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ORIGINAL RESEARCH

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S100A7 promotes endometrial carcinoma progression by activating the MAPK signaling pathway

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Abstract

S100 calcium binding protein A7 (S100A7) has been proofed to play a carcinogenic role in several cancers. However, its role and the regulatory mechanism in Endometrial carcinoma (EC) was unknown. Western blot was applied to determine the expression of S100A7 and Mitogen-activated protein kinase (MAPK) pathway-related protein in EC cells. Functional *in vitro* experiments were conducted to explore the effects of S100A7 on cell proliferation, apoptosis, migration, invasion and angiogenesis in EC. As a result, S100A7 expression was dramatically up-regulated in EC cells. Overexpression of S100A7 enhanced EC cells proliferation, migration, invasion and angiogenesis, and suppressed cell apoptosis, as well as activated MAPK signaling pathway. Whereas, knockdown of S100A7 exerted the opposite effects. Our finding suggested that S100A7 may promote the malignant progression of EC by activating MAPK pathway, implying S100A7 has significant potential to be used as an emerging therapeutic target for EC treatment.

Keywords

Endometrial carcinoma; S100A7; Proliferation; Apoptosis; Migration; Invasion; Angiogenesis

1. Introduction

Endometrial carcinoma (EC) is a malignancy of the female reproductive system, and morbidity and mortality of EC patients are rising worldwide [1]. Patients with early EC had a relatively good prognosis after surgery and chemotherapy treatment, but patients with advanced EC were less likely to respond to treatment and had a worse outcome [2, 3]. Invasive and metastasis of cells are the main factors contributing to poor therapeutic effect in patients with EC [4–6]. Therefore, exploring the molecular mechanism of EC progression and finding effective targets for therapy were urgently needed.

S100 calcium binding protein A7 (S100A7), part of the S100 family, regulates a variety of cell functions, including growth, invasion and calcium homeostasis [7]. In recent years, high expression of S100A7 had been proved in multiple cancers. Such as, Luo *et al*. [8] found that S100A7 was associated with bone metastasis of lung cancer. Lu *et al*. [9] verified that S100A7 promoted cell metastasis and tumor angiogenesis by regulating oncogenic pathways in esophageal cancer. Dey *et al*. [10] illuminated that S100A7 accelerated the cell invasion and metastasis of oral squamous cell cancer through activating the RAB2A-mediated p38 MAPK pathway. However, S100A7 expression and its role in EC remains elusive.

Herein, we analyzed the Cancer Genome Atlas (TCGA) (https://www.cancer.gov) and Kmplot database (https://kmplot.com/) and found S100A7 was upregulated in EC tissues and associated with poor survival among EC patients. Based on this, *in vitro* experiments were carried out to detect the effect of S100A7 expression on phenotypes of EC cells and explore the underlying mechanism.

2. Materials and methods

2.1 Cell culture

Human endometrial epithelial cells (hEEC) and EC cells (HEC1B, AN3CA and Ishikawa) for the study were obtained from American Type Culture Collection (ATCC, Manassas, VA, USA). All cells were cultured in Radio Immunoprecipitation Assay (RIPA) 1640 medium (Invitrogen, Carlsbad, CA, USA), supplement with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin.

2.2 Cell transfection

To overexpress S100A7, a S100A7 overexpression plasmid (S100A7) or control was constructed by GenePharma (Shanghai, China), and transfected into AN3CA cells with lipofectamine 2000 reagent (11668019, Invitrogen, Carlsbad, CA, USA). To knock down S100A7, two short hairpin RNAs (shRNAs) targeting S100A7 (shS100A7-1# and shS100A7-2#) were designed and shRNA S100A7 lentivirus were generated by GenePharma. After transfection, S100A7 protein levels in AN3CA cells were assessed by western blot.

2.3 Western blot

AN3CA cells were lysed with RIPA buffer (#89900, Thermo Fisher Scientific, Waltham, MA, USA). After denaturation, proteins samples were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and transferred to polyvinylidene fluoride (PVDF) membrane (GE Healthcare, Piscataway, NJ, USA). Following 2 h of membrane sealing with 5% bovine serum albumin (BSA), the membrane was incubated with S100A7 (ab275026, 1:1000, Abcam), BCL2-associated X (Bax, ab32503, 1:1000, Abcam), B-cell lymphoma-2 (Bcl2, ab32124, 1:500, Abcam), cleaved caspase3 (ab2302, 1:1000, Abcam), total caspase3 (ab32150, 1:5000, Abcam), extracellular regulated protein kinases (ERK, ab184699, 1:10,000, Abcam), phosphorylated ERK (p-ERK, ab79483, 1:500, Abcam), , c-Jun N-terminal kinase (JNK, ab76572, 1:5000, Abcam), phosphorylated JNK (p-JNK, ab124956, 1:5000, Abcam), p38 (ab59461, 1:1000, Abcam), phosphorylatedp38 (p-p38, ab178867, 1:1000, Abcam), and β-actin (ab6276, 1:5000, Abcam) primary antibodies dilution overnight at 4 ℃, respectively. Subsequently, the membrane was incubated with corresponding secondary antibodies for 2 h. Protein bands were observed and analyzed using enhanced chemiluminescence (ECL, Beyotime, Shanghai) and Image J.

