MicroRNA-183 affects the development of gastric cancer by regulating autophagy via MALAT1-miR-183-SIRT1 axis and PI3K/AKT/mTOR signals

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ABSTRACT
Gastric cancer (GC) remains to be a familiar malignant tumor with poor prognosis and daunting impacts on global health. We planned to grab the latent impacts of microRNA-183 in regulating cell autophagy, thus to clarify its possible regulatory principle in GC. The miR-183 level in GC tissues and cell lines was investigated. The impacts of miR-183 dysregulation on cell biological performances including viability, apoptosis and autophagy of GC cell lines including SGC-7901 were detected. Also, cells were disposed with 3-methyladenine (3-MA, an autophagy inhibition) before dysregulation of miR-183 to further investigate the correlation between cell autophagy and viability or apoptosis.

Introduction
Gastric cancer (GC) remains to be a familiar malignant tumor with poor prognosis and daunting impacts on global health [1–3]. It is always easy to reach the advanced stage in the majority of GC patients since there are no asymptomatic or nonspecific symptoms at the early stage [4]. The estimated 5-year survival rate of patients with GC is less than 10% [3]. Moreover, there is lack of efficacious therapeutic strategy for patients with advanced GC [5,6]. Accumulating reports have disclosed the crucial impacts of autophagy in the development of GC [7,8]. Autophagy inhibition can sensitize cisplatin cytotoxicity in human GC cells [9]. Anticancer effects of matrine is found associated with the induction of autophagy in human GC cells [10]. Therefore, elucidating the key autophagy-related mechanisms will help to design the new therapeutic goals for GC.

MicroRNAs (miRNAs) are small endogenous non-coding RNA molecules that have been identified to be key regulators in tumorigenesis, diagnosis, prognosis and progression of various cancers, including GC [11,12]. miRNAs are found to exhibit key roles in autophagy and can regulate the crosstalk between apoptosis and autophagy in disease progression [13]. It is reported that miR-143 can promote the chemosensitivity of Quercetin in GC cells via inhibition of autophagy [14]; miR-181a can inhibit autophagy and enhance the sensitivity of GC cells to cisplatin [15]; and miR-423-3p can induce oncogenic autophagy and promote the progression of GC [16]. Therefore, identification of key miRNAs associated with autophagy will have great significance in the therapy of GC. Recently, a widely reported miRNA, miR-183, has been pointed out to be pivotal in the processes of plenty of diseases, for instance, renal carcinoma [17], and colorectal cancer [18]. In GC, miR-183 is found to act as a suppressor to inhibit tumor progression [19]. However, Gu et al. pointed out that miR-183 played a carcinogenic role in GC cells [20]. In addition to the consistent findings, whether miR-183 contributes to GC progression via regulating autophagy is largely unknown. Therefore, the key roles in GC progression merit further investigation.

In this study, the miR-183 level in GC tissues and cells was investigated. The impacts of miR-183 dysregulation on cell viability, apoptosis and autophagy were detected. Also, cells were disposed with 3-methyladenine (3-MA, an autophagy...
inhibition) before dysregulation of miR-183 to further investigate the relationship between cell autophagy and cell viability or apoptosis. Furthermore, the regulatory mechanisms between miR-183 and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), silent mating type information regulation 1 (SIRT1) or PI3K/AKT/mTOR pathway were explored. The purpose of this research was to grab the potential roles of miR-183 in regulating cell autophagy, thus to offer a novel sight in viewing the potential regulatory principle of miR-183 in GC.

Materials and methods
Sample collection
A total of 20 GC tumor tissues and the matched normal gastric tissue samples were gained from GC patients in our hospital. All fresh samples were quick-frozen in liquid nitrogen and preserved at −80 °C. All samples were histopathologically confirmed by two pathologists independently. This study gained the approval of the local research ethics committee, and all enrolled patients were informed with consent for using their samples for research.

