock-down plasmid, respectively. SIRT2 full length cDNA and nonsense DNA were synthesized and cloned into pEX-2 vector by GenePharma (Shanghai, China) to construct SIRT2 overexpression plasmid and control overexpression plasmid.

**Pathway Measurement**

It is found that SIRT2 induce the cell proliferation, migration and invasion through RAS/ERK/ c-Jun N-terminal kinase (JNK) / matrix metalloproteinase-9(MMP-9) pathway in gastric cancer,\(^3\) and Ras/ERK pathway is identified as one of the major pathways in EC.\(^10\) As a result, in order to investigate whether SIRT2 was implicated in the regulation of RAS/ERK pathway in EC cells, the qPCR and western blot were performed to detect the Methyl Ethyl Ketone (MEK), phosphorylated MEK (pMEK), HRAS proto-oncogene GTPase (HRAS), RAF, ERK and phosphorylated ERK (p-ERK) expressions in SIRT2(-) cells, NC(-) cells, SIRT2(+) cells and NC(+) cells at 48 h after transfection.

**RT-qPCR**

Total RNA was extracted from cells using TRIzol\textsuperscript{TM} Reagent (Thermo, USA). After that, the synthesis of cDNA was performed by ReverTra Ace\textsuperscript{®} qPCR RT Kit (Toyobo, Japan), and then cDNA product was subjected to qPCR by SYBR\textsuperscript{®} Green Realtime PCR Master Mix (Toyobo, Japan). The PCR amplification was conducted as follows: 95\°C for 3 min, 40 cycles of 95\°C for 5 s, 61\°C for 10 s, 72\°C for 30 s. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was served as the internal reference. The calculation of mRNA expressions was based on 2\(^{-\Delta\Delta C_T}\) formula. Primers’ sequences were listed in Table 1.
Western Blot

Total protein was extracted from cells using RIPA Lysis and Extraction Buffer (Thermo, USA), and then, the concentration of total protein was detected by RIPA Lysis and Extraction Buffer (Thermo, USA). After thermal denaturation, protein was loaded into NuPAGE Bis-Tris Gels 4%-12% (Thermo, USA) for electrophoresis. Membranes were blocked and then incubated with primary antibody as well as appropriate secondary antibody in turn. The bands were visualized on X-ray film (Fuji, Japan) by using Novex™ECL Chemiluminescent Substrate Reagent Kit (Invitrogen, USA). The antibodies applied in western blot were list in Table 2.

Statistical Analysis

All data were presented as mean and standard deviation. Figure plotting and statistical analysis were performed using GraphPad Prism 7.01 (GraphPad, USA). Comparison between 2 groups were determined by the unpaired t test, and comparison among groups was determined by 1-way analysis of variation (ANOVA) followed by the Dunnett-t test. Statistically significant was defined as P value <0.05, and further displayed as *P < 0.05 **P < 0.01, ***P < 0.001, and NS (not significant).

Results

SIRT2 Expression in Human EC Cell Lines and HEEC

Compared to normal HEEC, SIRT2 mRNA (Figure 1A) and protein (Figure 1B) expressions were increased in most human EC cell lines, including HEC1A (P < 0.001), RL952 (P < 0.001), AN3CA (P < 0.001) cells. However, there was no difference in SIRT2 mRNA and protein expressions between Ishikawa cells and normal HEEC (P > 0.05).

SIRT2 Expression in Human EC Cell Lines and CRL-4003

Compared to CRL-4003 cells, SIRT2 mRNA (Figure 2A) and protein (Figure 2B) expressions were increased in most human EC cell lines, including HEC1A (P < 0.001), RL952 (P < 0.001), AN3CA (P < 0.001) cells. However, there was no difference in SIRT2 mRNA and protein expressions between Ishikawa cells and CRL-4003 cells (P > 0.05). Considering that SIRT2 expression was highest in HEC1A cells and lowest in Ishikawa cells among these human EC cell lines; meanwhile, the selection of 2 extreme cells might more obviously reflect the effect of SIRT2 on cellular function in EC, hence, HEC1A cells and Ishikawa cells were selected for transfection and detections in the subsequent experiments.

