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# Aberrant expression of SIRT3 is conversely correlated with the progression and prognosis of human gastric cancer

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ABSTRACT

SIRT3 is a $NAD^+$-dependent histone deacetylaseand and plays a critical role in various human carcinomas. However, its precise role in the pathogenesis of gastric cancer (GC) is still unclear. Western blot and Real-Time PCR were used to detect the protein and mRNA level of SIRT3 in freshly collected samples from GC patients. Immunohistochemistry staining was adopted to determine the expression of SIRT3 in 65 formalin-fixed, paraffin-embedded samples from GC patients. In addition, western blot was used to detect the protein levels of SIRT3 and HIF-1α in gastric cancer cells MGC-803 transfected with SIRT3 or control siRNA. Western blot analysis of 25 samples from GC patients showed that 64% (16/25) of patients exhibited decreased expression of SIRT3, whereas 4.0% (1/25) of patients displayed complete loss. In addition, Real-Time PCR analysis showed that GC patients had decreased expression of SIRT3 mRNA. Furthermore, immunohistochemistry analysis of 65 formalin-fixed, paraffin-embedded samples from GC patients showed that 67.7% (44/65) had decreased SIRT3 staining in the cancer tissues. Notably, the expression level of SIRT3 was inversely correlated with clinicopathological variable, including tumor infiltration, tumor differentiation and tumor stage and 5-year survival of these patients. *In vitro* experiment showed that knockdown of SIRT3 in MGC-803 gastric cancer cells significantly increased the expression of HIF-1α. Our results provide the first evidence showing that an aberrantly decreased expression of SIRT3 occurred in GC patients, suggesting that SIRT3 might function as a mitochondrial tumor suppressor in GC. Furthermore, the possible mechanism by which SIRT3 affect the progress of GC is its direct control of HIF-1α.


## 1. Introduction

Gastric cancer (GC) ranks the second mortality of cancer in the worldwide [1]. Both exogenous and endogenous factors contribute to its development and progression. It has been recognized that multiple genetic and epigenetic alteration or abnormality occurs in the development of GC [2]. In this regard, loss or altered function of tumor suppressor genes plays a critical role in GC etiology.

Sirtuins are $NAD^+$-dependent histone deacetylases (HDAC) and widely expressed in normal tissues in mammary animals. Seven members have been identified in human, including Sirt1–7, and play essential roles in cellular physiology, including cell metabolism, cell cycle, cell division and transcriptional regulation. Furthermore, they are also involved in the pathogenesis of series of diseases such as metabolic diseases [3], neurodegenerative diseases [4], cardiovascular diseases [5] and aging [6].

Human SIRT3 is a full-length 44-kD protein and localized mainly in cell mitochondrial. It has the capacity to activate fat oxidation, amino-acid metabolism and electron transport via interaction with various substrates [7–9].

Recently, it has been demonstrated that various types of clinical carcinomas, including hepatocellular carcinoma [10,11], breast carcinoma [12], lung NSC [12,13], medulloblastoma [12], neck carcinoma and prostate carcinoma [13,14] displayed decreased levels or deletion of SIRT3 and $SIRT3^{-/-}$ mice were more susceptible to develop mammary tumors compared with the wide type cohorts, suggesting that SIRT3 may function as a mitochondrial tumor suppressor [15–17]. However, its role in the pathogenesis of gastric cancer is still unclear.

In this study, we investigated the expression of SIRT3 and its correlation with the disease progress and prognosis of gastric cancer. Our data showed that there was significantly decreased expression of SIRT3 protein and mRNA levels in the tissues of 64.0% GC patients. Notably, the expression level of SIRT3 was closely correlated with the tumor infiltration, tumor differentiation

*Abbreviations:* SIRT3, sirtuin 3; GC, gastric cancer; HIF-1α, hypoxia inducible factor-1α.

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and tumor stage. Furthermore, our retrospective analysis of 65 GC patients showed that patients with high SIRT3 expression survived much longer than those with low SIRT3 expression. Taken together, our data demonstrate a critical role for SIRT3 in the progress and prognosis of clinical GC.

