

## ORIGINAL RESEARCH

# Knockdown of *FAM83D* inhibits endometrial cancer cell viability and induces autophagy via the PI3K/AKT/mTOR axis

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## Abstract

It is important to search new diagnostic and prognostic markers of endometrial cancer (EC) and uncover the possible mechanisms. *Family with sequence similarity 83 member D (FAM83D)* is proved to have carcinogenic properties and act as a new oncogene. *FAM83D* is overexpressed in endometrial cancer, but the role of *FAM83D* in EC is still unclear. Here the role of *FAM83D* was investigated in EC progression. *FAM83D* depletion inhibited the proliferation of EC cells. The knockdown of *FAM83D* induced EC cell cycle arrest. Moreover, its depletion stimulated the apoptosis and autophagy of EC cells. We further found *FAM83D* depletion inhibited progression of EC via targeting phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) axis. We therefore thought *FAM83D* could serve as a EC target.

## Keywords

*FAM83D*; Endometrial cancer (EC); Apoptosis; Autophagy; PI3K/AKT/mTOR pathway

## 1. Introduction

Endometrial cancer (EC) is known as one of the most type of common gynecological malignancies in the world, and its incidence is increasing rapidly [1]. In China, the number of patients dying from EC is on the rise, and EC is now the second largest gynecological malignancy to cervical cancer [2]. The EC 5-year survival rate of patients after surgery, chemotherapy and radiotherapy is about 80% [3]. However, the prognosis of patients with advanced EC remains poor [4, 5]. Therefore, it is important to find new diagnostic and prognostic markers of EC.

*FAM83D* is located on chromosome 20q [6]. More importantly, *FAM83D* has recently been proved to have oncogenic properties and act as a new oncogene in various human tumors [7, 8]. For example, in esophageal squamous cell carcinoma, knockdown of *FAM83D* inhibited cell invasion and induced apoptosis [9]. The overexpression of *FAM83D* in gastric cancer cell lines enhanced cell proliferation, motility, and tumor growth as well as metastatic transmission *in vivo* [10]. *FAM83D* is often upregulated in hepatocellular carcinoma (HCC) samples, and overexpression of *FAM83D* in HCC cell lines promoted their growth and colony formation [6]. *FAM83D* promoted the invasion and proliferation of ovarian cancer cells and inhibited autophagy via PI3K/AKT/mTOR axis [11].

Activation of phosphoinositol 3-kinase (PI3K) or mTOR is the most common event in the development of human cancers, including EC [12]. The alteration of PI3K/AKT/mTOR pathway is related to the pathogenesis of endometrial carcinoma

[13]. The PI3K/AKT/mTOR pathway can inhibit autophagy [14]. In addition, *FAM83D* contributed to the progression of several cancers via this pathway [13, 14]. Previous studies confirmed *FAM83D* had effects on the PI3K/AKT/mTOR axis, which could further affect multiple cellular processes in cancer progression, such as proliferation, apoptosis, and autophagy [12, 15]. We therefore thought *FAM83D* had the potential to affect EC via this pathway.

Previous study has shown that the level of *FAM83D* is increased in the serum of patients with EC, and the expression level of *FAM83D* in endometrial tumor is significantly higher than that in endometrium [15]. However, the role of *FAM83D* during EC progression is still unclear. Here, we investigated the role of *FAM83D* in the progression of endometrial carcinoma and uncovered the possible mechanism. Our data revealed that *FAM83D* promoted EC cell growth as well as induced autophagy through PI3K/AKT/mTOR axis.

## 2. Materials and methods

### 2.1 Antibodies, primers, and drugs

Anti-*FAM83D* (1:500, ab236882, Abcam, Cambridge, UK), anti-Bax (1:500, ab32503), anti-Bcl-2 (1:500, ab32124), anti-LC3 (1:1000, ab128025), anti-Beclin1 (1:500, ab210498), anti-p62 (1:500, ab109021), anti-mTOR (1:500, ab134903), anti-p-mTOR (1:500, ab109268), anti-AKT (1:500, ab8805), anti-p-AKT (1:500, ab38449), anti-PI3K (1:500, ab140307), anti-p-PI3K (1:500, ab278691), anti- $\beta$ -actin (1:2000, ab8226).

The quantitative Polymerase chain reaction (PCR) primer sequences of *FAM83D* are: forward, 5'-

AGAGCGGCAATTCCTTCG-3' and reverse, 5'-TGCCAGAATGAAGGCCAAGG-3'.

The small interfering RNAs (siRNAs) were bought from the Riobio plc (Guangzhou, China). Insulin like growth factor (IGF1) was bought from abcam (ab270062, Abcam), which was used for treating cells for 24 h.