Table 1. Primers Sequence.

| Gene  | Forward primer (5’-3’) | Reverse primer (5’-3’) |
|-------|------------------------|-----------------------|
| SIRT2 | ACGCTGTCGCAGAGTCAT     | CGCTCCAGG GTATCTATGTT |
| HRAS  | TGCCATCAACAACACCAAGCTT | CTGAGCCCTGCGGAGATTCCA |
| GAPDH | GACCACAGTCCATGCCATCAC  | ACGCTGTTCCACCACCTT    |

Table 2. Antibodies Information.

| Antibody | Company | Dilution |
|----------|---------|----------|
| Primary Antibody | | |
| Rabbit monoclonal to SIRT2 | Abcam (UK) | 1:1000 |
| Rabbit monoclonal to HRAS | Abcam (UK) | 1:500 |
| Rabbit monoclonal to ERK1 + ERK2 | Abcam (UK) | 1:1000 |
| Rabbit monoclonal to ERK1 + ERK2 (phospho) | Abcam (UK) | 1:1000 |
| Rabbit monoclonal to GAPDH | CST (USA) | 1:1000 |
| Secondary Antibody | | |
| Goat Anti-Rabbit IgG H&L (HRP) | Abcam (USA) | 1:10000 |

Figure 1. Comparison of SIRT2 expression between human EC cell lines and HEEC. (A) Comparison of SIRT2 mRNA expression between human EC cell lines and HEEC. (B) Comparison of SIRT2 protein expression between human EC cell lines and HEEC. SIRT2: sirtuin 2; EC: endometrial cancer; HEEC: human endometrial (uterine) epithelial cells; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.
SIRT2 Expression in HEC1A Cells and Ishikawa Cells After Transfection

After transfection, both mRNA (Figure 3A) and protein (Figure 3B) expressions of SIRT2 were greatly decreased in SIRT2(-) cells compared to NC(-) cells (P < 0.001) in HEC1A cells, suggesting successful transfection in HEC1A cells. In addition, both mRNA (Figure 3C) and protein (Figure 3D) expressions of SIRT2 were dramatically increased in SIRT2(+) cells compared to NC(+) cells (P < 0.001) in Ishikawa cells, suggesting successful transfection in Ishikawa cells.

The Effect of SIRT2 on Cell Proliferation in HEC1A Cells and Ishikawa Cells

In HEC1A cells, cell proliferation was decreased in SIRT2(-) cells compared to NC(-) cells at 48 h (P < 0.05) and 72 h (P < 0.05) (Figure 4A). Meanwhile, cell proliferation was increased in SIRT2(+) cells compared to NC(+) cells at 48 h (P < 0.05) and 72 h (P < 0.05) in Ishikawa cells (Figure 4B).

The Effect of SIRT2 on Cell Apoptosis in HEC1A Cells and Ishikawa Cells

In HEC1A cells, cell apoptosis was promoted in SIRT2(-) cells compared to NC(-) cells at 48 h (P < 0.01) (Figure 5A and B). Whereas in Ishikawa cells, cell apoptosis was inhibited in SIRT2(+) cells compared to NC(+) cells at 48 h (P < 0.01) (Figure 5C and D).

The Effect of SIRT2 on Cell Migration and Invasion in HEC1A Cells and Ishikawa Cells

In HEC1A cells, cell migration rate (P < 0.05) (Figure 6A and B) and invasion cells number (P < 0.01) (Figure 6C and D) were inhibited in SIRT2(-) cells compared to NC(-) cells. Whereas in Ishikawa cells, cell migration rate (P < 0.01) (Figure 6E and F) and invasion cells number (P < 0.01) (Figure 6G and H) were promoted in SIRT2(+) cells compared to NC(+) cells.