2.4 CCK8 and colony formation assays

For cell proliferation detection, 3×10^3 cells/well were grown in 96-well plates. Next, cell counting kit-8 (CCK8, C0037, Beyotime, Shanghai, China) was piped into each wells at 12 h, 24 h, 48 h, 72 h, respectively, and incubated for a further 4 h. The absorbance at 490 nm of every well was detected with a microplate reader (Multiskan MK3, Thermo Fisher Scientific,Waltham, MA, USA). For colony formation, about 3×10^3 cells were planted in 6-well plates, and grown for 14 d. Then, cells were stained with 5% crystal violet followed by the fixation of the cells with ethanol. Colonies with over 50 cells were counted microscopically.

2.5 Flow cytometry for apoptosis

The rate of cell apoptosis was monitored by staining with Annexin V-FITC/Propidium iodide (PI) (CA1020, Solarbio, Beijing, China) by flow cytometry. Cells were digested with trypsin and harvested, and re-suspended in 1× Binding buffer. Next, cells were labeled with 5 μL Annexin V-FITC for 15 min, followed by cultivation with PI for 5 min. Then, Flow cytometry (FACScan; BD Biosciences, San Jose, CA, USA) was utilized to detect cell apoptosis.

2.6 Transwell assay for migration and invasion

For cell migration, cells were digested with trypsin and re-suspended in FBS-free medium, and then cell suspension (about 4×10^4 cells/well) were stocked in the upper Transwell chamber (8 μm, Corning, Tewksbury, MA, USA). Next, the lower chamber was loaded with medium containing 10% FBS. After 24 h of culture, the migrated cells on the lower surface of the transwell were fixed with 4% paraformaldehyde and stained with 0.1% crystal violet, which were then counted under a microscope. For cell invasion, the upper chamber was covered with matrigel (Corning, USA) in advance.

2.7 Tube formation

Tube formation experiment was performed to assess human umbilical vein endothelial cell (HUVEC) angiogenesis *in vitro*. HUVEC (4×10^4 cells/well) were placed into 24-well plates, which had been coated with thawed Matrigel (100 μL/well). Cells were incubated at 37 ℃ for 45 min. After the cells were adhered, the culture medium was replaced with the transfected AN3CA cell supernatant, and incubated at 37 ℃ for 6 h. Tube formation was then observed and imaged under a microscope.

2.8 Statistical analysis

All the experiments were replicated three or more times. The data was expressed as mean ± standard deviation (mean ± SD). Statistical Product and Service Solutions 22.0 (SPSS 22.0, Chicago, IL, USA) was utilized for statistical analyses. *t*-test or one-way analysis of variance (ANOVA) was used to determine the significant differences between two or multiple groups. Differences with $p < 0.05$ were regarded as statistically significant.

3. Results

3.1 Expression of S100A7 is upregulated in EC

First, as analyzed by TIMER database (https://cistrome.shinyapps.io/timer/), S100A7 expression was queried in TCGA Pan-cancer samples. The results revealed that S100A7 was significantly differently expressed in multiple cancers, including EC (Fig. 1a). Further, we compared the mRNA expression of S100A7 in EC primary tumors samples with normal tissues in TCGA dataset, using the UALCAN database (http://ualcan.path.uab.edu/), and S100A7 mRNA levels were highly expressed in EC tissues compared to normal tissues (Fig. 1b). Besides, we queried the Kmplot database to analyze the association between the increased level of S100A7 gene and the prognosis of EC patients. The results showed that increasingly expression of S100A7 was linked with poor overall survival (OS) of EC patients, but not Relapse free survival (RFS) (Fig. 1c). Consistently, the protein expression of S100A7 was verified to be upregulated in EC cell lines (HEC1B, AN3CA and Ishikawa) compared to human endometrial epithelial cell (hEEC) by western blot (Fig. 1d). These data elucidated that S100A7 was highly expressed in EC tissues and cells.