Cell culture test
Human gastric mucosal cell line GES-1 and human GC cell lines BGC-823, SGC-7901 and HGC-27 were provided by Jiangsu Key Laboratory of Biological Cancer Therapy, Xuzhou Medical College, China. Thereinto, BGC-823 is a poorly-differentiated human gastric adenocarcinoma-derived cell line with strong proliferation capacity and migration activity, SGC-7901 is a moderately differentiated human gastric adenocarcinoma cell line, and HGC-27 is an undifferentiated gastric cancer cell line. All cells were then grown in RPMI-1640 medium (Gibco, Carlsbad, CA, USA) mixed with 10% fetal bovine serum (FBS) (Invitrogen, CA, USA) at 37 °C incubator with 5% CO₂.

Cell transfection
Cells with a density of 2 × 10⁵ were seeded in 6-well plates until up to 70–80% of confluence. Cells were then treated with 5 mM of 3-MA (Sigma-Aldrich, MS, USA) or transfected with miR-183 mimic, miR-183 inhibitor, sh-MALAT1, si-SIRT1 and/or the corresponding controls using Lipofectamine 2000 Reagent (Life Technologies, NY, USA) in according to the manufacturer's introduction.

Cell viability assay
Cells were seeded in 96-well plates after 48 h of transfection, and MTT test was then applied to detect cell viability. Briefly, cells were incubated with MTT solution (0.5 mg/mL) at 37 °C for 4 h, followed by the addition of 100 µL of dimethyl sulfoxide (DMSO) to dissolve the precipitated formazan. After shaking for 15 min, µQuant universal microplate spectrophotometer (BioTekinstruments, Winooski, VT, USA) was chosen for the absorbance of cells in each well at 570 nm.

Cell apoptosis detection by flow cytometry
Cells (5 × 10⁵) were harvested and resuspended after 48 h of transfection, and then flow cytometry was chosen for assessing cell apoptosis. To measure apoptosis, cells were double stained with fluorescein isothiocyanate-labelled annexin V (Invitrogen) and propidium iodide, followed by flow cytometry analysis on a FACS Calibur flow cytometer (Becton-Dickinson, San Jose, CA, USA) equipped with Cell Quest software (Becton, Franklin Lakes, NJ, USA).

Luciferase reporter test
We chose dual-luciferase activity test to detect the regulatory association of miR-183 vs. SIRT1. Briefly, the full-length 3’-UTR sequence of SIRT1 mRNA containing the miR-183 binding site was amplified by PCR and then inserted into the pGL3 vector (Promega, WI) to produce pGL3-SIRT1 wild type (WT) reporter construct. The pGL3-SIRT1 mutated (MUT) reporter construct with point mutations in the seed sequence was synthesized using a site-directed mutagenesis kit (Stratagene, CA, USA). Cells were then cotransfected with 50 pmol of miR-183 mimic (or mimic control), 1 µg of pGL3-SIRT1-WT (or pGL3 pGL3-SIRT1-MUT) plasmid, and 1 µg of a Renilla luciferase expression construct, pRL-TK (Promega, WI, USA) using Lipofectamine 2000 Reagent. Renilla luciferase activity was used as a reference. Luciferase activity was measured with the dual luciferase assay system (Promega, WI, USA) at 36 h of transfection.

The binding sites between miR-183-3p and MALAT1 were predicted via the bioinformatics analysis. The full length of MALAT1 with the miR-183-3p binding site was amplified and then inserted into the pGL3-basic vector to produce pGL3-MALAT1. Then the generated vector (1 µg), together with pRL-TK (50 ng) were co-transfected into HEK293 cells that were seeded in the 24-well plates for 24 h incubation. Afterward, the transfected cells were cultured for 24 h, then miR-183 mimic/mimic NC (20 nM) were co-transfected into cells for another 6 h of incubation. Finally, cells were lysed for luciferase activity detection. The targeted sequence between miR-183-3p and MALAT1 was 5’...GUGGGUGGUGUUAGGUAUUUUGJGJUAGU...3’, and hsa-miR-183-3p, 5’...AAUCACGGGAAGCCAUUAGUG...3’.