## 2.2 Bioinformation analysis

The expression levels of FAM83D in tumor tissues and normal tissues were analyzed based on the following database: TCGA (<http://gepia.cancer-pku.cn/index.html>); TIMER database (<https://cistrome.shinyapps.io/timer/>); as well as UALCAN database (<http://ualcan.path.uab.edu/>).

## 2.3 Cell culture

The endometrial cancer cell line Ishikawa, human endometrial cancer-1B, HEC-1B, KLE, RL-952, and normal endometrial epithelial cell (hEEC) were all purchased from American type culture collection (ATCC). Both of cells were maintained in Dulbecco's modified Eagle's medium (DMEM), supplemented with 10% of fetal bovine serum (FBS) and incubated at 37 °C in a 5% carbon dioxide (CO<sub>2</sub>) incubator. EC cells were seeded into 6-well plates and 0.5 μg plasmids or 10 μL siRNAs were used for the transfection.

## 2.4 Immunoblot assay

The cell samples were lysed with the cell lysis buffer (Radio Immunoprecipitation Assay Lysis buffer (RIPA, Beyotime, Beijing, China)), and then separated by a 10% SDS-polyacrylamide gel electrophoresis (PAGE) experiment. Then, the total proteins were transferred onto polyvinylidene fluoride (PVDF) membranes (Millipore, MA, USA) and the membranes were then blocked by 5% dry milk at TBS with Tween-20 (TBST) buffer and antibodies. After washing, the membranes were treated with horseradish peroxidase (HRP)-labelled secondary antibodies for 45 min. Each blot was then visualized using enhanced chemiluminescence (ECL) kit (GE Healthcare, Sacramento, CA, USA).

## 2.5 Cell viability assays

For cell counting kit-8 (CCK-8) assays, cells were seed onto the 96-well plates (1000 cell per well) and maintained in media (10% FBS) at 37 °C. Cells were treated with CCK-8 reagent (Beyotime, Beijing, China) at 37 °C for 3 h. The relative cell viability was assessed by microplate spectrophotometer at 450 nm wavelength (Bio-Rad, Hercules, CA, USA) for 24, 48, and 72 h.

For colony formation, cells were plated into the 6-well plates (500 cell per well) and maintained in complete medium for 10 days at 37 °C. Then, cells were fixed with paraformaldehyde (PFA) and stained for 20 min with 0.1% crystal violet. Finally, cells were photographed.

## 2.6 RT-quantitative (q) PCR

TRIzol® (cat. no. 15596026; Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA) reagent was used to isolate RNA. Total RNA was reversely transcribed into complementary DNA (cDNA) at 42 °C for 1 h using moloney mouse leukemia virus (M-MLV) reverse transcriptase (cat. no. M1701; Promega Corporation, Madison, WI, USA) to a final volume of 25 μL. The 2<sup>-ΔΔC<sub>q</sub></sup> method was used to quantify the results.

## 2.7 Cell cycle and apoptosis assay

The cells were washed with PBS. Subsequently cells were fixed with 70% ethanol at -20 °C for 2 h. Subsequently, cells were stained with ethidium bromide (PI) at 4 °C for 10 min (Cell cycle) or ethidium bromide (PI) and FITC-labelled Annexin V (Apoptosis) at 4 °C for 15 min and the apoptosis levels were measured by BD FACS caliber.

## 2.8 Statistics

Data was represented as mean ± Standard Deviation (SD). The unpaired Student's *t*-test was used to compare between two groups, and *p* < 0.05 was considered as significant difference.

