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ORIGINAL RESEARCH

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SHCBP1 a potential target in ovarian cancer growth and stemness

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Abstract

Background: Ovarian cancer (OC) is a prevalent form of gynecological malignancy. Abnormal expression of SHC-adaptor protein (SHC) binding and spindle-associated protein 1 (SHCBP1) is reported critical in various cancers, whereas its role in OC is unknown. Here we investigated the function of SHCBP1 in OC. **Methods**: The expression of SHCBP1 in OC and the survival probability of OC patients were analysed using bioinformatics. Cell growth was evaluated by Cell Counting Kit-8 (CCK-8) as well as colony formation. Cell motility was examined using the wound-healing and Transwell assays. The stemness of OC cells stemness was evaluated through sphere formation assay. Key factors associated with the wingless (Wnt)/β-catenin axis were analysed using Immunoblot. The expression of SHCBP1 was elevated in OC, and SHCBP1 was associated with the survival probability of OC patients. **Results**: Silencing SHCBP1 suppressed the proliferation of SKOV3 as well as A2780 cells, as well as their migration and invasion. Additionally, knockdown of SHCBP1 impaired the stemness of OC cells. Furthermore, SHCBP1 knockdown inhibited the Wnt/β-catenin axis in OC cells. Our findings indicate that silencing SHCBP1 repressed the growth, motility, and stemness of OC cells by inhibiting the Wnt/β-catenin axis. **Conclusions**: The abundance of SHCBP1 was enhanced in OC. Silencing SHCBP1 repressed the proliferation, migration, invasion, and stemness of OC cells by inhibiting the Wnt/β-catenin pathway. These results suggest that SHCBP1 may serve as a possible target in OC.

Keywords

SHCBP1; Ovarian cancer; Growth; Stemness; Wnt/β-catenin signaling pathway

1. Introduction

Ovarian cancer (OC) is known as a common gynecological malignancy, has become a global concern [1]. OC originates in the ovarian tissues of women, typically arising from the surface epithelial cells of the ovaries [2]. In its early stages, OC often lacks noticeable symptoms, making early diagnosis challenging. OC is usually detected at an advanced stage, which complicates treatment [3]. Therefore, the search for effective biomarkers for OC is of great significance for the early diagnosis. Although progress has been made in clinical treatment, there is still no effective treatment for OC. Additionally, due to the metastasis of OC cells, the survival is still less than 47% [4, 5]. Therefore, investigating the underlying mechanism of OC metastasis is crucial for the development of effective therapeutic drugs [6].

SHCBP1 is a widely expressed in humans and other mammals, with multiple biological functions and important roles [7]. SHCBP1 contains multiple structural domains, including the Src homology 2 (SH2) domain, which is a common protein structural domain typically involved in protein-protein interactions. The SH2 domain of SHCBP1 allows it to bind with other proteins, participating in cellular signal transduction [8]. SHCBP1 is vital in cell signaling and the maintenance of cell polarity. It has been found to interact with multiple pathways and proteins, including Src family kinases, Cbl proto-oncogene (Cbl) proteins, PI3K (phosphoinositide 3-kinase), and others. These interactions can influence numerous biological processes in cells, such as migration, adhesion, and apoptosis [9]. Aberrant expression or mutations of SHCBP1 have been associated with certain diseases and cancers. For example, some studies have found overexpression of SHCBP1 in certain tumors, which may be related to the growth and spread of tumor cells [10]. Furthermore, SHCBP1 has been associated with the pathogenesis of other diseases, but research is ongoing to gain a deeper understanding of its roles. Abnormal SHCBP1 expression promotes tumor growth suggesting that SHCBP1 may act as an oncogene [7]. Overexpression of SHCBP1 contributes to the progression of prostate cancer [11]. SHCBP1 plays a central role in modulating cervical cancer cell growth and activation of nuclear factor kappa-B (NF-κB) through eukaryotic translation initiation factor 5A (EIF5A) [12]. SHCBP1 activates the Wnt pathway, characterized by promoting cisplatin induced apoptosis resistance and metastasis in lung cancer cells [13]. However, the function of SHCBP1 in OC remains unclear.

Here, we examined the impact of SHCBP1 on OC and analysed its regulatory signaling pathways. Our investigation aims to provide novel strategies for managing OC and identify potential targets.