The Effect of SIRT2 on RAS/ERK Pathway in HEC1A Cells and Ishikawa Cells

In order to deeply explore the effect of SIRT2 on RAS/ERK pathway in EC pathogenesis, we detected HRAS, ERK and p-ERK expressions in HEC1A cells and Ishikawa cells after transfection. In HEC1A cells, both mRNA (Figure 7A) and protein (Figure 7B) expressions of HRAS were reduced in SIRT2(-) cells compared to NC(-) cells (P < 0.05), and western blot assay revealed that protein expressions of MEK and ERK were similar, but pMEK, pERK and RAF were decreased in SIRT2(-) cells compared to NC(-) cells (Figure 7B). In Ishikawa cells, both mRNA (Figure 7C) and protein (Figure 7D) expressions of HRAS were increased in SIRT2(+) cells compared to NC(+) cells (P < 0.05), and western blot assay disclosed that protein expressions of MEK and ERK were similar, but pMEK, pERK and RAF were enhanced in SIRT2(+) cells compared to NC(+) cells (Figure 7D).

Discussion

In this study, we discovered that (1) SIRT2 was highly expressed in most human EC cell lines compared to normal HEEC, and it increased cell proliferation, while decreased apoptosis in EC; (2) SIRT2 possessed regulatory effect on RAS/ERK pathway in EC cells.

Sirtuins, a protein family with high conservation, exert regulatory effects on the viability, metastasis as well as invasion of various malignancies, and a relationship between different sirtuin members and neoplasia depends on their function on multiple critical biological processes (including energy metabolism, chromatin remodeling, DNA damage response, and genomic stability). A number of studies have suggested...
Figure 3. SIRT2 expression after transfection. (A) SIRT2 mRNA expression after transfection in HEC1A cells; (B) SIRT2 protein expression after transfection in HEC1A cells; (C) SIRT2 mRNA expression after transfection in Ishikawa cells; (D) SIRT2 protein expression after transfection in Ishikawa cells. SIRT2: sirtuin 2; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; NC: normal control.

Figure 4. The regulation of SIRT2 on cell proliferation. (A) In HEC1A cells, comparison of cell proliferation between SIRT2(-) cells and NC(-) cells; (B) In Ishikawa cells, comparison of cell proliferation between SIRT2(+) cells and NC(+) cells. SIRT2: sirtuin 2; CCK-8: cell counting kit-8; OD: optical density; NC: normal control.
the oncogenic roles of different sirtuin members in various cancers, including genital cancers. For EC, limited information about the role of sirtuins in EC is discovered. Just one previous study displays that SIRT7 is overexpressed in EC cells compared with normal endometrial cells, and its downregulation suppresses cell proliferation, migration and invasiveness but promotes apoptosis via regulating the nuclear factor (NF)-κB signaling pathway. These previous evidences suggest that several sirtuins are important in the tumorigenicity of various carcinomas, including EC.

SIRT2 is localized to the chromosome and acts as a histone deacetylase with a preference for histone H4 lysine 16(H4K16Ac), which is deeply implicated in diverse diseases, particular in carcinomas. For instance, an interesting study discloses that SIRT2 is highly expressed in cervical cancer cell lines (HeLa and SiHa cells) compared to the immortalized cell counterpart (HaCaT cells). Also, SIRT2 participants in the deacetylation and activation of protein kinase B to affect the glycogen synthase kinase-3β/β-catenin signaling pathway, which subsequently regulates epithelial-mesenchymal transition (EMT) to induce cell metastasis and invasion in HCC. Another previous study reveals that SIRT2 interacts with histone deacetylase 6 (HDAC6) synergistically to activate cell proliferation, migration and invasion in bladder cancer. Furthermore, SIRT2 also has been reported to mediate the inactivation of p73, subsequently promote proliferation and tumorigenicity of glioblastoma cells. As mentioned above, SIRT2 has been classified as an oncogenic role in various carcinomas, while the function of SIRT2 on cellular activities in EC remains elusive. In the current study, we discovered that SIRT2 expression were increased in most human EC cell lines compared to normal HEEC, and intriguingly, SIRT2 promoted cell proliferation, but inhibited apoptosis in EC cells, suggesting that SIRT2 has oncogenic function in EC cells, which was in line with previous data. The possible explanations were that (1) SIRT2 (as its role in breast cancer) extended Slug stability to promote tumorigenesis of EC, thus, EC cell lines were featured in increased expression of SIRT2. (2) SIRT2 (as its role in neuroblastoma and pancreatic cancer) decreased neural precursor cell expressed developmentally downregulated protein 4 (NEDD-4) gene expression but increased N-Myc and c-Myc expressions to accelerate cell proliferation in EC. (3) SIRT2 (behind mentioned in our study) upregulated RAS/ERK pathway to promote cell perforation, while