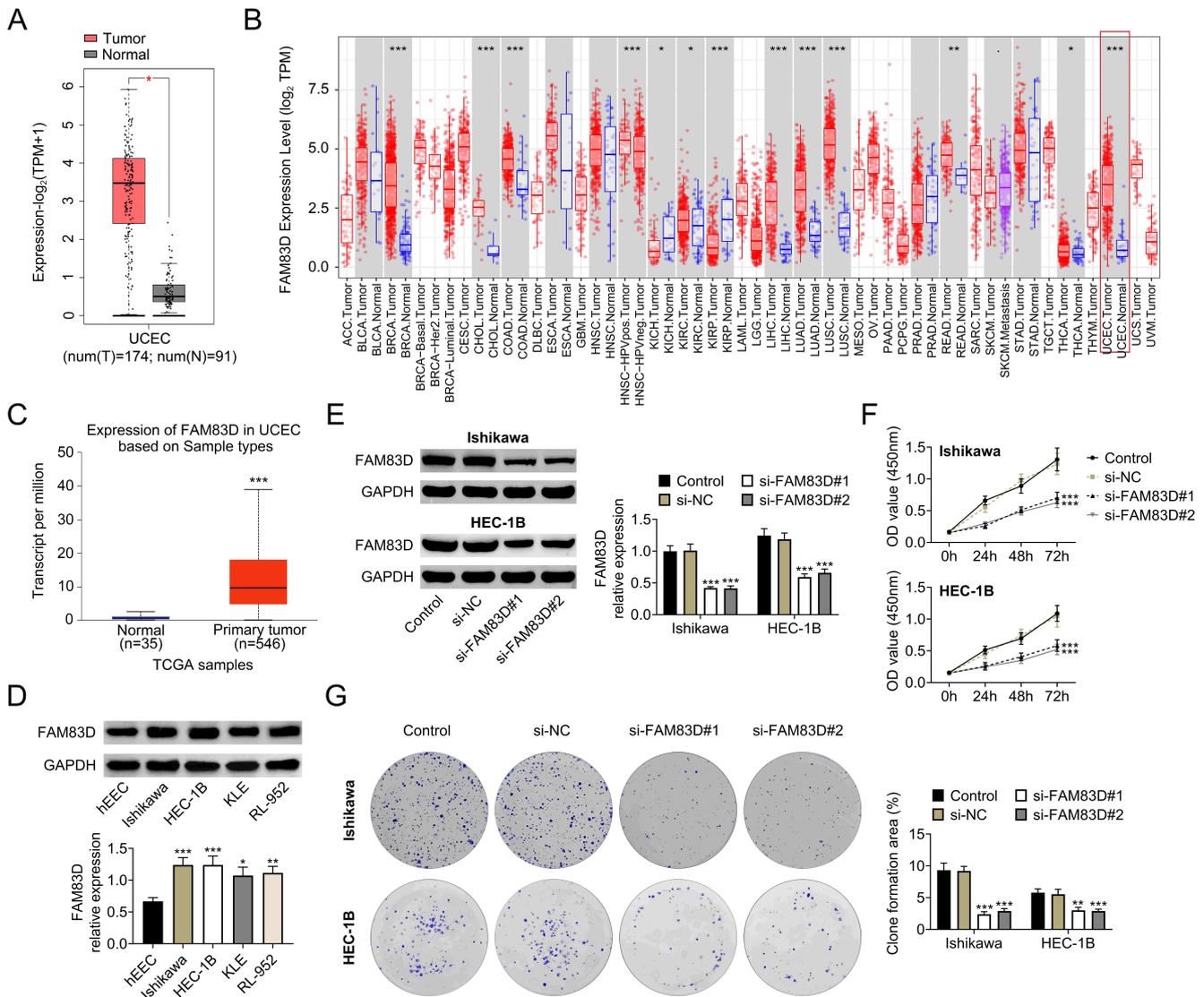
## 3. Results

### 3.1 FAM83D was highly expressed in human EC and promoted cell growth

To uncover the possible effects of *FAM83D* on EC, the expression of *FAM83D* was explored in EC tissues through the bioinformation analysis. We found *FAM83D* was highly expressed in 174 EC tissues, compared to 91 normal tissues (Fig. 1A). The expression of *FAM83D* was also higher in several types of tumor tissues compared to normal according to the TIMER (Fig. 1B). The data from the UALCAN database further revealed *FAM83D* was highly expressed in 546 EC tissues compared to 35 normal (Fig. 1C).

*FAM83D* expression level was then detected in EC cell lines, including Ishikawa, HEC-1B, KLE, RL-952, and normal endometrial epithelial cell line hEEC. Immunoblot assays revealed that the expression of *FAM83D* was higher in EC cell lines compared to endometrial epithelial cell line such as hEEC (Fig. 1D).

To further detect its effects on EC, two siRNAs of *FAM83D*, including si-FAM83D#1 and si-FAM83D#2, were used to deplete its expression in two types of EC cell lines, including Ishikawa and HEC-1B. It was found that *FAM83D* siRNA transfection obviously decreased the expression of *FAM83D* in Ishikawa and HEC-1B cells, compared to control and negative-control siRNA groups (Fig. 1E). CCK-8 assays revealed the ablation of *FAM83D* suppressed the growth of Ishikawa and HEC-1B cells (Fig. 1F). In addition, colony formation showed that *FAM83D* knockdown decreased the colony numbers (Fig. 1G). We therefore thought *FAM83D* depletion restrained cell proliferation of EC.