## 2. Methods

### 2.1. Patients and tissue samples

All the patients were diagnosed according to the 6th edition of AJCC cancer staging manual. The matched fresh tissue samples of primary gastric cancer and adjacent normal tissues from the same patient used for western blot and Real-Time PCR were collected from 25 GC patients, including 18 male and 7 female with a mean age of 61.8 ± 12.5 years, undergoing surgical resection at Longgang District Central Hospital of Shenzhen and Shenzhen People's Hospital (Shenzhen, China) from 2011 to 2012. All patients had received neither chemotherapy nor radiation therapy before surgical tumor resection. Adjacent normal gastric tissues were obtained from the sites 2.5–5 cm apart from main tumor lesion. All samples were snap-frozen in liquid nitrogen after surgery and stored at −80 °C before the following RNA and protein extraction. Each case was reviewed by two experienced histopathologists who were blinded to the original diagnosis. Written informed consent was obtained from each patient.

Another 65 samples for immunohistochemistry assay were collected from patients with a mean age of 60.8 ± 12.2 years, and formalin-fixed and paraffin-embedded in Longgang District Central Hospital of Shenzhen and Shenzhen People's Hospital. All the patients did not receive thermotherapy or radiotherapy before surgery.

All research involving human participants were approved by the Ethics Committee of Longgang District Central Hospital of Shenzhen and Wuhan University. The present research was carried out in accordance with the Helsinki Declaration.

### 2.2. Cell culture

Gastric cancer cells MGC-803 were purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). Cells were cultured in the RPMI1640 medium supplemented with 10% fetal bovine serum (FBS), 100 mg/l penicillin and 100 mg/l streptomycin at 37 °C in a humidified atmosphere of 5% $CO_2$.

### 2.3. Reagents

Antibody against SIRT3, HIF-1α, β-actin and GAPDH were purchased from Cell Signaling Technology (Beverly, MA, USA). siRNA SIRT3(sc-615555) was purchased from Santa Cruz Biotechnology (Texas, USA). Lipofectamine 2000 was from Invitrogen (CA, USA).

### 2.4. Western blot analysis

Western blot was used to detect the protein expression levels. Briefly, the tissues were sonically homogenized and lysed with RIPA buffer with protease inhibitor (cocktail, Roche). Protein was loaded at a concentration of 30 g per lane, separated on a 12% sodium dodecyl sulfate polyacrylamide (SDS–PAGE) gel, and then transferred onto a nitrocellulose membrane. Next, the membrane was blocked with 5% nonfat milk in TBST and then incubated with primary antibodies SIRT3 and β-actin at 1:1000 overnight at 4 °C. The appropriate secondary antibodies were used at 1:2000 for all antibodies. Positive antibody reactions were detected with the enhanced chemiluminescence system (Biorad, PA, USA) and gel image was detected and processed by ChemiDoc MP System (Bio-rad). Data were analyzed using Image Lab software (Bio-rad).

### 2.5. Real-Time PCR

We selected 16 pairs of frozen samples from the former 25 pairs of gastric cancer and their corresponding nonneoplastic epithelia tissues to further examine the SIRT3 mRNA level. These 16 pairs of samples were examined by microscopy to ensure that at least 90% of each cancer sample composed of tumor cells. Total RNA was isolated using an RNeasy Mini Kit (Qiagen, Valencia, CA), according to the manufacturer's recommendations. After the purity and integrity of the obtained RNA was assessed, cDNA was synthesized using Superscript III platinum kit (Invitrogen) according to manufacturer's instructions. Real-Time PCR was performed using SYBR Green Master Mix (Applied Biosystems) and run on an ABIPrism 7900 sequence detector (Applied Bisosystems). The housekeeping gene *Gapdh* was set as internal control. The sequences of the primers used were as follows:

SIRT3-F: 5′-CTTGGCGGCAGGGACGAT-3′
SIRT3-R: 5′-CCCCGGCGATCTGAAGTCTG-3′
Gapdh-F: 5′-TCCCACTCTTCCACCTTCGA-3′
Gapdh-R: 5′-AGTTGGGATAGGGCCTCTCTT-3′

The cycle parameters were as follows: denaturing for 15 s at 95 °C, annealing for 20 s at 62 °C, and extending for 20 s at 72 °C for a total of 40 cycles. Values were calculated using the comparative threshold cycle (Ct) method after normalization to the control housekeeping gene Gapdh and are reported as GC:GN ratios.