3.2 Knockdown of S100A7 suppresses proliferation of EC cells

To confirm that S100A7 expression affects the biological function of EC cells, AN3CA cells were transfected with sh-S100A7 or S100A7-overexpression vector. The result of western blot showed that compared to control, the protein expression of S100A7 was elevated in the S100A7 overexpression group, and decreased after sh-S100A7 transfection (Fig. 2a). Then, CCK8 assays showed that S100A7 overexpression sig-

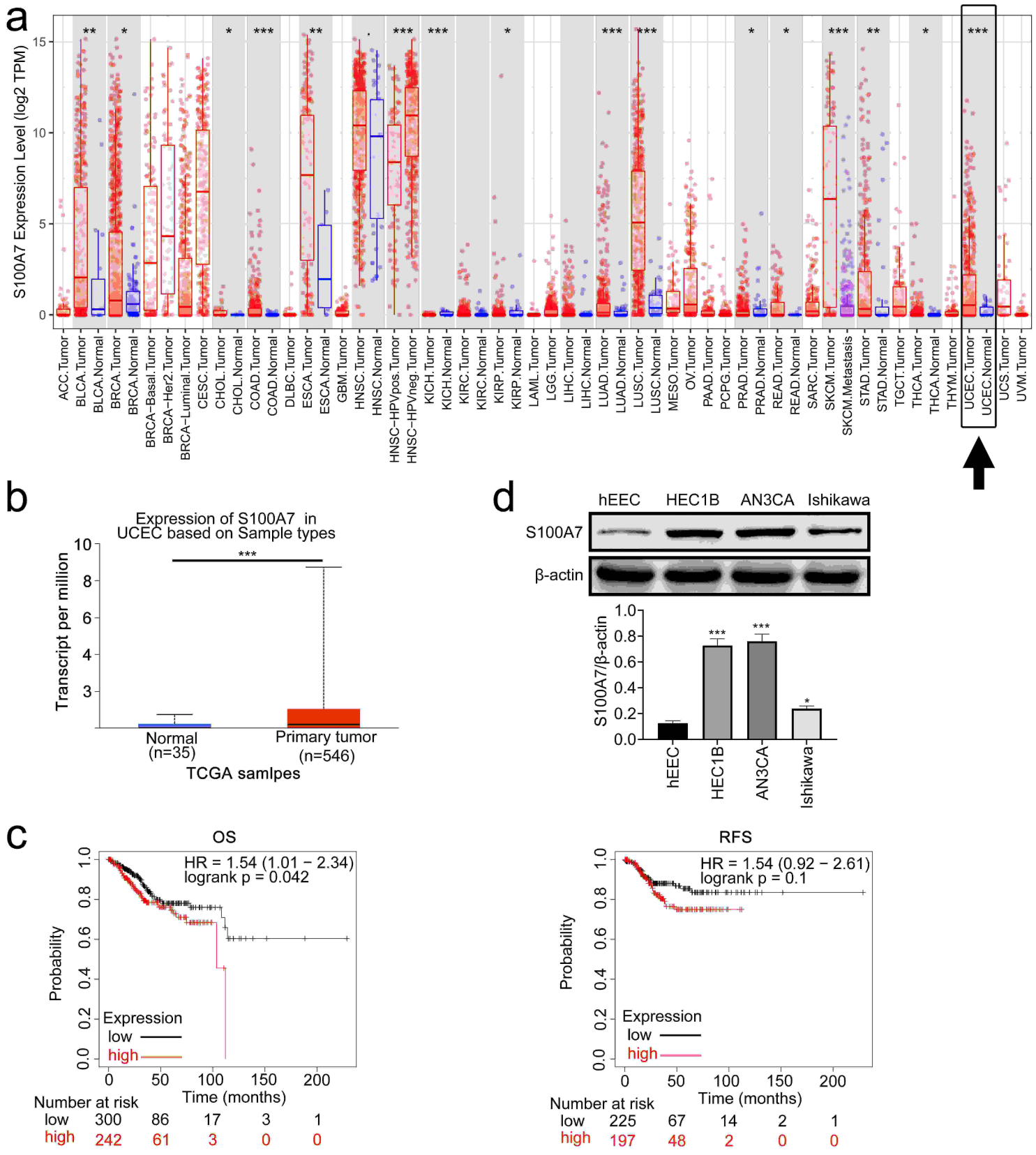

FIGURE 1. S100A7 is highly expressed in EC. (a) Differential expression of S100A7 in TCGA Pan-cancer specimens analyzed by TIMER database. (b) Comparison of the expression of S100A7 in normal and EC primary tumor using the UALCAN database. $^{***}p < 0.001$, compared with the primary tumor. (b) The survival rate of low and high expression of S100A7 in EC patients using Kmplot database. (d) S100A7 protein levels in different cell lines were detected by western blot. $^{*}p < 0.05$, $^{***}p < 0.001$, compared with the hEC cells. S100A7: S100 calcium binding protein A7; OS: Overall Sruvival; RFS: Recurrence free survival.

