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ORIGINAL RESEARCH

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CENPU affects the paclitaxel resistance of cervical cancer cells by regulating the FOXM1/ABCC5 pathway

Xia Zhang[1,*], Yuanyi Zhang[1], Min Wang[1]

[1]Department of Pathology, Zhaoqing Medical College, 526020 Zhaoqing, Guangdong, China

***Correspondence**
Zhangxia_668@163.com
(Xia Zhang)

Abstract

In cervical cancer (CC), the efficacy of chemotherapy is often hindered by the development of paclitaxel (PTX) resistance, even in patients who initially responded to chemotherapy. However, the mechanisms underlying PTX resistance in CC patients remain unclear. In this study, we uncover a unique role played by CENPU (centromeric protein U, also known as PBIP1/KLIP1/CENP-50/MLF1IP) in association with paclitaxel resistance in CC cells. First, we established paclitaxel-resistant cell lines from Hela and SiHa cells (designated as Hela/PTX and SiHa/PTX) and confirmed their resistance by determining the half-maximal inhibitory concentration (IC_{50}) values and assessing cell viability. The results demonstrated that Hela/PTX and SiHa/PTX cells exhibited an elevated IC_{50} and enhanced cell proliferation, accompanied by a decrease in apoptosis. Subsequently, si-CENPU was used to silence CENPU in Hela/PTX and SiHa/PTX cells, which led to a reduction in cell viability and an increase in cell apoptosis, indicating that the silencing of CENPU mitigated paclitaxel resistance in Hela/PTX and SiHa/PTX cells. Furthermore, CENPU knockdown suppressed Forkhead box M1 (FOXM1) and Adenosine Triphosphate (ATP) binding cassette subfamily C member 5 (ABCC5) expression in Hela/PTX and SiHa/PTX cells. Interestingly, the alleviating effects of CENPU silencing on paclitaxel resistance in CC cells were compromised when FOXM1 levels were supplemented, indicating that CENPU knockdown could attenuate PTX resistance by downregulating the FOXM1/ABCC5 signaling pathway. In conclusion, our study reveals an elevated expression of CENPU in paclitaxel-resistant CC (Hela/PTX and SiHa/PTX) and demonstrates that the knockdown of CENPU can mitigate paclitaxel resistance in CC cells by deregulating the FOXM1/ABCC5 signaling pathway.

Keywords

Paclitaxel resistance; Cervical cancer; CENPU; FOXM1; ABCC5

1. Introduction

Cervical cancer (CC) is a significant global health concern, ranking fourth in terms of cancer-related female mortality rates worldwide, with its incidence steadily rising, particularly in developing countries [1]. The management of CC relies heavily on tumor staging, with various treatment approaches employed at different clinical stages, including combination chemotherapy, second-line chemotherapy, neoadjuvant chemotherapy and concurrent chemoradiotherapy [2–4]. Paclitaxel (PTX), an anticancer drug, is commonly used in these treatments; however, its effectiveness is often hampered by the development of PTX resistance [5]. Therefore, it is important to uncover the molecular mechanisms underlying PTX resistance in CC cells to improve the prognosis of CC patients [6].

FOXM1 is known to be upregulated in multiple cancer types, and accumulating evidence suggests its active role in driving tumor progression. Notably, its expression has been shown to be closely associated with ATP-binding cassette (ABC) transporters [7, 8]. Elevated levels of ABC transporters at the cell membrane result in increased efflux of drugs and decreased drug influx [9]. Among these transporters, ATP-binding cassette subfamily C member 5 (ABCC5) belongs to the multidrug resistance protein (MRP) family, which is a highly specialized group of drug transporters situated in the C branch of the ABC transporter superfamily [10]. These transporters function as efflux pumps, facilitating the transport of various molecules out of the cell membrane. Excessive efflux of anticancer drugs, in particular, leads to the development of drug resistance [10]. FOXM1 plays a pivotal role in promoting paclitaxel resistance in CC by increasing the expression of ABCC5 [9].

CENPU (centromere protein U), also known as PBIP1/KLIP1/CENP-50/MLF1IP, encodes a 47 kDa protein. Growing evidence suggests that dysregulation of CENPU is observed in various cancer types, including ovarian [11],

breast [12], non-small-cell lung cancer [13], and hepatocellular cancers [14], suggesting its potential significance in tumor progression and development. Our prior research has previously shown that CENPU knockdown can inhibit CC migration and stemness through the FOXM1/Wnt/β-actin pathway [15]. However, the precise role of CENPU in CC resistance remains unclear. Therefore, we aimed to investigate the role of CENPU in association with paclitaxel resistance in CC cells.