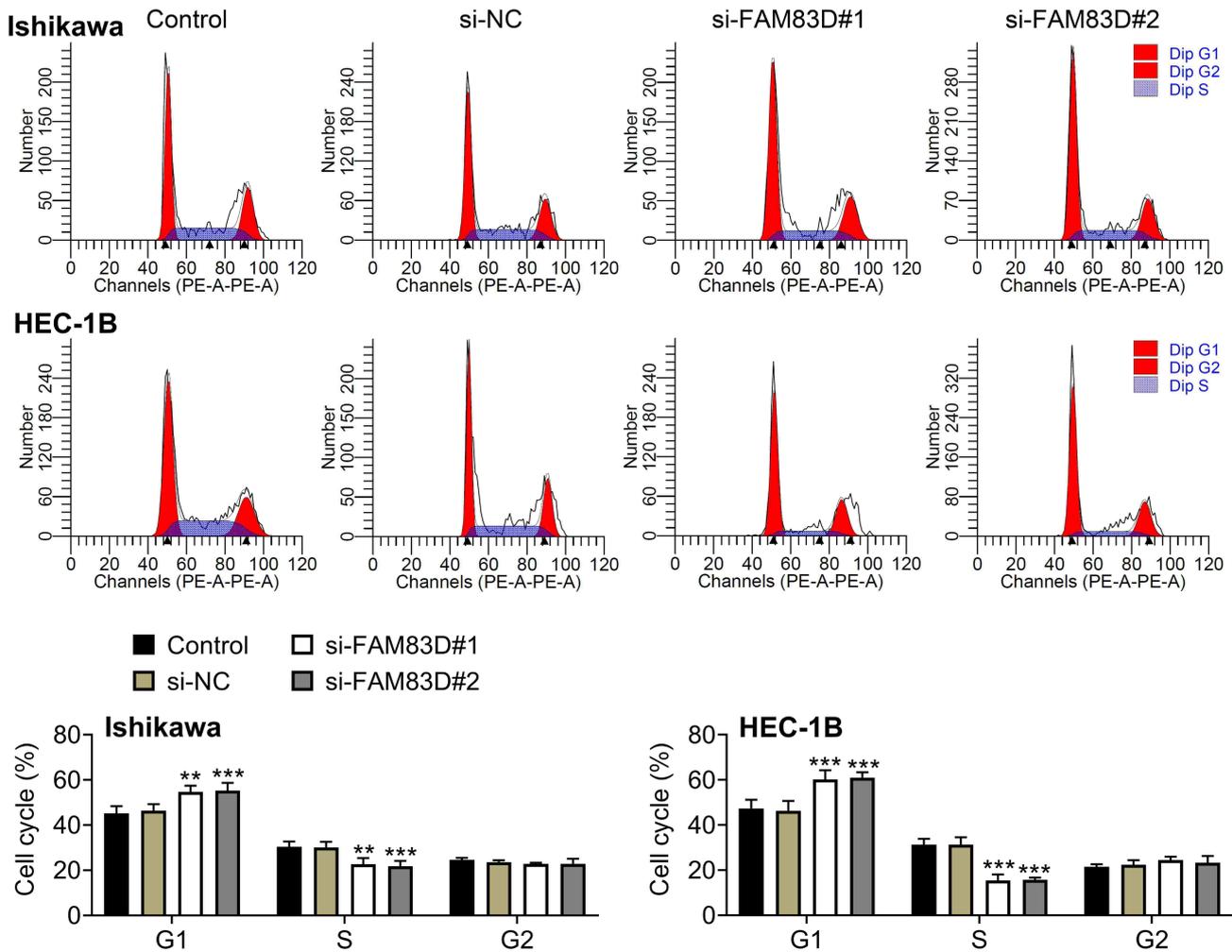
**FIGURE 1. *FAM83D* was highly expressed in human endometrial cancer and promoted cell growth.** (A). TCGA database showed the expression of *FAM83D* in endometrial cancer tissues. (B). TIMER database showed the expression of *FAM83D* in different types of cancers. (C). TCGA database showed the expression of *FAM83D* in endometrial cancer tissues. (D). Immunoblot assays showed the expression of *FAM83D* in endometrial cancer cell line Ishikawa, HEC-1B, KLE, RL-952, and normal endometrial epithelial cell line hEEC. (E). Immunoblot assays showed the expression of *FAM83D* in endometrial cancer cell line Ishikawa and HEC-1B, transfected by the indicated siRNAs. (F). CCK-8 assays showed the OD value at the wavelength of 450 nm in Ishikawa and HEC-1B cells, transfected with the indicated siRNAs at 24, 48, and 72 h. (G). Colony formation assays showed the colony numbers, transfected with indicated siRNAs. The experiment was repeated for 3 times. Data was presented as mean  $\pm$  SD. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ . *FAM83D*: Family with sequence similarity 83 member D; hEEC: normal endometrial epithelial cell; siRNAs: small interfering RNAs; OD: optical density; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase; SD: Standard Deviation.