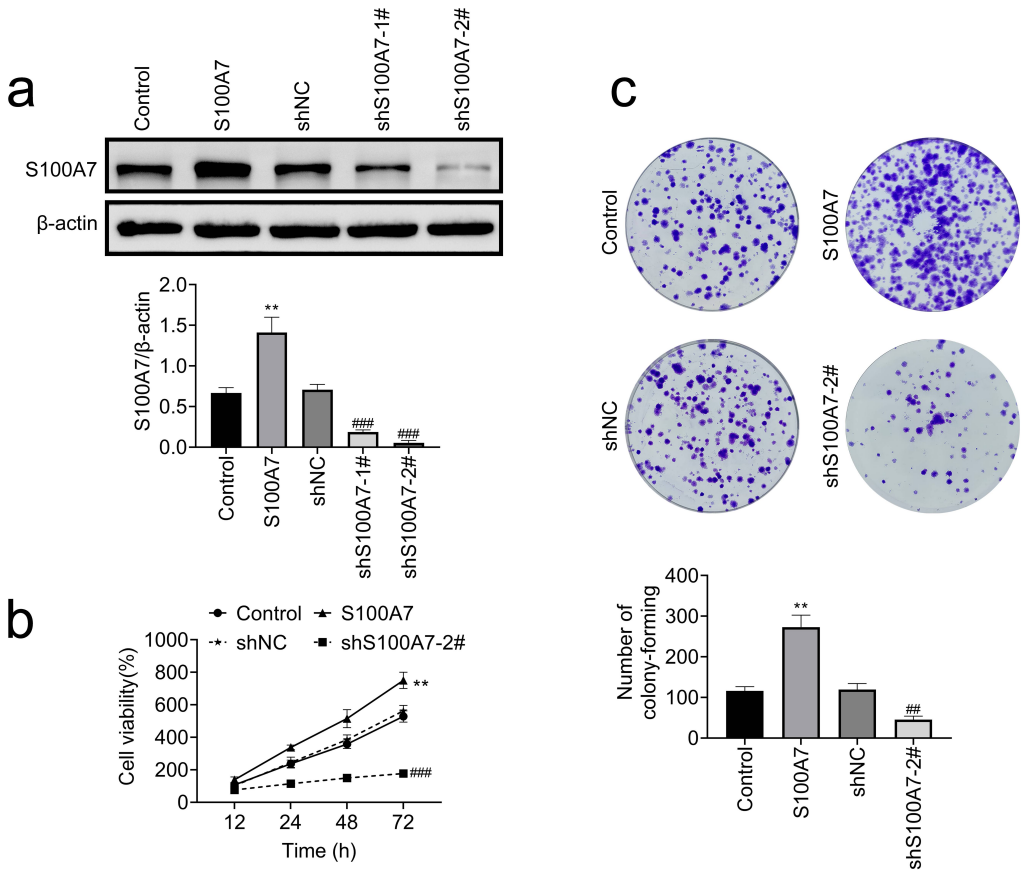

FIGURE 2. S100A7 silencing inhibits EC cells proliferation. (a) S100A7 protein expression was examined by western blot in AN3CA cells transfected with pcDNA-S100A7, sh-S100A7 or their control. $^{**}p < 0.01$, compared with the control group. $^{###}p < 0.001$, compared with the shNC group. (b,c) The proliferation activity was assessed by CCK8 and colony formation assay. $^{**}p < 0.01$, compared with the control group. $^{##}p < 0.01$, $^{###}p < 0.001$, compared with the shNC group. S100A7: S100 calcium binding protein A7; shNC: short hairpin RNA negative control.

nificantly promoted the proliferation activity of AN3CA cells. In contrast, the loss of S100A7 expression greatly inhibited cell proliferation (Fig. 2b). Consistently, a colony formation assay showed that S100A7 overexpression facilitated the colony formation ability of AN3CA cells, and silencing S100A7 had the opposite effect (Fig. 2c). Taken together, the data suggested that inhibition of S100A7 impaired the growth of EC cells *in vitro*.