In this study, we uncovered that the knockdown of CENPU can effectively restrain the proliferation and induce apoptosis in paclitaxel-resistant cells. Additionally, our findings indicate that silencing CENPU mitigates paclitaxel resistance in CC cells by disrupting the FOXM1/ABCC5 signaling pathway.

2. Methods

2.1 Cell culture

The human CC cell lines HeLa (CRM-CCL-2) and SiHa (HTB-35) were purchased from the American Type Culture Collection (ATCC). They were cultured in a 5% CO_2 environment using DMEM (Dulbecco's Modified Eagle Medium) (catalog number 12800017, Gibco, Waltham, MA, USA), supplemented with 10% fetal bovine serum (catalog number 10099-141, Gibco, Waltham, MA, USA).

2.2 Paclitaxel resistance mold

Parental HeLa and SiHa cells were subjected to a dose escalation of paclitaxel (range: 1 to 20 nM) until surviving cells had fully recovered and exhibited a normal exponential growth rate. Subsequently, the surviving cells were collected and cultured in a medium devoid of paclitaxel. After seven months, both HeLa and SiHa cells were found to have developed stable resistance to paclitaxel at a concentration of 5 nM. These resistant cells were further propagated in a paclitaxel-free medium for a minimum of an additional two months.

2.3 The suppression of CENPU

The CENPU gene was silenced using an siRNA transfection kit (SR312518, OriGene, Beijing, China) along with specific siRNA sequences: si-CENPU (Forward: 5′-CCACCUAGAGCAUCAACAATT-3′; Reverse: 5′-UUGUUGAUGCUCUAGGUGGGT-3′) and a non-targeting siRNA control (si-negative control (NC), Forward: 5′-UUCUCCGAACGUGUCACGUTT-3′; Reverse: 5′-ACGUGACACGUUCGGAGAATT-3′). Hela and SiHa cells (1×10^4/well in 6-well plates) were transfected with the siRNAs by adding 10 μL of Lipofectamine RNAiMAX complex (Invitrogen, Carlsbad, CA, USA) with siRNA (35 pmol) to the culture mix for 6 hours. Subsequently, this was replaced with a normal culture medium for a further 24 hours. The Lipofectamine RNAiMAX and siRNA were used at a ratio of 1.5 μL:5 pmol per well.

2.4 Cell counting kit-8 (CCK8) assay

Hela and SiHa cells were seeded at a density of 1×10^4 cells per well in 96-well plates. Following a 24-hour incubation period, 10 μL of CCK8 solution was added to each well and incubated for 4 hours before measuring the optical density (OD) at 450 nm. The IC_{50} values were determined using concentration-effect relationships with GraphPad Prism software (version 8.0.2, GraphPad Software, San Diego, CA, USA). To calculate the resistance index (RI), the formula RI = IC_{50} of drug-resistant cells/IC_{50} of parental cells was applied.

2.5 Colony formation assay

Hela and SiHa cells were plated at a density of 2×10^5 cells per well in DMEM supplemented with 10% Fetal Bovine Serum (FBS). Fresh media and medication were replenished every three days, and cell colonization was allowed to proceed for two weeks. Subsequently, the cells were stained using a 1% crystal violet solution (C0121, Beyotime, Shanghai, China), followed by rinsing with Phosphate-Buffered Saline (PBS) (Gibco, 11965092, Waltham, MA, USA) and fixation using 4% paraformaldehyde (P0099, Beyotime, Shanghai, China) at 37 °C for 15–20 minutes to visualize the colonies. Finally, data analysis and image acquisition were performed using the ImageJ software program (version 1.54, CK software, Bethesda, MD, USA).

2.6 Flow cytometry

For the quantification of apoptotic cells, the Apoptosis Detection Kit (eBioscience, 88-8005-72, Waltham, MA, USA) was used. Hela and SiHa cells were seeded at a density of 3×10^5 cells per well in 6-well plates and allowed to culture for 24 hours. Subsequently, the cells were washed with PBS and supplemented with Annexin V-FITC (ab14085, Abcam, Cambridge, UK) for a 15-minute incubation period. Following this step, the cells were resuspended in a binding buffer and assessed using a FACS-Calibur flow cytometer (Batch No. 58816, BD biosciences, Franklin Lakes, NJ, USA) after the addition of propidium iodide (PI) in suspension.