### 3.2 *FAM83D* depletion induced cell cycle arrest of EC cells

Since it was previously found *FAM83D* depletion inhibited the growth of EC cells, its effects on the cell cycle of EC cells via FCM assays was subsequently detected. The percentage of G1 phase cells was increased in both Ishikawa and HEC-1B cells (Fig. 2). Therefore, we thought *FAM83D* depletion induced EC cell cycle arrest.

### 3.3 Knockdown of *FAM83D* stimulated EC cell apoptosis

It was found that *FAM83D* depletion suppressed cell growth and induced cell cycle arrest in EC cells. The influence of *FAM83D* on the apoptosis of EC cells was then detected through FCM assays. The depletion of *FAM83D* significantly increased the percentage of apoptotic cells, compared to control and negative-control siRNA groups (Fig. 3A). We also performed Immunoblot assays, and found *FAM83D* depletion



**FIGURE 2. *FAM83D* depletion induced cell cycle arrest of endometrial cancer cells.** FCM assays showed the proportion of Ishikawa and HEC-1B cells transfected with the indicated siRNAs. The quantification was analyzed. The experiment was repeated for 3 times. Data was presented as mean  $\pm$  SD. \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ . si-NC: siRNA negative control. PE-A: Phycoerythrin-area. HEC-1B: Human endometrial cancer-1B.

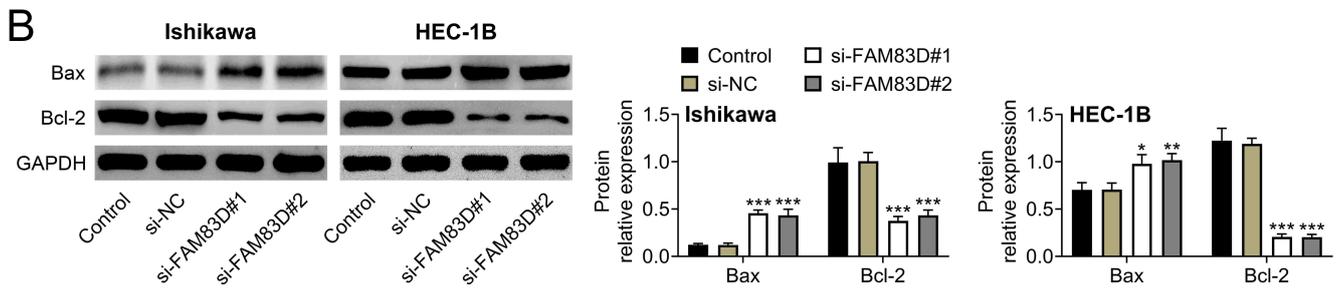
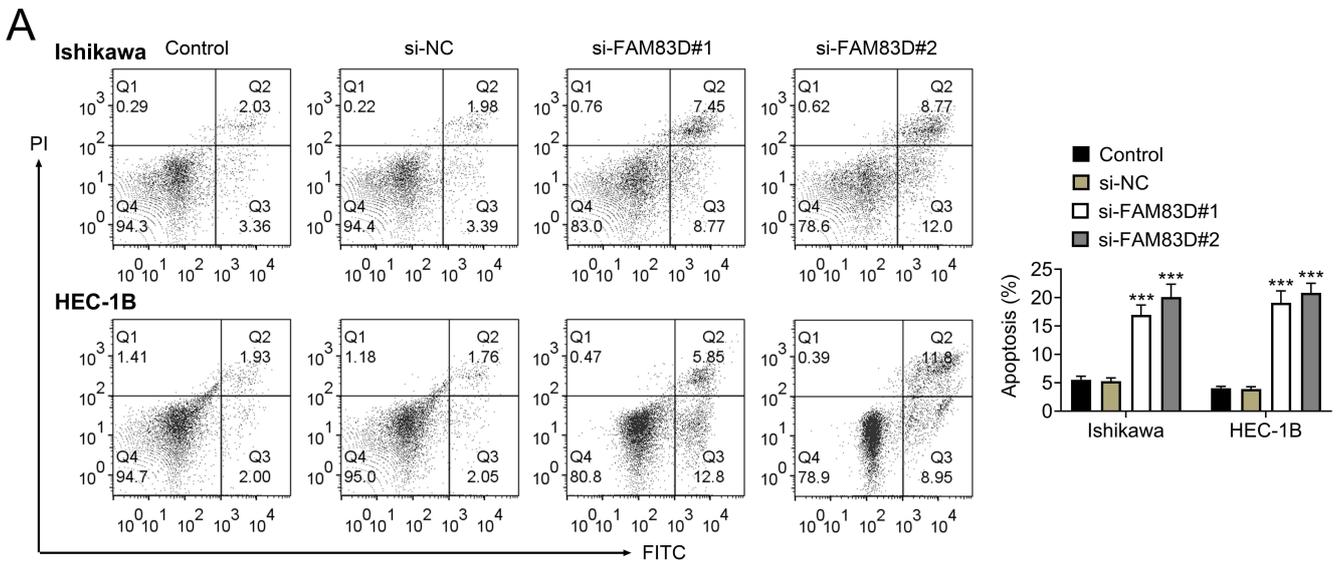
separately increased and decreased the expression of apoptosis biomarkers including Bax and Bcl-2 (Fig. 3B). Therefore, knockdown of *FAM83D* stimulated EC cell apoptosis.