### 2.6. Immunohistochemistry

65 Pairs of formalin-fixed, paraffin-embedded gastric cancer and the adjacent normal tissues were cut into 4-mm sections. The sections were de-paraffinized in xylene and rehydrated in a series of descending ethanol concentrations. For antigen unmasking, sections were immersed in antigen-unmasking solution and boiled in a microwave oven for 15 s. Tissue sections were incubated using anti-SIRT3 at room temperature for 60 min, followed by the standard procedure for the S-P immunohistochemical kit (Fuzhou Maixin Biological Technology Ltd., Fujian, China) and stained with streptavidin–biotin-peroxidase complex at room temperature. Immunohistochemical reactions were developed in freshly prepared 3, 30-diamino-benzidine tetrahydrochloride (DAB kit; Fuzhou Maixin Biological Technology Ltd., Fujian, China) for immune complex visualization and then lightly counterstained with hematoxylin for 30 s before mounting. The immunohisochemical scoring of SIRT3 was based on the percentage of immunopositive levels based on preliminary results. Tumors with less than 10% SIRT3 expression were regarded as negative. Also, because the nuclear and cytoplasmic stains paralleled, total cellular (instead of separate nuclear and cytoplasmic) scores were assessed. In cases showing separate foci of the same histologic pattern, an average score of staining for the same histologic pattern was used. Final scores were assigned after discussion by 2 independent observers.

### 2.7. SIRT3 siRNA transfection

Briefly, MGC-803 cells were transfected with SIRT3 siRNA and control siRNA according to the manufacturer's instructions. Fresh RPMI 1640 medium without antibiotics was added after 8 h of incubation.

### 2.8. Statistical analysis

The means of the different groups were compared using two-sided chi-squared test. The Kaplan–Meier method was used to analyze the distribution of survival curve. All statistical analyses were performed with the SPSS 17.0 software. $p < 0.05$ was considered as statistical significance.

## 3. Results

### 3.1. Expression of SIRT3 is decreased or completely absent in human GC tissues

It was previously shown that SIRT3 could function as either oncogene or tumor suppressor gene. To assess if SIRT3 was involved in the pathogenesis of gastric cancer, we firstly detected the expression of SIRT3 in 25 GC patients using western blot assay. All the GC patients were newly diagnosed and did not receive any treatment before surgical resection. Interestingly, western blot revealed that 64.0% of patients with GC (16/25) had significant reduction of SIRT3 compared with the adjacent normal tissues (Fig. 1A). Remarkably, 4.0% of patients with GC (1/25) exhibited undetectable SIRT3.

To further investigate whether the aberrant expression of SIRT3 occurred in the transcriptional level, we adopted Real-Time PCR to determine its mRNA expression. Consistent with previous results by western blot, SIRT3 mRNA expression GC tissues was strongly decreased when compared with the adjacent normal tissues (Fig. 1B, $p < 0.05$). Together, these data demonstrate that the reduction of SIRT3 expression in GC patients occurred both on protein and mRNA levels.