Figure 5. The regulation of SIRT2 on cell apoptosis. (A-B) In HEC1A cells, comparison of cell apoptosis between SIRT2(-) cells and NC(-) cells; (C-D) In Ishikawa cells, comparison of cell apoptosis between SIRT2(+) cells and NC(+) cells. SIRT2: sirtuin 2; AV: Annexin V; PI: propidium iodide; NC: normal control.
Figure 6. The regulation of SIRT2 on cell migration and invasion. In HEC1A cells, comparison of cell migration (A-B) and invasion (C-D) between SIRT2(-) cells and NC(-) cells; In Ishikawa cells, comparison of cell migration (E-F) and invasion (G-H) between SIRT2(+) cells and NC(+) cells. SIRT2: sirtuin 2; NC: normal control.
repress cell apoptosis in EC. (4) SIRT2 (as its role in gastric cancer) promoted RAS/ERK/JNK/MMP-9 pathway to induce cell growth in EC.5 (5) SIRT2 (as its role in HCC) activated EMT to target the AKT/GSK3β/β-catenin signaling pathway (as its role in HCC), thereby enhanced cell viability in EC.17

RAS and ERK proteins are considered as the most powerful cancer drivers, and RAS/ERK pathway controls diverse cell decisions (such as survival, differentiation, and proliferation) in tumor progression.20 Based on recent evidence, SIRT2 mediates RAS/ERK/JNK/MMP-9 pathway to accelerate cell proliferation, migration and invasion in gastric cancer,5 meanwhile, RAS/ERK pathway has been reported to be one of the important pathways in EC pathology.10 Considering above mentions, we hypothesized SIRT2 might be critical factor in the regulation of RAS/ERK pathway in EC. In order to explore whether SIRT2 was involved into the regulation of RAS/ERK pathway in EC cells, we detected the HRAS, ERK and pERK expressions in SIRT2 regulated EC cells, and we found that SIRT2 increased HRAS, pERK, but decreased ERK in EC cells. These data suggested that SIRT2 might promote RAS/ERK pathway in EC cells. Although these data provided a novel sight for understand the molecular mechanism of SIRT2 underlying EC pathology, additional rescue experiments for further validation are needed. However, the expression of SIRT2 in carcinoma and normal endometrial specimens was not detected due to limited operations or ethical issue. further study was needed.

In conclusion, SIRT2 contributes to tumorigenicity of EC through accelerating cell proliferation and inhibiting cell apoptosis; intriguingly, it is implicated in RAS/ERK pathway in EC. These data indicate that SIRT2 appears as a promising therapeutic target in EC.

**Authors’ Note**

Study conception and design: Yanjuan Guo; data analysis: Yanjuan Guo, Nannan Zhao and Xing Wang; sample collection and experiment: Jianli Zhou and Jianxin Dong; manuscript drafting: Nannan Zhao, Jianli Zhou and Jianxin Dong; manuscript revising: Yanjuan Guo and Xing Wang. All authors reviewed and approved the final manuscript.
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