### 3.4 *FAM83D* depletion induced autophagy of EC cells

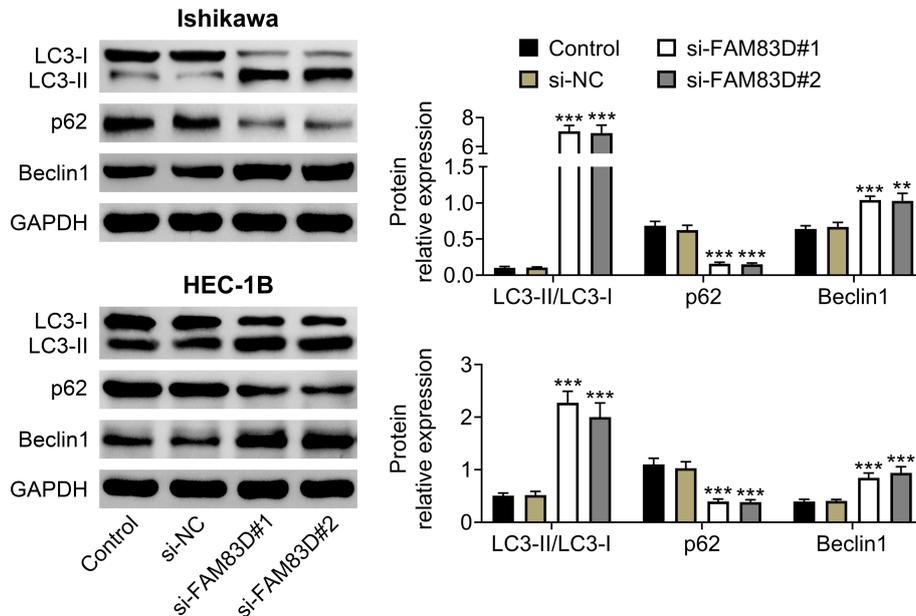
The effect of *FAM83D* on the autophagy of EC cells was further detected. The expression of LC3-II, LC3-I, p62, and Beclin1, critical markers of autophagy in cells transfected with *FAM83D* siRNAs was detected by Immunoblot assays. We found knockdown of *FAM83D* increased the ratio of LC3-II/LC3-I, and the expression of Beclin1. The depletion of *FAM83D* decreased p62 expression (Fig. 4). All these data confirmed that *FAM83D* depletion induced the autophagy of EC cell.