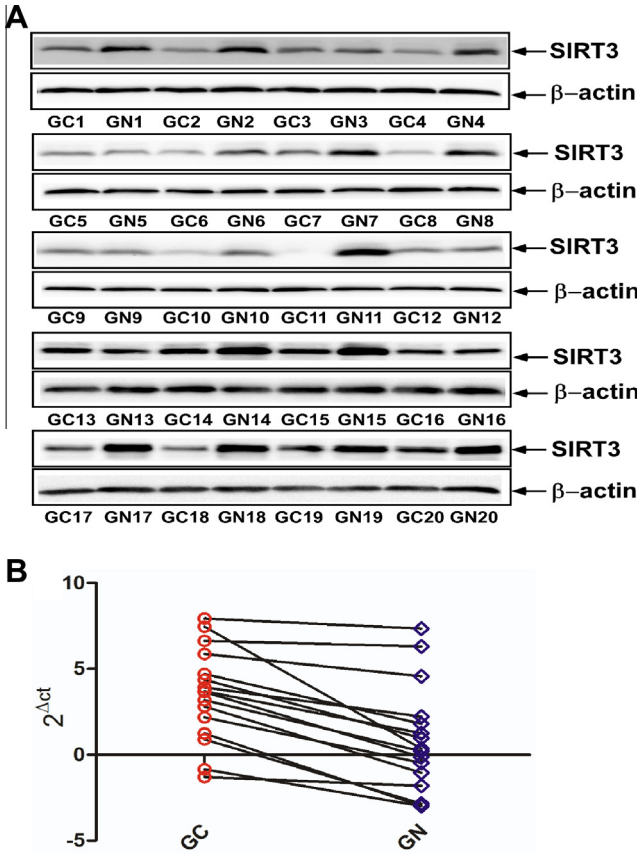


**Fig. 1.** Expression of SIRT3 protein in the GC samples. (A) Western blot analysis of SIRT3 expression in paired fresh tissues from GC patients. An aberrantly decreased expression of SIRT3 occurred in 16/25 gastric cancer tissues compared with adjacent normal tissues. β-Actin was used as an internal control. GC, gastric cancer tissues; GN, adjacent normal tissues. (B) Real-Time PCR analysis of SIRT3 mRNA expression in 16 GC patients who showed decreased expression of SIRT3 protein expression by western blot analysis. Each dot represents one patient. The two dots linked by a line present GC and GN from the same patient. GAPDH was used as an internal control. The *y* axis represents $2^{\Delta ct}$.

### 3.2. Association between SIRT3 expression and clinicopathological variables

Next, we further examined the expression of SIRT3 in formalin-fixed, paraffin-embedded tissues in 65 GC patients using immunohistochemistry staining. These slides were collected from patients with GC without treatment during 2006–2007. H&E staining showed that tumor was composed of irregularly shaped and sized neoplastic tubules lined by stratified atypical columnar cells (Fig. 2B). As shown in Fig. 2C, in the adjacent normal tissue, SIRT3 was mainly localized in the cytoplasm in the cells. Out of 65 patient samples, 32.3% (21/65) showed SIRT3 positive staining and 67.7% (44/65) of patients had decreased SIRT3 expression in the cancer tissues, whereas approximately 63.1% of the adjacent normal tissues exhibited positive or strong SIRT3 staining (Table 1).

To further investigate whether the expression of SIRT3 was correlated with tumor progress, we determined the association between SIRT3 and several clinicopathological factors, including age, gender, tumor infiltration, tumor differentiation, lymph node involvement and tumor grade. Notably, the expression of SIRT3 was negatively correlated with tumor infiltration ($p = 0.017$), tumor differentiation ($p = 0.000$) and tumor stage ($p = 0.034$), but not with age, gender and lymph node involvement.

### 3.3. SIRT3 was inversely correlated with survival of GC patients

Next, we evaluated whether SIRT3 was correlated with the survival of GC patients. Retrospective analysis of 65 patients with GC showed that patients with low expression of SIRT3 had poor survival rate when compared with those with high expression of SIRT3 (Fig. 3, $p = 0.017$).

### 3.4. Knockdown of SIRT3 in gastric cancer cells resulted in increased expression of HIF-1α

To further investigate the possible mechanism by which SIRT3 affects the progression of GC, we transfected GC cells MGC-803 with siRNA SIRT3. As shown in Fig. 4, knockdown of SIRT3 resulted in the increased expression of HIF-1α, while control SIRT3 had no effect on its expression.

## 4. Discussion

SIRT3 has been reported to be correlated with a panel of human tumors, such as hepatocellular carcinoma, breast carcinoma, medulloblastoma, lung NSCO and varian carcinoma, where SIRT3 was obviously deleted [18].

These data have indicated that SIRT3 might function as a mitochondrial tumor suppressor. However, SIRT3 seems to also function as an oncogene in several tumors (e.g. oral carcinoma). SIRT3 was overexpressed in oral squamous cell carcinoma (OSCC) cell lines and down-regulation of SIRT3 inhibited OSCC cell growth and proliferation [19].