2. Materials and methods

2.1 Data collection and analysis

The SHCBP1 data of 426 OC tumor samples and 88 normal samples were gained from The Cancer Genome Atlas (TCGA) (https://portal.gdc.cancer.gov). In addition, cross-validation of survival probability-associated biomarkers in OC was performed using the Kaplan-Meier database (http://kmplot.com/analysis) of 1656 OC patients.

2.2 Cell lines and transfection

In this investigation, human OC cell lines (SKOV3 as well as A2780) were obtained from the Chuan Qiu Biotechnology (Shanghai, China) and maintained in dulbecco's modified eagle medium DMEM (11965084, Invitrogen, Carlsbad, CA, USA) with 10% fetal bovine serum (FBS) (A5670701, Invitrogen, Carlsbad, CA, USA), 100 U/mL penicillin (P2132, Solarbio, Beijing, China), and 100 μg/mL streptomycin (S1010, Solarbio, Beijing, China). All cells were grown with 5% carbon dioxide (CO_2) at 37 ℃. The small interference RNA (siRNA) targeting SHCBP1 (si-SHCBP1) and the negative control for siRNA (si-NC) were purchased from Ribobio (Guangzhou, China). The final concentration of siRNA used in the transfection experiments was 50 nM. Cells were transfected using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA), and gene knockdown was confirmed 48 h post-transfection. After transfection, cells were harvested for subsequent for analysis after 48 h.

2.3 CCK-8 assay

OC cell growth was assessed using CCK-8 assay. OC cells (2×10^3 cells/well) were inoculated in 96-well plates. CCK-8 solution (96992, 10 μL/well; Sigma, St. Louis, MO, USA) was added and incubated for 2 h. The absorbance was measured at 450 nm using a micro-plate reader (SpectraMax M5, Molecular Devices, Shanghai, China).

2.4 Colony formation analysis

After various treatments, OC cells were seeded in 6-well plates. After 14 days, SKOV3 and A2780 cells were fixed with paraformaldehyde (PFA) (4%; P1110, Solarbio, Beijing, China), and stained with crystal violet (C0145, 0.5%; Solarbio, Beijing, China). The colonies were observed and photographed.

2.5 Wound-healing assay

Following different treatments, OC cells (2×10^5 cells/well) were inoculated in 6-well plates. The monolayer cells of SKOV3 and A2780 were wounded using a sterile 10-μL pipette tip when they reached 90% confluence. Subsequently, OC cells were maintained in DMEM (Invitrogen) supplemented with 1% FBS (Invitrogen) for 24 h. Then, the wound healing were observed and imaged through a light microscope (IX83, Olympus, Tokyo, Japan).

2.6 Transwell assay

Following various treatments, OC cells were collected for performing a Transwell assay to assess cell invasion. Transwell chamber (Invitrogen) was per-coated with Matrigel (Invitrogen). SKOV3 or A2780 cells (1×10^5) in DMEM (Invitrogen) were inoculated in the higher chamber, whereas DMEM (Invitrogen) comprising 10% FBS (Invitrogen) was supplemented to the lower chamber. After 24 h, the cells in the bottom chamber were fixed with 70% ethanol (E0100, Solarbio, Beijing, China) for 10 min and stained with to 0.1% crystal violet (C0145, 0.5%; Solarbio, Beijing, China) for 15 min. The invasive cells were observed.

2.7 Sphere formation assay

The stemness of SKOV3 and A2780 cells was determined using a sphere formation assay, as described previously [14]. In brief, SKOV3 and A2780 cells were resuspended in DMEM/F12 medium (1:1; Invitrogen) which was supplemented with 1% FBS (Invitrogen), 1% penicillin/streptomycin (P1400, Solarbio, Beijing, China), recombinant fibroblast growth factor (10 ng/mL; Invitrogen), and recombinant epidermal growth factor (20 ng/mL; Invitrogen). All cells were cultured in 6-well ultra-low attachment plates (Invitrogen). After 14 d, the formed spheres were assessed using a light microscope (IX83, Olympus, Tokyo, Japan).