3.3 Knockdown of S100A7 promotes apoptosis of EC cells

The result of flow cytometry showed that overexpression of S100A7 led to a lower apoptosis rate compared with that in the control group. On the contrary, AN3CA cells transfected with sh-S100A7 had a higher apoptosis rate than cells transfected with shNC (Fig. 3a). In addition, western blot was carried out to examine the expression of apoptosis-related proteins (Bax, Bcl2 and caspase3). The results showed that Bax and cleaved caspase3 protein levels were decreased and Bcl2 level was increased in AN3CA cells with S100A7 overexpression. However, AN3CA cells depleted of S100A7 had higher levels of Bax and cleaved caspase3 as well as a decreased expression of Bcl2 compared to control group (Fig. 3b). These data indicated that silencing S100A7 accelerated EC cells apoptosis *in vitro*.

3.4 Knockdown of S100A7 inhibits migration, invasion and angiogenesis of EC cells

Further, the effects of S100A7 on the migration and invasion of EC cells were tested by transwell assays. As a result, the number of migrated and invasive cells was observably increased in S100A7 overexpression group in comparison to the control group. Whereas, knockdown of S100A7 resulted in fewer migrated and invasive cells compared to the shNC group (Fig. 4a–b). Furthermore, upregulation of S100A7 could dramatically facilitate angiogenesis, while downregulation of S100A7 reduced the number of branches of cells in comparison to the control group (Fig. 4c–d). These results revealed that knockdown of S100A7 could remarkably inhibited the migration, invasion and angiogenesis of EC cells *in vitro*.

3.5 S100A7 is involved in the activation of MAPK signaling pathway

The MAPK pathway consists of ERK, JNK and p38, the activation of which impacts cellular functions [11, 12]. Herein, western blot analysis for MAPK signaling protein expression was conducted to determine whether S100A7 was involved in