These contradictory results might suggest that SIRT3 may function as either a tumor suppressor or oncogene, which is dependent on the tumor type. However, to date there is no report demonstrating the correlation between SIRT3 and gastric cancer (GC). In the present study, we provide the first evidence that SIRT3 might

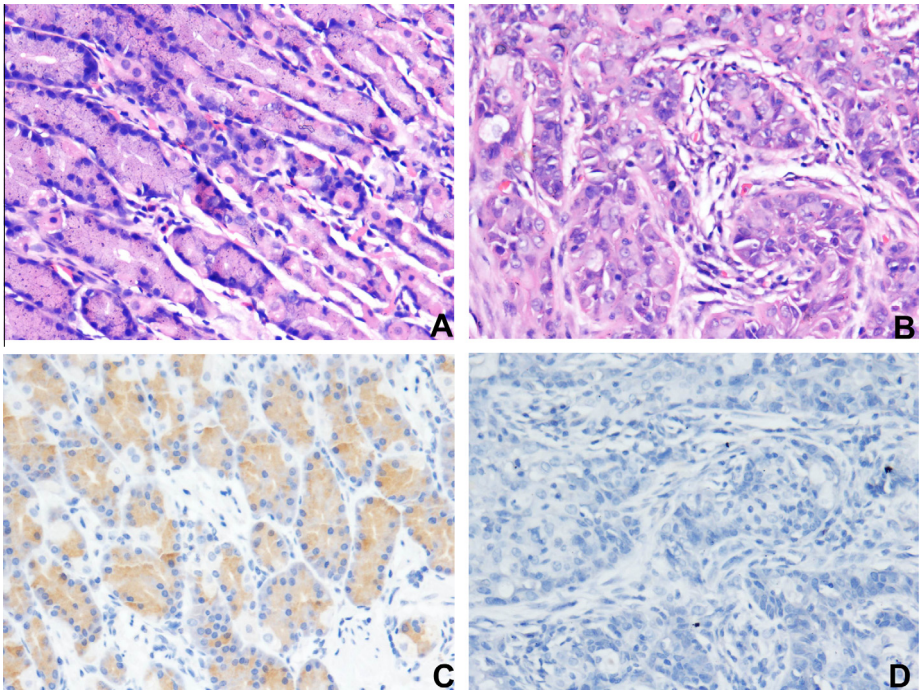


**Fig. 2.** Immunohistochemistry assay of SIRT3 in the formalin-fixed, paraffin-embedded GC tissues (A) and adjacent normal tissues (B). H&E staining indicated the tumor was composed of irregularly shaped and sized neoplastic tubules lined by stratified atypical columnar cells. The original magnification is 200×. Expression of SIRT3 was indicated by dark brown staining. The left (C) and right (D) images represents adjacent normal tissues and cancer tissues, respectively. Adjacent normal tissues express strong SIRT3 staining, cancer tissues exhibit weak or undetectable levels of SIRT3.

**Table 1**
Associations between SIRT3 expression and clinicopathological variables in patients with gastric cancer ($n = 65$).

| Variable | SIRT3 | | | $X^2$ | *P value* |
|---|---|---|---|---|---|
| | All cases | Positive | Negative | | |
| *Overall frequency* | | | | 12.334 | 0.000 |
| Adjacent normal tissues | 65 | 41 | 24 | | |
| Gastric cancer | 65 | 21 | 44 | | |
| *Age* | | | | 0.469 | 0.493 |
| ⩾60 | 41 | 12 | 29 | | |
| <60 | 24 | 9 | 15 | | |
| *Gender* | | | | 2.128 | 0.145 |
| Male | 52 | 19 | 33 | | |
| Female | 13 | 2 | 11 | | |
| *Tumor infiltration* | | | | 5.716 | 0.017 |
| T1–2 | 21 | 11 | 10 | | |
| T3–4 | 44 | 10 | 34 | | |
| *Tumor differentiation* | | | | 15.340 | 0.000 |
| Well-Moderate | 27 | 16 | 11 | | |
| Poor-Undifferentiation | 38 | 5 | 33 | | |
| *Lymphode invasion* | | | | 0.758 | 0.384 |
| Negative | 42 | 12 | 30 | | |
| Positive | 23 | 9 | 14 | | |
| *Stage* | | | | 4.485 | 0.034 |
| I–II | 28 | 13 | 15 | | |
| III–IV | 37 | 8 | 29 | | |