2.8 Western blot

The proteins were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to a polyvinylidene fluoride (PVDF) membrane (Invitrogen). After blocking, the PVDF membrane was incubated with the primary antibodies: anti-β-catenin (ab32572; 1:1000; Abcam, Cambridge, MA, USA), anti-c-myc (ab32072; 1:1000; Abcam, Cambridge, MA, USA), anti-Matrix Metalloproteinase-7 (MMP-7) (ab207299; 1:1000; Abcam, Cambridge, MA, USA), and anti-β-actin (ab8226; 1:1000; Abcam, Cambridge, MA, USA) at 4 °C overnight. Subsequently, the membrane was incubated with secondary antibody (ab205718; 1:2500; Abcam, Cambridge, MA, USA) for 1 h. Afterward, an enhanced chemiluminescence (ECL) kit (E4100, Solarbio, Beijing, China) was used to visualize the protein blots.

2.9 Statistical assay

Data were analyzed utilizing GraphPad Prism 7 (GraphPad Inc., La Jolla, CA, USA), and values were exhibited as mean $\pm$ standard deviation (SD). Each experiment was performed in triplicate. Clinical factors linked with survival probability in OC sufferers were determined utilizing Cox regression and the Kaplan-Meier. Student's *t*-test or analysis of variance (ANOVA) was conducted for paired or multiple comparison. $p < 0.05$ was considered significant.

3. Results

3.1 SHCBP1 was highly expressed in OC

First, we analyzed the expression level of SHCBP1 in OC. According to the data of TCGA, the expression of SHCBP1 was significantly upregulated in OC tumor samples (Fig. 1A). Additionally, we observed that the high expression of SHCBP1 was associated with a poor survival probability (p = 0.00025; hazard ratio (HR) = 1.29; 95% Confidence Interval (CI): 1.13–1.48) in OC patients (Fig. 1B). As a result, we confirmed that SHCBP1 expression is elevated in OC and its high expression is correlated with reduced survival probability in OC patients.

3.2 Silencing SHCBP1 suppressed the proliferation of OC cells

Next, we investigated the effect of SHCBP1 on OC cells proliferation. We detected that the cell viability (Fig. 2A) and colony formation (Fig. 2B) were significantly reduced following SHCBP1 knockdown in both SKOV3 and A2780 cells. Therefore SHCBP1 depletion suppresses the proliferation of OC cells.

3.3 Silencing SHCBP1 suppressed the motility of OC cells

Here, we examined the impact of SHCBP1 on OC cells metastasis. Our findings revealed that both cell migration (Fig. 3A) and invasion (Fig. 3B) were significantly reduced in SKOV3 and A2780 cells after transfection with si-SHCBP1. Therefore silencing SHCBP1 inhibited the metastasis of OC cells.

3.4 Silencing SHCBP1 repressed OC cells stemness

We then evaluated the role of SHCBP1 in regulating the stemness of OC cells. Sphere formation assay demonstrated that the number of spheres formed by SKOV3 and A2780 cells was significantly lessened upon downregulation of SHCBP1 (Fig. 4). These findings confirmed that silencing SHCBP1 repressed OC cells stemness.

3.5 Knockdown of SHCBP1 inhibited the Wnt/β-catenin axis in OC cells

Finally, we examined the related molecular mechanism by which SHCBP1 regulates OC cells. The expression of β-catenin (Fig. 5A), c-myc, and MMP-7 (Fig. 5B) in SKOV3 as well as A2780 cells were reduced after si-SHCBP1 transfection. Thus, we hypothesized that knockdown of SHCBP1 inhibited the Wnt/β-catenin axis in OC cells.

4. Discussion

In this study, we revealed that SHCBP1 expression was elevated in OC, and SHCBP1 was associated with survival probability of OC patients. We observed that silencing SHCBP1 suppressed the proliferation of SKOV3 as well as A2780 cells. Moreover, silencing SHCBP1 reduced the motility of OC cells. In addition, we found that silencing SHCBP1 repressed OC cells stemness. Knockdown of SHCBP1 repressed the Wnt/β-catenin pathway in OC cells. In summary, our findings confirmed that silencing SHCBP1 suppressed the growth, motility and stemness of OC cells by inhibiting the Wnt/β-catenin pathway.