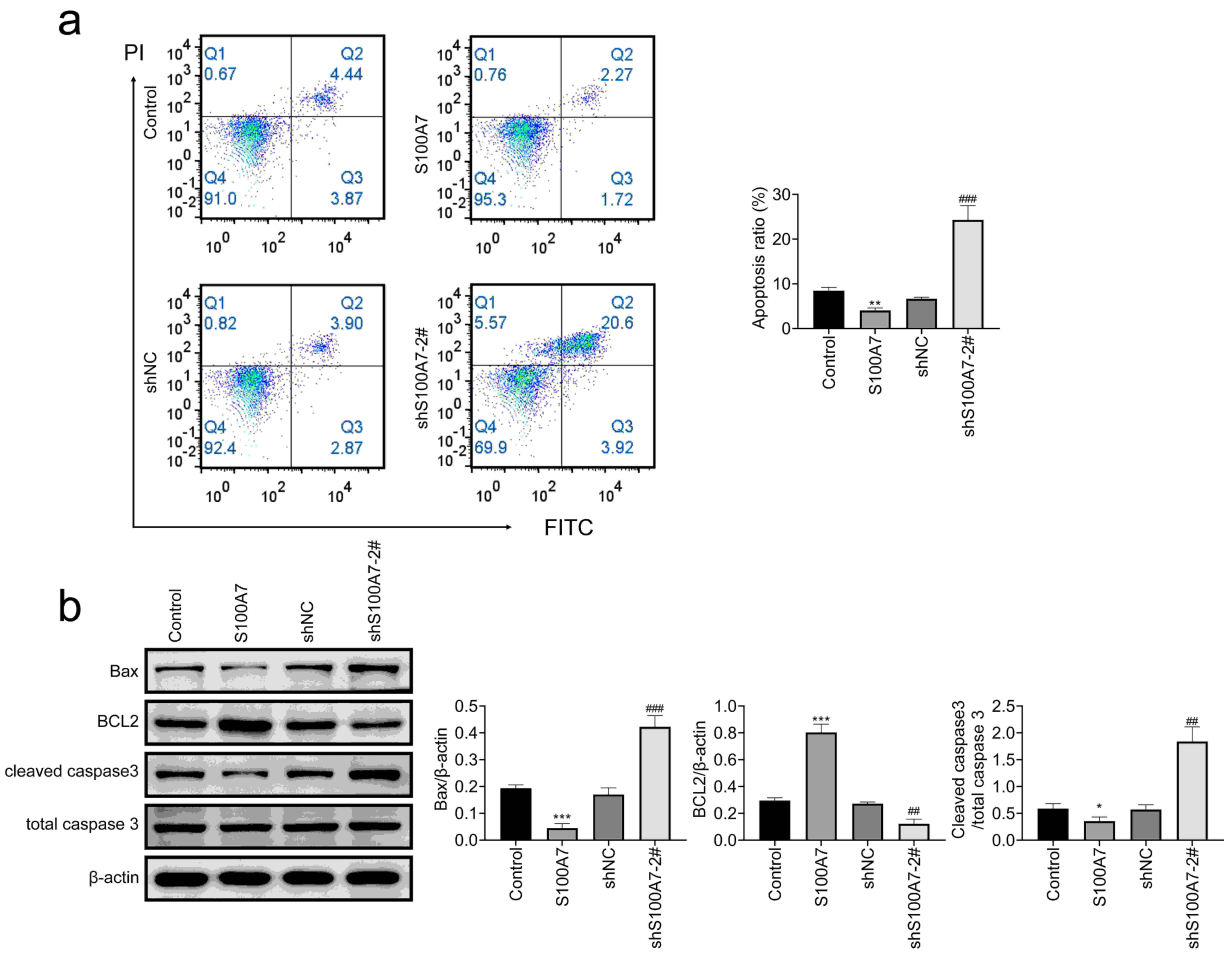

FIGURE 3. The apoptosis rate of EC cells was promoted by knockdown of S100A7. (a) Apoptosis rates were measured by flow cytometry. (b) Western blot analysis for apoptosis-related proteins expression were performed. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, compared with the control group. $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, compared with the shNC group. S100A7: S100 calcium binding protein A7; shNC: short hairpin RNA negative control; FITC: fluoresceine isothiocyanate; PI: propidium iodide; Bax: BCL2-Associated X; BCL2: B-cell lymphoma-2.

activating the MAPK signaling pathway. The results showed that the phosphorylation levels of ERK, JNK and p38 (p-ERK, p-JNK and p-p38) in AN3CA cells were significantly elevated by overexpression of S100A7. Moreover, knockdown of S100A7 obviously reduced p-ERK, p-JNK and p-p38 expression (Fig. 5). These data demonstrated that the expression of S100A7 may affect the phosphorylation of ERK, JNK and p38, and activate MAPK signaling pathway.

4. Discussion

Early invasion, metastasis and recurrence of the tumor introduces huge difficulties for EC treatment [13]. Hance, it is critical to study the regulatory mechanism of EC deterioration to improve clinical outcomes of patients. The S100 proteins are a group of calcium-binding proteins with low molecular weight [14]. Most S100 proteins could bind Ca^{2+} after conformational changes, and the ability to bind to different proteins enables them to exhibit a wide range of intracellular activities, including the regulation of cell cycle cycling, cell growth and migration, and molecular regulation of transcription [15, 16]. In past years, much attention was attracted to the association between S100 and tumors [17]. Studies have shown that some S100 proteins may interact with tumor-related proteins and regulate tumour factors such as p53, nuclear factor-κ-gene binding (NF-κB) and β-catenin, thus contributing to tumor progression [18–20]. Moreover, several members of S100 proteins were found to be novel biomarkers for gynecological [21–23]. Further studies are warranted to unravel the function of S100A7 in EC.

S100A7 is a calcium-binding protein secreted by epithelial cells, and regulates the activities of target protein in a Ca^{2+} dependent manner to bind calcium [24]. Recently, S100A7 was found to be aberrantly expressed in varieties of malignancies, suggesting its crucial regulatory role in tumorigenesis [25]. Muoio *et al.* [26] reported that activation of S100A7 expression may prompt angiogenic of breast cancer. Mishra *et al.* [27] verified that blocking S100A7 signaling contributed to the aggression of breast cancer. Herein, we found that S100A7 was upregulated in EC cells. Functional analysis showed that S100A7 overexpression facilitated proliferation, migration, invasion and angiogenesis of EC cells, as well as inhibited cell apoptosis. Nevertheless, knockdown of S100A7 exerted the opposite effect. These findings suggested a tumor-promoting role for S100A7 in EC. Currently, there are few