RNA extraction and qRT-PCR analysis
We isolated the total RNA from cells using TRIzol Reagent (Life Technologies), followed by a measurement for RNA quantity with a SmartSpec Plus spectrophotometer (Bio-Rad). qRT-PCR for analyzing the expression of miR-183 was carried out by miScript II RT Kits (Qiagen, Hilden, Germany) and miScript SYBR Green PCR Kits (Qiagen) by means of the Mx3005P QPCR System (Stratagene). qRT-PCR for determining the level of MALAT1 and SIRT1 were carried out with a GoTag 2-Step RT-qPCR System (Promega, Madison, WI, USA) in a Mx3005P QPCR System (Stratagene, La Jolla, CA, USA). GAPDH and U6 were chosen as the internal controls. Relative quantification of gene expression was conducted with the 2−ΔΔCt method.
**Western blot assay**

We isolated the total proteins from cells that harvested and lysed with cell lysis buffer (Sangon Biotech). The obtained protein samples (50 μg/lane) were adjusted and divided on 12% SDS-polyacrylamide gels and transferred onto polyvinylidene fluoride (PVDF) membranes (Millipore, Billerica, MA, USA). Immunoblotting of protein bands on each membrane was performed using the primary antibodies to Bcl-2, Bax, pro-caspase-3, cleaved-caspase-3, pro-caspase-9, cleaved-caspase-9, Beclin-1, LC3, P62, SIRT1, Pten, p-PI3K, PI3K, p-AKT, AKT, p-mTOR, mTOR and GAPDH (Abcam, Cambridge, MA, USA; 1:1000 dilution) overnight at 4°C, followed by incubation with the recommended secondary antibodies. The immune-blots were analyzed with the Odyssey Infrared Imaging System (LI-COR, Lincoln, NE, USA). GAPDH was chosen as the internal control.

**Statistical analysis**

We carried out all experiments independently in triplicate. The data from multiple experiments are displayed as the mean ± SD. Two-tailed Student’s t-tests or one-way ANOVA were conducted to evaluate the differences between two groups or among three groups or more using SPSS Statistics 20.0 software (IBM, Armonk, NY, USA). p < .05 was chosen as statistically significant.

**Results**

**miR-183 was down-regulated in GC tissues and cells**

The levels of miR-183 in GC tissues and cells were detected. As shown in Figure 1(A), miR-183 n in GC tissues was dramatically depressed than that in normal gastric tissues (P < 0.05). Moreover, the levels of miR-183 in GC cells including BGC-823, SGC-7901 and HGC-27 that are in different stages of gastric cancer differentiation rather than cancer stages, were all obviously lower than those in gastric mucosal GES-1 cells (p < .01, Figure 1(B)). Because miR-183 level was the lowest in SGC-7901 cells, SGC-7901 cells were selected for subsequent tests. Also, we analyzed the mRNA level of SIRT1 in human GC tissues, and the data revealed that SIRT1 was highly expressed in GC tissues compared to that in the non-tumor tissues (p < .01, Figure 1(C)). Since miR-183 is one of the miRNAs of the miR-183/96/182 cluster, we also preliminarily detected the levels of miR-182 and miR-96 in the tumor tissues, and the data uncovered that both miR-96 and miR-192 were dramatically decreased in tumor tissues relative to the non-tumor samples (p < .05, Figure 1(D,E)).