The exact causes of OC are not fully understood, but several risk factors have been identified, including genetic factors (a family history of the disease), age (risk increases with age), nulliparity, early menarche and late menopause, among others [4, 15]. Early symptoms of OC are often difficult to detect, but in advanced stages, they may include abdominal bloating, abdominal masses, digestive problems, frequent urination, constipation, irregular menstrual cycles, weight loss, and fatigue [16]. Diagnosis of OC typically involves various tests, including physical examination, ultrasound imaging, computed tomography (CT) scans, and blood marker tests. A definitive diagnosis often requires surgical removal of tissue for pathological examination [17]. Treatment for OC usually includes surgery, followed by chemotherapy or radiation therapy [18–20]. The prognosis for OC depends on early detection and treatment of the disease. Because it is often detected at an advanced stage, the prognosis is generally poor. However, if diagnosed and treated in the early stages, the prognosis can be more favorable [21]. Early diagnosis and treatment of OC are crucial for improving patient survival rates [22]. In this study, we analyzed the functions of SHCBP1 in OC.

The function of SHCBP1 is closely related to cell biology and developmental processes [23]. Its abnormal expression or mutations are associated with certain illnesses, like cancer, as it regulates cell growth, proliferation, and survival [10]. Wang *et al*. [23] reported that SHCBP1 expression is elevated in most types of cancer, such as lung adenocarcinoma and hepatocellular carcinoma. Additionally, SHCBP1 was identified by survival analysis as a possible diagnostic biomarker [24]. Dong *et al*. [25] demonstrated that the expression of SHCBP1 was high in gastric cancer. SHCBP1 could promote tumor growth and invasiveness in GC and may act as a novel target in GC. In this study, we found that the levels of SHCBP1 was increased in OC, and SHCBP1 was linked with survival probability of OC patients. In line with these findings, Wang *et al*. [23] and Dong *et al*. [25], our results indicate that SHCBP1 is a potential therapeutic target in OC. Moreover, Ren *et al*. [26] discovered that the SHCBP1 was overexpressed in esophageal cancer tissues. Knockdown of SHCBP1 inhibited the growth and motility of esophageal squamous cell carcinoma cells. Scientists have focused their research on SHCBP1's role in cell signaling, cell division, and its associations with health and disease [9]. In this study, we first observed that silencing SHCBP1 repressed the proliferation, migration, invasion, and stemness of SKOV3 and A2780 cells, which were comparable with the outcomes of Ren *et al*. [26]. This research helps deepen our understanding of cell biology and molecular medicine, potentially providing insights for future therapeutic approaches.

The Wnt/β-catenin axis is a highly conserved and crucial cellular signaling pathway that plays a fundamental role in numerous biological processes, including tissue regeneration and maintenance of adult tissue homeostasis. Dysregulation of this pathway has been implicated in numerous diseases, including cancer [27–29]. The pathway is initiated by a family