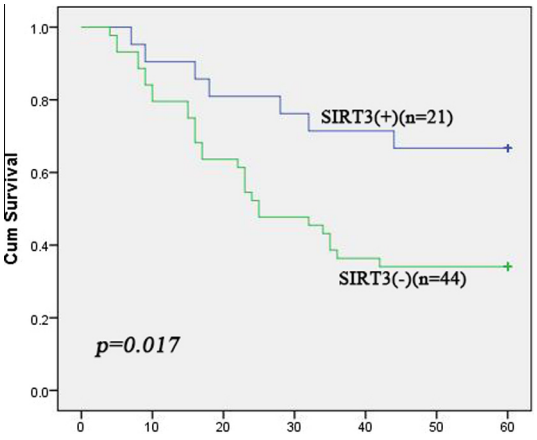


**Fig. 3.** Inverse correlation of SIRT3 with the survival of GC patients. Kaplan–Meier curves depict overall survival according to expression pattern of SIRT3 in patients with gastric cancer. *p*-Values were calculated using SPSS software.

function as a mitochondrial tumor suppressor in GC as 64.0% of GC patients exhibited significantly decreased expression of SIRT3 in comparison with the adjacent normal tissues. Interestingly, approximately 4.0% patients had deletion of SIRT3. Our results were consistent with the recent preclinical and clinical studies where SIRT3$^{-/-}$ mice was more susceptible to develop mammary tumors compared with SIRT3 WT mice after the tumor inoculation, and 20% of clinical cancer patients had one copy of the SIRT3 gene deletion [12].

We further analyzed the relationship between SIRT3 and several clinicopathological variables. Interestingly, SIRT3 was inversely correlated with tumor infiltration, tumor differentiation and tumor stage. Notably, patients with low SIRT3 expression had relatively poor survival when compared with those with high SIRT3 expression, demonstrating the role of SIRT3 as a tumor suppressor in GC.

It has been demonstrated that mitochondrial ROS has the potential ability to regulate the stability of HIF-1α which is a key transcriptional factor regulating hundreds of essential genes in tumorigenesis and tumor progression. Nearly recently, Finley and colleagues have reported that genetic loss of SIRT3 resulted in an

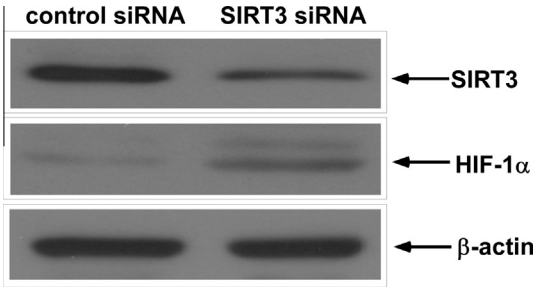


**Fig. 4.** Knockdown of SIRT3 increased the expression of HIF-1α in MGC-803 cells. MGC-803 cells were cultured in RPMI1640 medium, supplemented with 10% FBS for 2 days, followed by the addition of siRNA SIRT3 and control. Cells were then harvested and lysed with RIPA buffer with protease inhibitor. The left and right bands represent the control siRNA and siRNA SIRT3, respectively.

obviously strengthened tumor formation in a murine model in a ROS-dependent manner. Notably, they have provided convincing evidence showing that loss of SIRT3 in patients with breast cancers is closely correlated with the strengthened expression of various HIF-1α dependent genes (e.g. VEGF, glucose transporters...) [20–22]. Our *in vitro* experiment showed that knockdown of SIRT3 significantly increased the expression of HIF-1α in MGC-803 gastric cancer cells, suggesting that SIRT3 might affect the progression of GC via the control of HIF-1α. Together, SIRT3 might function as a mitochondrial tumor suppressor through regulation of cellular ROS and subsequent stability of HIF-1α.

To our knowledge, our study is the first to demonstrate the association between the aberrant expression of SIRT3 and clinical GC. However, we could not differentiate whether the aberrant expression of SIRT3 in GC patients is a causal factor or just the subsequent effect of tumor progression. Another unanswered question is whether there is a mutation in SIRT3 gene in GC patients. These questions still need further investigation.

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