![Figure 1](image-url)

**Influences of miR-183 on SGC-7901 cell biological processes**

To disclose the impact of miR-183 in GC, miR-183 was successfully up-expressed or under-expressed in SGC-7901 cells by transfection of miR-183 mimic or inhibitor (p < .01, Figure 2(A)). MTT test uncovered that miR-183 mimic remarkably suppressed cell viability compared with mimic control, while miR-183 inhibitor markedly enhanced cell viability relative to inhibitor control (p < .05, Figure 2(B)). Western blot test showed that miR-183 mimic markedly inhibited Bcl-2 expression but enhanced the levels of Bax, cleaved-caspase-3 and cleaved-caspase-9 compared to mimic control, whereas miR-183 inhibitor exhibited opposite effects on the expression of these apoptosis (Figure 2(C)). These data indicated that miR-183 mimic enhanced cell apoptosis and miR-183 inhibitor.
inhibited cell apoptosis, which was confirmed by flow cytometry (Figure 2(C)). Furthermore, the impacts of miR-183 dysregulation on the cell autophagy were investigated. As shown in Figure 2(D), miR-183 mimic dramatically induced the expression levels LC3II/I and Beclin-1 but depressed p62, indicating that overexpression of miR-183 promoted cell autophagy. Inhibition of miR-183 had opposite effects. To further investigate the relationship between cell autophagy and cell

Figure 2. Effects of miR-183 on cell viability and apoptosis may be mediated by affecting the activation of cell autophagy. SGC-7901 cells were transfected with miR-183 mimic or mimic control with or without pretreatment with 3-methyladenine (3-MA). (A) The expression of miR-183 in different groups. (B and F) Cell viability in different groups. (C and G) Cell apoptosis in different groups. (D and E) The mRNA and protein expressions of autophagy-related proteins, including LC3II/I, Beclin-1 and p62. Data are presented as means ± SD. *p < .05, **p < .01, and ***p < .001.
viability or apoptosis, cells were disposed with 3-MA before
transfection with miR-183 mimic or mimic control. Western
blot assay uncovered that 3-MA disposes markedly depressed
the levels LC3II/I and Beclin-1, but depressed p62, which
were reversed by miR-183 mimic (Figure 2(E)). Moreover, we
found that 3-MA alone could not change cell viability and
apoptosis, but the impacts of miR-183 mimic on decreased
 cell viability and increased apoptosis were reversed by 3-MA
after treatment with 3-MA and miR-183 mimic simultaneously
\((p < .05, \ *p < .01, \ and \ \ **p < .001).\)

MALAT1 depressed the level of miR-183 in GC

It is reported that miR-183 could enhance the process of mel-
anoma through regulation by lncRNA MALAT1 [21]. We thus
explored the regulatory principles of miR-183 vs. MALAT1.

The levels of MALAT1 in GC tissues and cells were deter-
mined and data uncovered showed that MALAT1 was dra-
natically up-expressed in GC tissues and 3 kinds of cell lines
(BGC-823, SGC-7901 and HGC-27) relative to their corre-
ponding controls \((p < .01, \ Figure 3(A,B)).\) To investigate the
role of MALAT1 in GC, MALAT1 was further depressed in
SGC-7901 cells by sh-MALAT1 approach \((p < .01, \ Figure 3(C)).\)
The depressed MALAT1 markedly inhibited SGC-7901 cell via-
bility \((p < .05, \ Figure 3(D)),\) induced cell apoptosis \((p < .01, \ Figure 3(E)),\) and promoted cell autophagy \((p < .01, \ Figure 3(F)).\) Furthermore, the results showed that miR-183 was negatively
associated with MALAT1 \((R = -0.8782, \ p < .0001, \ Figure 3(G)).\) qRT-PCR assay also uncovered that miR-183 was up-regulated
after knockdown of MALAT \((p < .001, \ Figure 3(H))\) and lucifer-
ase reporter assay confirmed that there was a targeted regu-
lation relationship between MALAT1 and miR-183 \((p < .01, \ Figure 3(I)).\) These data indicate that MALAT1 can suppress miR-183 expression in GC.
MALAT1 regulated GC development through suppressing miR-183 expression

To elucidate whether MALAT1 regulated GC development through suppressing miR-183 expression, sh-MALAT1 and/or miR-183 inhibitor were transfected into the SGC-7901 cells. Expected results were obtained that the impacts of MALAT1 suppression on cell viability ($p < .05$, Figure 3(J)), apoptosis ($p < .001$, Figure 3(K)) and autophagy (Figure 3(L)) were significantly reversed by miR-183 inhibitor when cells were co-transfected with sh-MALAT1 and miR-183 inhibitor (all $p < .05$).