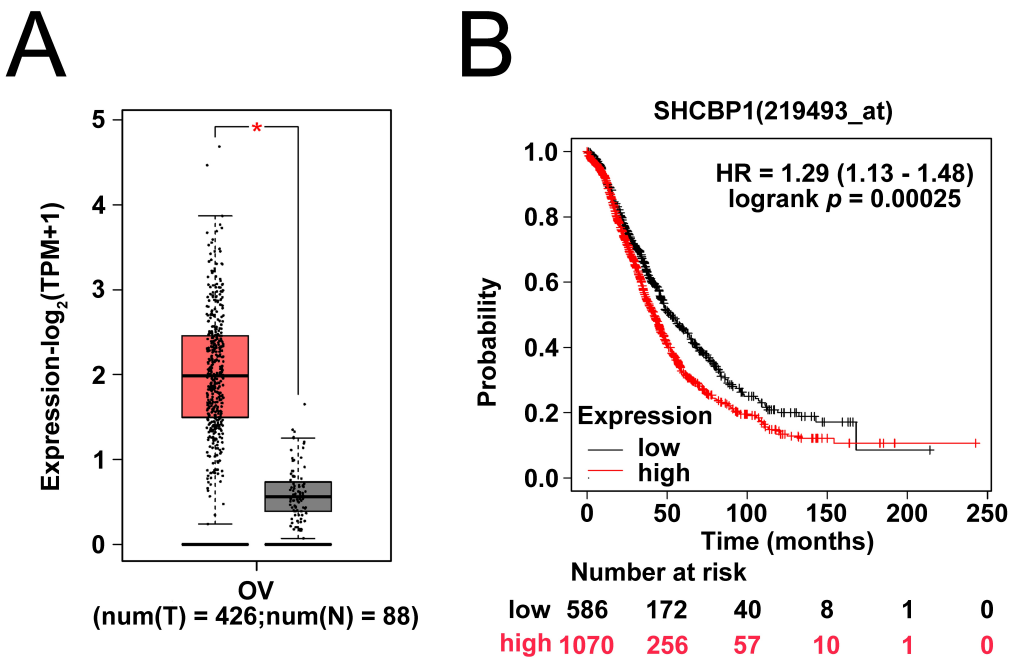

FIGURE 1. SHCBP1 was highly expressed in OC. (A) The transcripts per million (TPM) value of SHCBP1 in OC tissues and normal tissues. (B) The survival probability of OC patients with low or high level of SHCBP1. *$p < 0.05$. OV: Ovarian Cancer; SHCBP1: SHC-adaptor protein (SHC) binding and spindle-associated protein 1; TPM: transcripts per million; HR: hazard ratio.

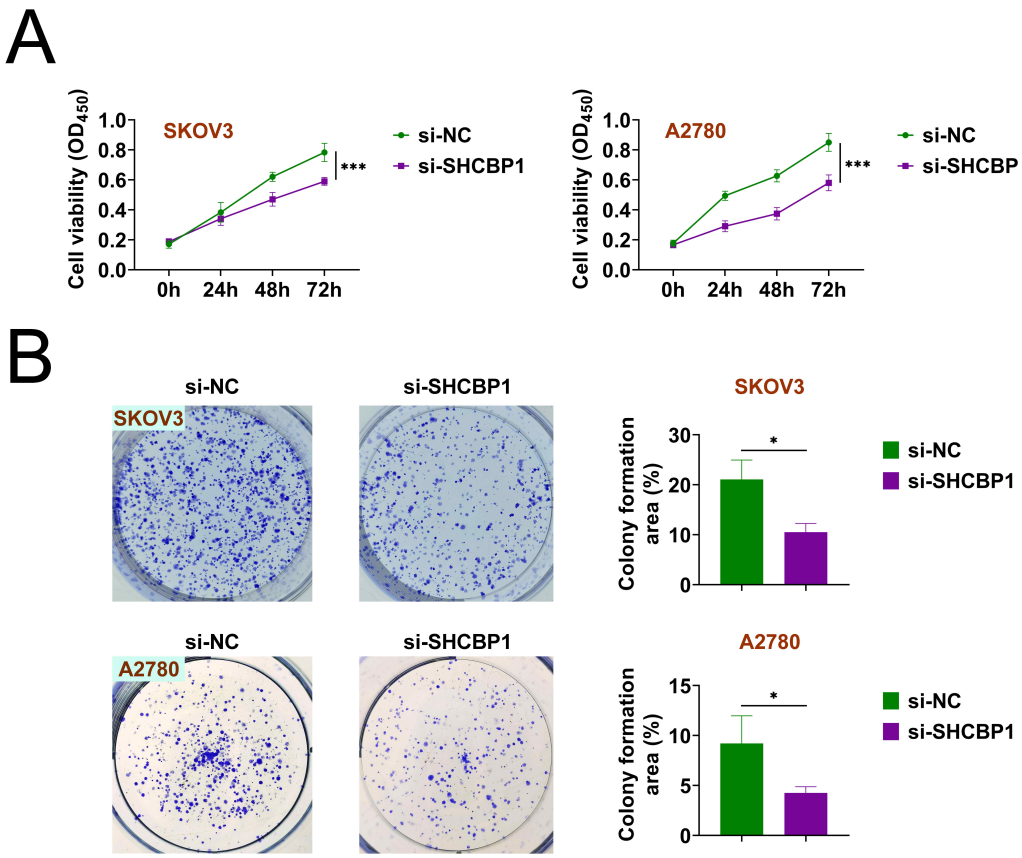

FIGURE 2. Silencing SHCBP1 suppressed the proliferation of OC cells. (A) The cell viability was estimated by CCK-8 assay in SKOV3 as well as A2780 cells upon the indicated transfection. OD_{450} value was measured. (B) The cell proliferation degree in SKOV3 as well as A2780 cells upon the indicated transfection was assessed by calculating colony numbers. *$p < 0.05$, ***$p < 0.001$. si-NC: small interfering RNA control; OD_{450}: Optical Density at 450 nm; SHCBP1: SHC-adaptor protein (SHC) binding and spindle-associated protein 1.