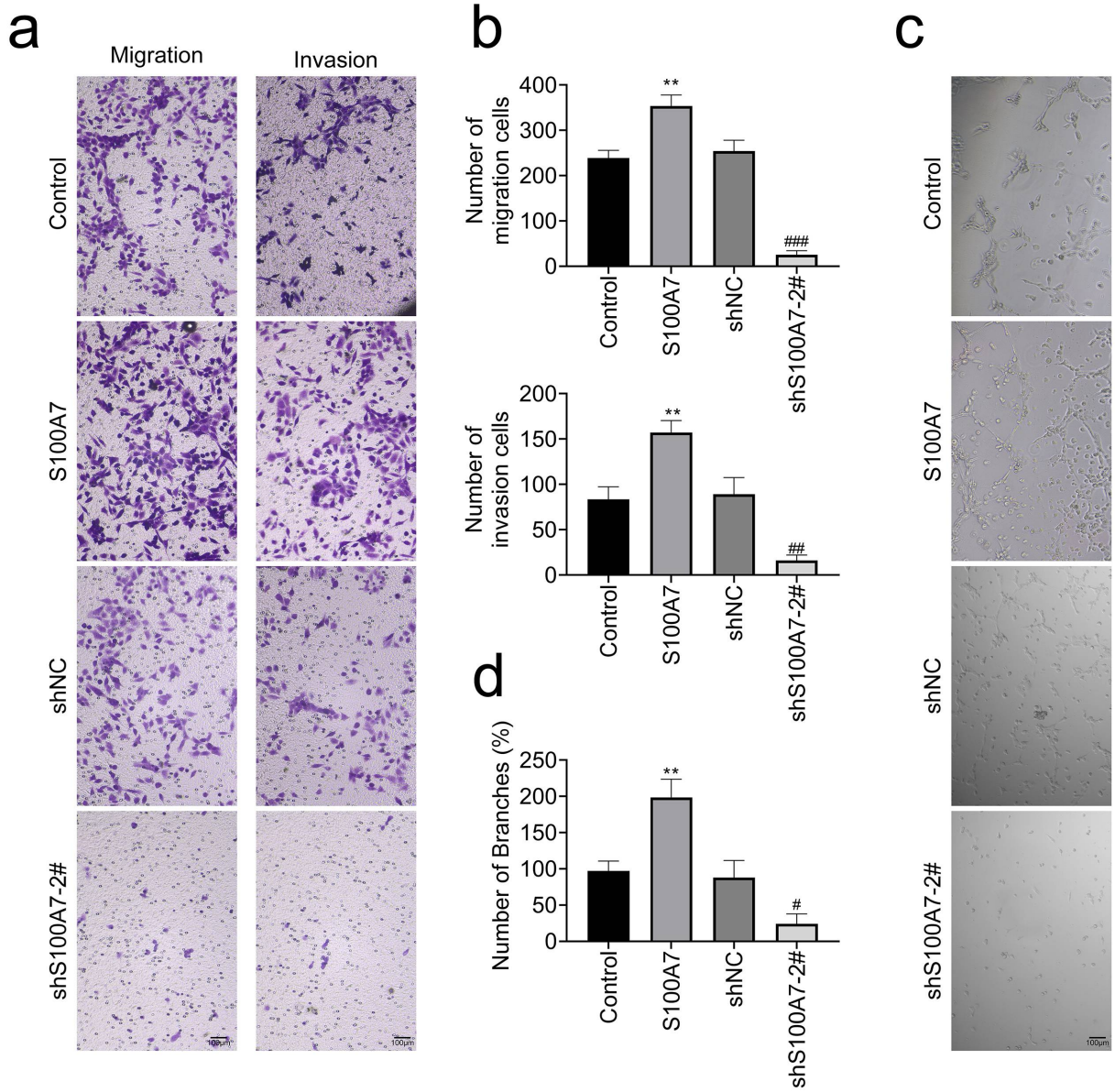

FIGURE 4. Decreased migration, invasion and angiogenesis of EC cells with knockdown of S100A7. (a,b) The cell migration and invasion were determined by transwell assays. (c,d) The tube formation of HUVEC cells was examined. $^{**}p < 0.01$, compared with the control group. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, compared with the shNC group. S100A7: S100 calcium binding protein A7; shNC: short hairpin RNA negative control.

reports on the mechanism of S1007A regulation of tumor [9]. Subsequently, the potential mechanism of S100A7 regulating EC cell behaviors were explored in this study.

Mitogen-activated protein kinase (MAPK) is a family of serine/threonine kinases, which include ERK, JNK and p38 signaling pathways [28]. Different MAPKs are related with specific MAPK kinases (MAPKK) and MAPKK kinase (MAPKKK), forming a conserved cascade of enzymatic reaction [29]. Through this cascade, upstream signals are transduced from MAPK to cytoskeletal proteins, nuclear transcription, and so on, forming a complete MAPK signaling pathway, and finally completing the regulation of cell physiological activities [30, 31]. Previous researches have indicated that the abnormal activation of MAPK pathway often caused rapid cell growth and tumorigenesis [11]. For example, Epithelial membrane protein 1 (EMP1) was reported to facilitate the growth and metastasis of ovarian cancer by activating MAPK pathway [32]. Prostate transmembrane protein androgen-induced 1 (PMEPA1) was found to be upregulated in pancreatic cancer (PC) and played an oncogenic role in PC *via* activating MAPK pathway [33]. The tumor-promoting effect of Kin7 in thyroid cancer was achieved through p38 MAPK pathway activation [34]. In our study, we found that phosphorylation level of ERK, JNK and p38 was elevated by S100A7 overexpression and reduced by S100A7 silence. In EC, studies have demonstrated that the abnormally high expression of MAPK pathway-related proteins was clearly involved in the malignant progression and chemoresistance of EC [35, 36]. Our finding suggested that S100A7 may activate ERK, JNK and p38 MAPK to accelerate EC progression. However, one point we need to point is that the experimental data in this study were derived from *in vitro* cell experiments, and the cellular