### 3.5 *FAM83D* promoted the progression of EC via mediating PI3K/AKT/mTOR pathway

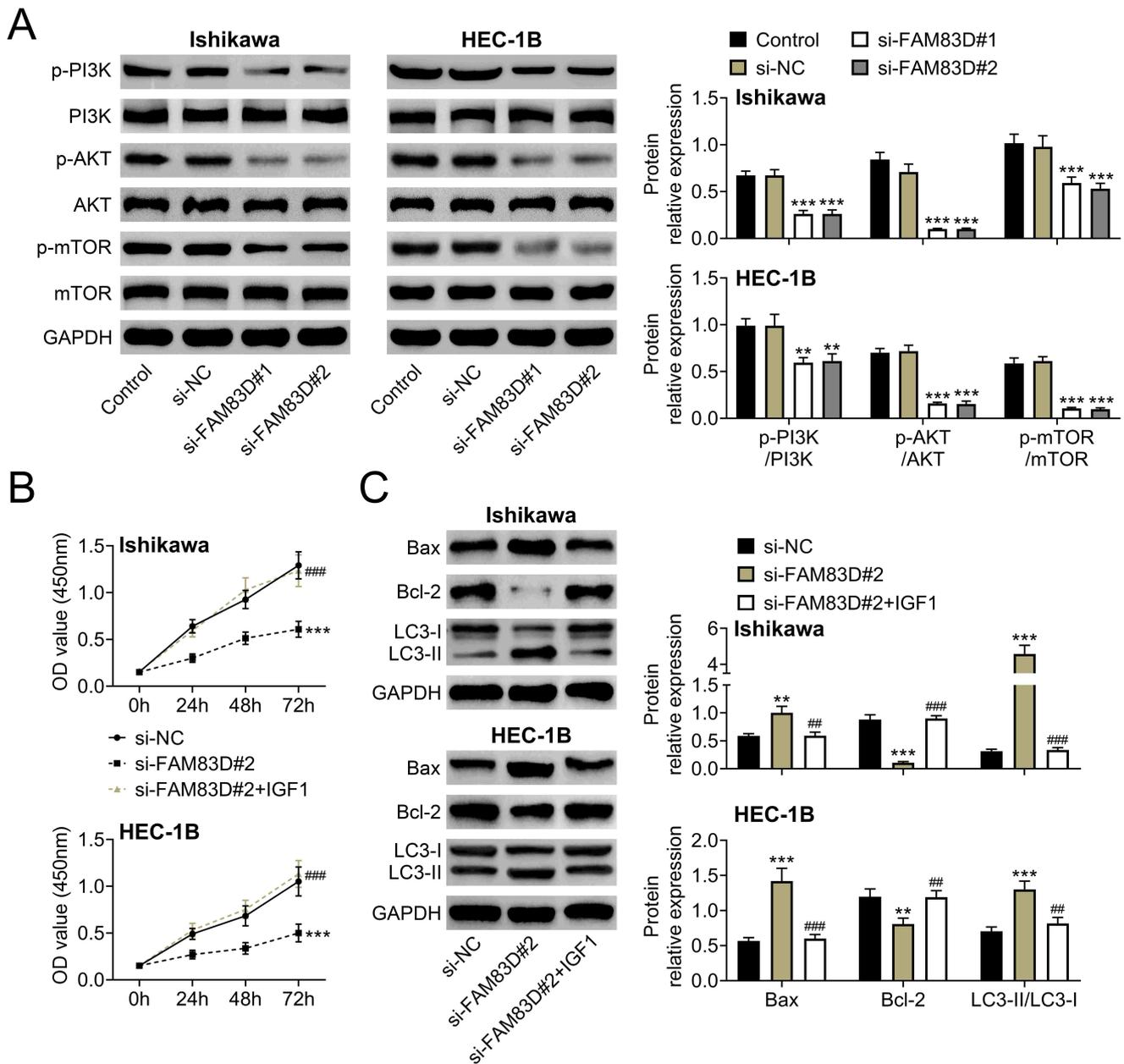
Through Immunoblot assays, we revealed *FAM83D* depletion decreased the phosphorylation levels of PI3K, AKT, and mTOR in both Ishikawa and HEC-1B cells (Fig. 5A), suggesting the inhibition of PI3K/AKT/mTOR axis. As an inhibitor of PI3K/AKT/mTOR axis, IGF1 was further used in Ishikawa and HEC-1B cells after the depletion of *FAM83D*. CCK-8 assays revealed IGF1 treatment rescued the inhibition of cell growth caused by *FAM83D* depletion in Ishikawa and HEC-1B cells (Fig. 5B). Immunoblot assays demonstrated the treatment of IGF1 could reverse the stimulation of apoptosis and autophagy of Ishikawa and HEC-1B cells caused by *FAM83D* knockdown, with the decreased Bax expression, increased Bcl-2 and decreased ratio of LC3-II/LC3-I (Fig. 5C). Therefore, *FAM83D* promoted the progression of EC via mediating PI3K/AKT/mTOR axis.



**FIGURE 3. Knockdown of *FAM83D* stimulated endometrial cancer cell apoptosis.** (A). The apoptosis cell numbers of Ishikawa and HEC-1B cells transfected with the indicated siRNAs. (B). The expression of Bax and Bcl2 in Ishikawa and HEC-1B cells transfected with the indicated siRNAs. The experiment was repeated for 3 times. Data was presented as mean  $\pm$  SD. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .



**FIGURE 4. *FAM83D* depletion induced autophagy of endometrial cancer cells.** The expression of LC3-II, LC3-I, p62, and Beclin1 in Ishikawa and HEC-1B cells transfected with the indicated siRNAs. The experiment was repeated for 3 times. Data was presented as mean  $\pm$  SD. \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .