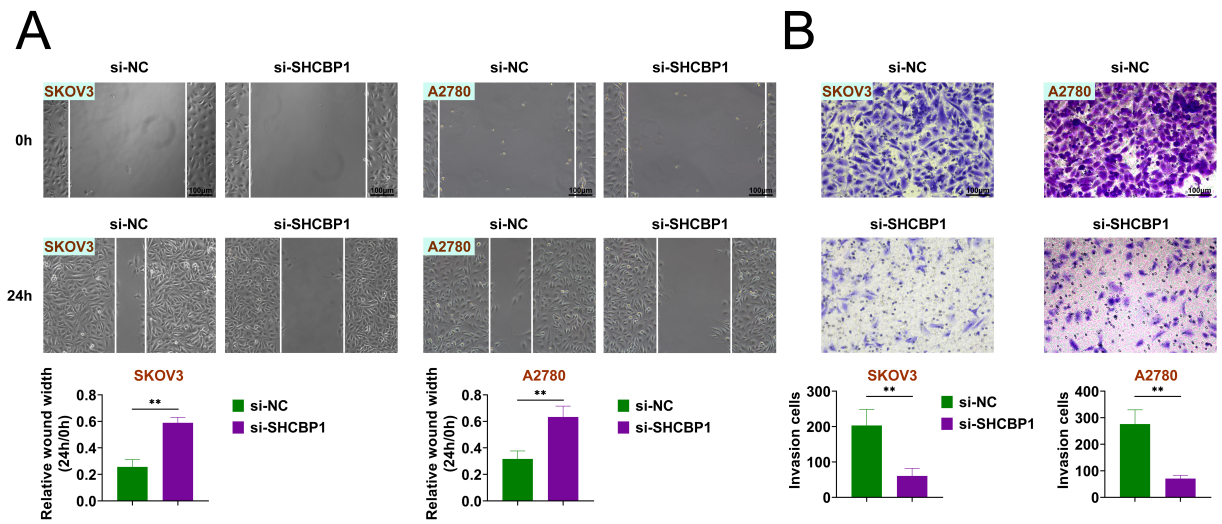

FIGURE 3. Silencing SHCBP1 reduced the migration and invasion of OC cells. (A) The cell migration of SKOV3 as well as A2780 cells upon the indicated transfection was examined by wound-healing assay. Wound width was measured. (B) The cell invasion was inspected by transwell assay. The invasive cell numbers were counted per field. $^{**}p < 0.01$. si-NC: small interfering RNA control; SHCBP1: SHC-adaptor protein (SHC) binding and spindle-associated protein 1.