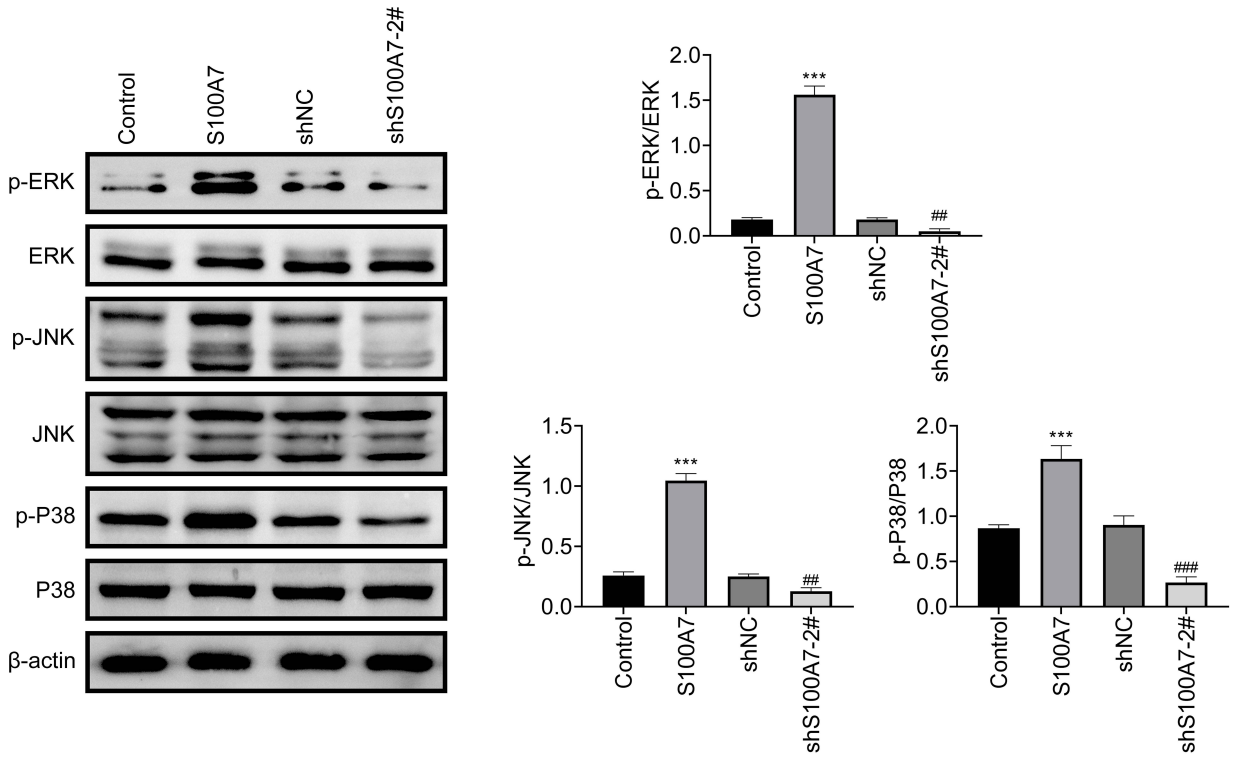

FIGURE 5. Expression of p-ERK, ERK, p-JNK, JNK, p-p38 and p38 were detected by western blot. $^{***}p < 0.001$, compared with the control group. $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, compared with the shNC group. ERK: extracellular regulated protein kinases; p-ERK: phosphorylated ERK; JNK: c-Jun N-terminal kinase; p-JNK: phosphorylated JNK.

environment may be different from *in vivo* tumor environment. Therefore, further *in vivo* experiments are required to verify these effects.

5. Conclusions

In conclusion, our results revealed that S100A7 acted as an oncogene in EC. Mechanically, we speculated that S100A7 mediated cell proliferation, apoptosis, migration, invasion and angiogenesis of EC *via* activating ERK, JNK and p38 MAPK signaling pathway. Our founding demonstrated that there was an important role of S100A7 in the treatment of EC.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

XJS and XZ—designed the study and carried; XJS, XZ, LHY and XYZ—supervised the data collection, analyzed the data, interpreted the data; XJS, XZ and YQF—prepare the manuscript for publication and reviewed the draft of the manuscript. XJS and XZ contributed equally to the work and should be considered co-first authors. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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