**FIGURE 5. *FAM83D* promoted the progression of endometrial cancer via mediating PI3K/AKT/mTOR pathway.** (A). Immunoblot assays showed the expression and phosphorylation levels of PI3K, AKT, and mTOR in Ishikawa and HEC-1B cells transfected with the indicated siRNAs. (B). CCK-8 assays showed the OD450 in Ishikawa and HEC-1B cells, upon the indicated treatment at 24, 48, and 72 h. (C). Immunoblot assays showed the expression of Bax, Bcl-2, and the ratio of LC3-II/LC3-I in Ishikawa and HEC-1B cells. Data was presented as mean  $\pm$  SD. \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ . siFAM83D + IGF1 vs. siFAM83D, ##  $p < 0.01$ , ###  $p < 0.001$ .

#### 4. Discussion

Endometrial cancer (EC) is known as a group of epithelial malignant tumors occurring in the endometrium tissues, most commonly occurring in perimenopausal as well as postmenopausal women [1]. In addition, EC is a female reproductive system tumor, with approximately 200,000 new cases and is the 3rd most common gynecological malignancy causing death. Surgical excision, radiotherapy, chemotherapy and hormone therapy are the common treatment methods for EC, but they are still ineffective for advanced tumors [15].

Recently, the targeted therapy becomes a promising treatment for EC. [16]. However, more effective targets still need to be developed. In this study, we identified *FAM83D* could serve as a promising target of EC. Our data confirmed *FAM83D* promoted proliferation and suppressed apoptosis as well as autophagy of EC cells.

Bioinformation analysis found that the expression of *FAM83D* was high in EC tissues. Immunoblot revealed *FAM83D* was highly expressed in EC cells. CCK-8 and colony formation assays demonstrated that *FAM83D* promoted proliferation of EC cells. FCM assays revealed

*FAM83D* induced cell cycle arrest as well as apoptosis. We also performed Immunoblot assays, and found *FAM83D* had effects on the autophagy and PI3K/AKT/mTOR pathway of EC cells. Our data confirmed *FAM83D* could serve as a target of EC. *FAM83D* ablation exhibited antitumor effects in glioblastoma [17]. Similarly, *FAM83D* had an influence on PI3K/AKT axis. *FAM83D* ablation enhanced radiosensitivity with irradiation by suppressing EMT via the Akt/GSK-3 $\beta$ /Snail axis in esophageal cancer cells [9]. *FAM83D* also modulated MAP kinase as well as AKT pathway [18]. *FAM83D* contributed to the epithelial-mesenchymal transition (EMT), invasion, as well as cisplatin resistance via mediating the AKT/mTOR pathway in non-small cell lung cancer (NSCLC) [19]. Interestingly, this study also found the effects of *FAM83D* on the progression of EC via PI3K/AKT/mTOR pathway. All these data confirmed *FAM83D* could serve as a target of multiple cancers.

In this study, it also revealed that *FAM83D* affected the cell cycle and apoptosis of EC cells. The cell cycle and apoptosis were two critical factors, which affected the progression of EC. In addition, we also found *FAM83D* affected the autophagy of EC cells. Recently, the effect of autophagy on the progression of EC has been revealed. Therefore, we thought *FAM83D* mediated the progression of EC via mediating cell cycle, apoptosis, and autophagy.

Activation of phosphoinositol 3-kinase (PI3K) or mTOR is the most common event in cancers, including ECs [12]. The alteration of PI3K/AKT/mTOR signaling pathway corrected with the pathogenesis of endometrial carcinoma [12]. Activation of the PI3K/AKT/mTOR signaling pathway can inhibit autophagy [20]. In addition, this pathway affected multiple cellular processes in cancer progression, such as EMT and drug resistance [21]. In this study, we found the effects of *FAM83D* on the growth, cell cycle, apoptosis, and autophagy of ECs. Our data further confirmed that *FAM83D* mediated these cellular processes via targeting PI3K/AKT/mTOR pathway. However, the precise mechanism needs further study, and the *in vivo* assays should be performed in the future.

## 5. Conclusions

In summary, this study investigated *FAM83D*'s role in EC progression. Our data confirmed the high expression of *FAM83D* in EC. *FAM83D* contributed to the growth of EC cells. Further, its depletion induced cell cycle arrest as well as the apoptosis of EC cells. The knockdown of *FAM83D* also induced autophagy as well as activation of PI3K/AKT/mTOR axis of EC cells. *FAM83D* could therefore serve as a promising target of EC.

## AUTHOR CONTRIBUTIONS

ZC—designed the experiments and YM carried them out. XYJ—analyzed and interpreted the data, RQL—prepared the manuscript with contributions from all co-authors.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## ACKNOWLEDGMENT

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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