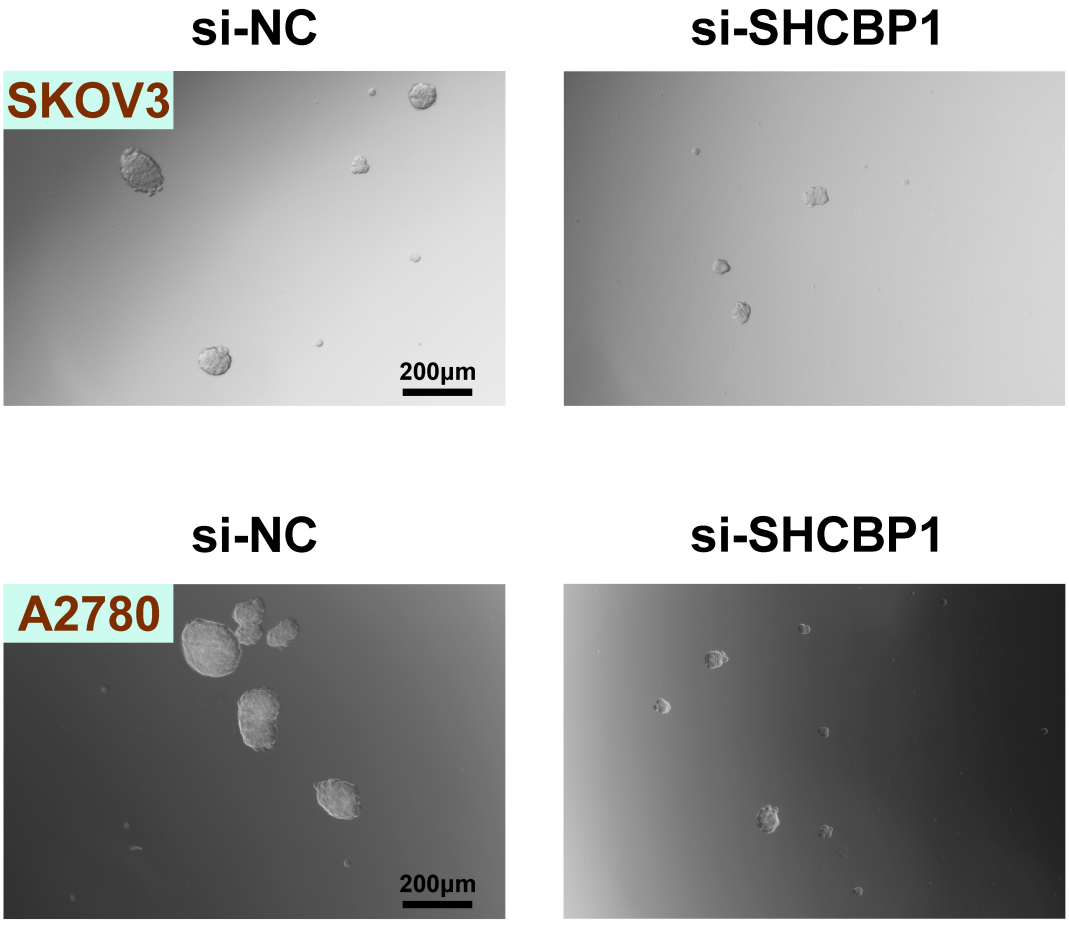

FIGURE 4. Silencing SHCBP1 repressed OC cells stemness. The stemness of SKOV3 as well as A2780 cells upon the indicated transfection was assessed by sphere formation assay. si-NC: small interfering RNA control; SHCBP1: SHC-adaptor protein (SHC) binding and spindle-associated protein 1.