SIRT1 was detected as a potential target of miR-183

To better understand the regulatory principle of miR-183, the possible target of miR-183 was predicted with HumanTargetScan tool. Results showed that SIRT1 was a latent target of miR-183 (Figure 4(A)). Luciferase reporter test further confirmed that the luciferase activity of SIRT1 3’-UTR-WT could be markedly inhibited by miR-183, indicating that there was a targeted regulation relationship between miR-183 and SIRT1 ($p < .05$, Figure 4(B)). Moreover, the levels of SIRT1 were dramatically under-expressed after miR-183 overexpression and obviously down-regulated after miR-183 suppression (Figure 4(C,D)), indicating that SIRT1 was negatively correlated with miR-183.

miR-183 regulated GC development via modulating SIRT1 expression

To further confirm whether miR-183 played key roles in GC development via regulating SIRT1, we depressed the level of miR-183 and SIRT1 in SGC-7901 cells at the same time. Figure 5(A) showed that SIRT1 was successfully knocked down by si-SIRT1 ($p < .01$). After knockdown of miR-183 and SIRT1 at the same time, knockdown of SIRT1 significantly reversed the impacts of knockdown of miR-183 alone on cell viability (Figure 5(B)), apoptosis (Figure 5(C)) and autophagy (Figure 5(D)). These data confirm that miR-183 may play key roles in GC development via regulating SIRT1.

Effects of miR-183 on GC development were mediated by PI3K/AKT/mTOR signals

PI3K/AKT/mTOR signals is a key mechanism to mediate GC development and is reported to have prognostic and predictive significance in GC [22]. We thereby grabbed the relationship between miR-183 and PI3K/AKT/mTOR signals. We discovered that miR-183 depression produced a remarkable increase effect on the levels of p-PI3K, p-AKT and p-mTOR, and an obvious depressed level of PTEN, which were neutralized after the depression of miR-183 and SIRT1 at the same time (Figure 5(E)). These data indicate that the effects of miR-183 on GC development may be mediated by PI3K/AKT/mTOR signals. Subsequently, we verified our findings using BGC-823 cell line by overexpressing miR-183-3p and SIRT1 synchronously. SIRT1 was highly expressed by the pc-SIRT transfection ($p < .001$, Figure 5(F)). After transfected with miR-183-3p mimic, the BGC-823 cell viability was dramatically depressed while apoptosis was remarkably enhanced by miR-183 mimic alone ($p < .05$, Figure 5(G,H)), but these impacts were changeover by the co-transfection of miR-183-3p mimic and pc-SIRT ($p < .05$, Figure 5(G,H)). Also, the autophagy-related proteins were also changeover by the co-transfection of miR-183-3p mimic and pc-SIRT (Figure 5(I)). Furthermore, the impacts of the co-transfection of miR-183-3p mimic and pc-SIRT on the PI3K/AKT/mTOR signals were revealed in BGC-823 cell (Figure 5(J)). Based on the verified experiments, we
thereby deducting the grabbed conclusion of miR-183-3p in regulating the process of GC.

**Discussion**

Result of this research pointed out that miR-183 was under-expressed in GC tissues and cells. miR-183 mimic suppressed SGC-7901 cell proliferation and promoted cell apoptosis and autophagy, whereas miR-183 inhibitor exhibited opposite effects. Moreover, the impacts of miR-183 on SGC-7901 cell viability and apoptosis were mediated by affecting the activation of autophagy. In addition, MALAT1 suppressed miR-183 expression and SIRT1 experimented as a target of miR-183. MALAT1-miR-183-SIRT1 axis may be a mechanism to mediate autophagy in GC. Furthermore, SIRT1 is considered as a key regulator of autophagy that can regulate tumorigenesis in GC through its effect on autophagy [29]. Qiu et al. also revealed that SIRT1-autophagy axis could be used as a prognostic indicator in GC [30]. Moreover, miR-138 is found to inhibit lung cancer cell proliferation and metastasis via downregulation of SIRT1 and activation of cell autophagy [31]. In our study, knockdown of SIRT1 changeover the impacts of depression of miR-183 alone on SGC-7901 cell viability, apoptosis and autophagy. We thereby deducted that miR-183 may regulate cell autophagy via regulating SIRT1 expression.