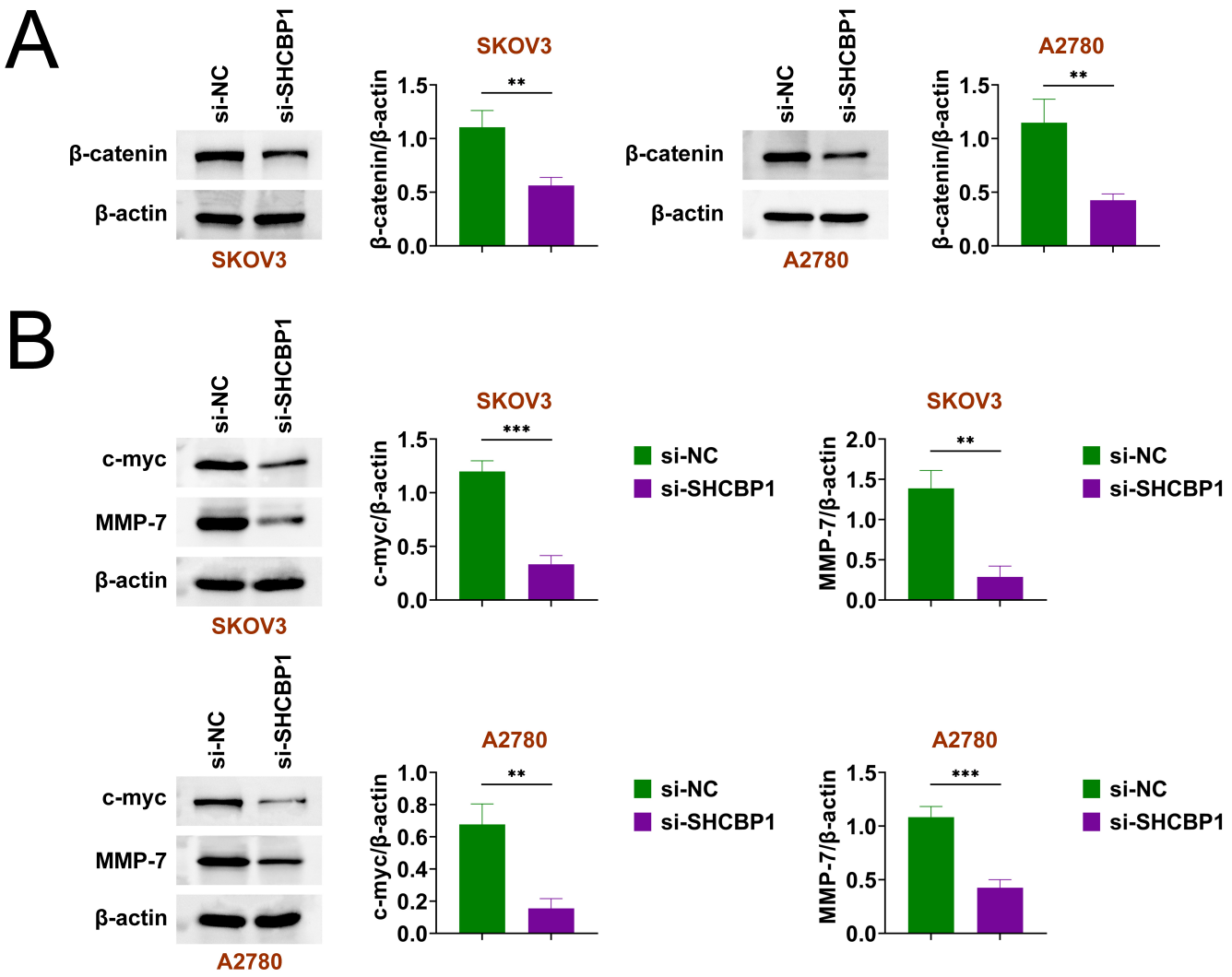

FIGURE 5. Knockdown of SHCBP1 inhibited the Wnt/β-catenin pathway in OC cells. (A) The contents of β-catenin, c-myc, and MMP-7 in SKOV3 as well as A2780 cells upon the indicated transfection were analyzed by Immunoblot. (B) The contents of c-myc, and MMP-7 in SKOV3 as well as A2780 cells upon the indicated transfection were analyzed by Immunoblot. $^{**}p < 0.01$, $^{***}p < 0.001$. si-NC: small interfering RNA control; SHCBP1: SHC-adaptor protein (SHC) binding and spindle-associated protein 1; MMP-7: Matrix Metalloproteinase-7.

of secreted signaling proteins called Wnts. Wnt proteins act as ligands and bind to cell surface receptors to initiate the signaling cascade. In the absence of Wnt binding, a protein complex known as the "destruction complex" is active [30]. Activation of the Wnt/β-catenin axis leads to various cellular responses, such as the regulation of stem cell maintenance, tissue development, and cell differentiation. In the context of cancer, aberrant activation of this pathway can promote uncontrolled cell growth and tumor formation. Mutations or dysregulation of components within the Wnt/β-catenin axis are associated with several diseases, including colorectal cancer, hepatocellular carcinoma, and developmental disorders like familial adenomatous polyposis [31]. In addition, a growing number of studies report that continuous activation of typical Wnt/β-catenin axis is critical for maintaining cancer stem cell signatures in lots of cancer [32, 33]. Similarly, it has been reported that cancer stem cell in OC requires Wnt/β-catenin axis [34]. Zou *et al.* [13] observed that SHCBP1 could promote cisplatin induced migration and invasion in lung cancer cells via activating Wnt pathway. Besides, Sun *et al.* [35] indicated that SHCBP1 could positively modulate Wnt/β-catenin signalling in head and neck cancer. In this research, we confirmed for the first time that the knockdown of SHCBP1 inhibited the Wnt/β-catenin pathway in OC cells, which were equal with the upshots of Sun *et al.* [35]. However, there are limitations to this research. We only studied the biological function and molecular mechanism of SHCBP1 at the cellular level. In future studies, we will further carry out animal and clinical experiments to further verify the conclusions of this research.

5. Conclusions

In conclusion, the results of this study confirmed that silencing SHCBP1 inhibits the growth, motility and stemness of OC cells by blocking the Wnt/β-catenin axis. These findings suggest that knockdown of SHCBP1 could potentially impede the progression of OC and SHCBP1 may serve as a potential

target in OC. The conclusion of this research provides a novel insights into the development of targeted molecular therapies for OC.

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

DDL—designed the study and carried them out. DDL, LPW—supervised the data collection, analyzed the data, interpreted the data, prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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