Accumulating evidences have confirmed that PI3K/Akt/mTOR signals are a key principle in regulating plenty of cell development through regulation by lncRNA MALAT1 [19]. LncRNA MALAT1 has been found to promote tumorigenicity, metastasis and progression in GC [26,27]. Furthermore, MALAT1 is found to promote proliferation and metastasis in aggressive pancreatic cancer via the stimulation of autophagy [28]. In our study, MALAT1 suppressed miR-183 expression. The impacts of MALAT1 knockdown on SGC-7901 cell viability, apoptosis and autophagy were significantly reversed by miR-183 inhibitor. Moreover, the impacts of miR-183 on cell viability and apoptosis were mediated by affecting the activation of cell autophagy. Therefore, we speculate that miR-183 may regulate cell autophagy via negatively regulated by MALAT1.

**Figure 5.** miR-183 regulated GC development through modulating SIRT1 expression. SGC-7901 cells were transfected with miR-183 inhibitor and/or si-SIRT1. (A) The mRNA and protein expression levels of SIRT1 in different groups. (B–D) Effects of miR-183 inhibitor and/or si-SIRT1 on SGC-7901 cell viability (B), apoptosis (C), and the mRNA and protein level of autophagy-related protein (D). (E) The expression of PI3K/AKT/mTOR pathway-related proteins; SGC-7901 cells were transfected with miR-183 inhibitor and/or si-SIRT1. (F) SIRT1 was overexpressed in BGC-823 cells. (G–J) Influences of the co-transfection of miR-183 mimic and pc-SIRT1 on BGC-823 cell viability (G), apoptosis (H) and autophagy (I), as well as the PI3K/AKT/mTOR signals (J). Data are presented as means ± SD. *p < .05, and **p < .01.
processes, including cell proliferation, apoptosis and autophagy [32–34]. The activated PI3K/Akt/mTOR signals are confirmed as a potential prognostic and predictive indicator in GC [22]. Li et al. demonstrated that knockdown of RAS-related protein (Rap1b) promoted GC cell apoptosis and autophagy through the PI3K/Akt/mTOR signals [35]. Singh et al. revealed that rrotlinder induced autophagy in human pancreatic cancer stem cells via depression of PI3K/Akt/mTOR signals [36]. Our results showed knockdown of miR-183 activated PI3K/Akt/mTOR pathway, which was neutralized after knockdown of miR-183 and SIRT1 at the same time. Considering the regulatory relationship between autophagy and PI3K/Akt/mTOR pathway, we speculate that the effects of miR-183 on autophagy in GC may be mediated by PI3K/AKT/mTOR signals.

From the above, our results uncover that miR-183 is under-expressed in GC cells and miR-183 depression may promote GC cell viability and inhibit cell apoptosis by affecting the activation of cell autophagy. MALAT1-miR-183-SIRT1 axis and PI3K/AKT/mTOR pathway may be mechanisms to mediate autophagy in GC. miR-183 may act as a potential therapeutic target for GC. Interestingly, this study uncovered that miR-96 and miR-192 were also displayed decreased levels in GC tissues. On the identity of a cluster, miR-182/miR-183/miR-96 performed a unified decreased expression in GC tissues, implying the possible important correlation among the three factors in GC. However, we will further carry out experiments to verify the pivotal effect of miR-183 and its cluster members of miR-96 and miR-192 in GC in the animal model.

Disclosure statement
No potential conflict of interest was reported by the authors.

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