2.7 Western blot

Cell lysis was performed using the RIPA buffer (P0013B, Beyotime, Shanghai, China), followed by centrifugation to eliminate protein debris. Protein concentration was quantified using the bicinchoninic acid kit (ab102536, Abcam, Cambridge, MA, USA). Equal amounts of proteins were separated by electrophoresis, following which the proteins were transferred onto polyvinylidene fluoride (PVDF) membranes and blocked with 5% non-fat dry milk for 1 hour at room temperature. After washing with Tris Buffered Saline with Tween (TBST) (#9997, Cell Signaling, Danvers, MA, USA), the membranes were incubated overnight at 4 °C with the respective primary antibodies, treated with secondary antibodies at 37 °C for 1 hour and protein bands were visualized using the Enhanced Chemiluminescence (ECL) detection technique (GE Healthcare, Piscataway, NJ, USA). Specific primary antibodies from Abcam were utilized, including CENPU (#ab259855, 1:1000), FOXM1 (#ab207298, 1:1000), ABCC5 (#ab197406, 1:1000), and β-actin (#ab8226, 1:1000). Peroxidase-conjugated secondary antibodies, anti-mouse (#4410, 1:10,000) and anti-rabbit (#4414, 1:10,000), were purchased from Cell Signaling

Technologies.

2.8 Statistical analysis

Data analysis was conducted using SPSS 22.0 (IBM, Armonk, NY, USA). Significance among groups was assessed using the Student *t*-test and analysis of variance (ANOVA) analysis. The results from three experiments are presented as means and standard deviations (SD). A *p*-value of less than 0.05 was considered statistically significant.

3. Results

3.1 CENPU expression is upregulated in CC-resistant cells

It is well-documented that cancer drugs often lead to the development of chemoresistance in cancer cells. In this study, our objective was to identify a novel target for anticancer therapy that could regulate paclitaxel-resistant CC cells. Initially, we established paclitaxel-resistant HeLa and SiHa cells through a gradual exposure to increasing paclitaxel concentrations over several months, which resulted in a significant increase in the IC_{50} values for paclitaxel and a significant enhancement in the viability of CC cells, as demonstrated by CCK8 assays (Fig. 1A). Furthermore, we observed an elevation in cell numbers and a decrease in apoptosis rates in paclitaxel-resistant HeLa (HeLa/PTX) and SiHa (SiHa/PTX) cells, as shown by the colony formation assays (Fig. 1B) and flow cytometry analysis (Fig. 1C), respectively. Additionally, our western blot analysis revealed an upregulation of CENPU expression in HeLa/PTX and SiHa/PTX cells compared to their non-resistant counterparts (Fig. 1D). Collectively, these findings demonstrate that CENPU expression is heightened in paclitaxel-resistant CC cells.

3.2 Knockdown of CENPU attenuates paclitaxel resistance in CC cells

To investigate the potential impact of CENPU on paclitaxel-resistant CC cells, we used siRNA (si-CENPU) to silence CENPU expression in Hela/PTX and SiHa/PTX cells. Western blot analysis confirmed the successful reduction in CENPU levels in si-CENPU-treated cells (Fig. 2A). Notably, the IC_{50} values for paclitaxel were reduced in si-CENPU-treated cells (Fig. 2B). Colony formation assays demonstrated that si-CENPU treatment led to a decrease in cell proliferation (Fig. 2C), and flow cytometry analysis revealed an increase in apoptosis among si-CENPU-treated cells (Fig. 2D), further supported by the western blot data indicating an elevated expression of the apoptotic marker, Bax (Fig. 2E). These findings demonstrate that si-CENPU could effectively mitigate the degree of paclitaxel resistance in CC cells.

3.3 CENPU regulates FOXM1/ABCC5 axis

The FOXM1/ABCC5 axis has previously been implicated in various aspects of tumorigenesis [7, 16, 17]. In this study, we investigated the impact of CENPU on the FOXM1/ABCC5 pathway. Western blot assays were conducted to evaluate the protein levels of FOXM1, ABCC5 and β-actin in cells subjected to si-CENPU, si-NC or control treatments, and the results revealed a significant reduction in FOXM1 and ABCC5 expression upon CENPU knockdown (Fig. 3), indicating that the silencing of CENPU could effectively restrain the activation of the FOXM1/ABCC5 axis.

3.4 CENPU affects paclitaxel resistance in CC cells by regulating FOXM1

To confirm whether the attenuation of paclitaxel resistance in CC cells by CENPU silencing is indeed mediated through the control of the FOXM1/ABCC5 axis, we artificially increased the expression of FOXM1 in si-CENPU-treated cells. The results indicated that compared to si-CENPU cells, the IC_{50} values (Fig. 4A) were significantly elevated, while the apoptosis rate (Fig. 4B) was reduced in the si-CENPU + FOXM1 group. Overall, these results suggest that the knockdown of CENPU may alleviate paclitaxel resistance in cells by modulating FOXM1.

4. Discussion

Cancer cells often develop resistance to anticancer drugs due to alterations in the expression levels of their target proteins following prolonged treatment. Herein, we revealed that CENPU knockdown could effectively inhibit cell proliferation, suggesting a potential therapeutic strategy for CC, particularly in patients with paclitaxel-resistant CC.

The initial phase of our study involved the establishment of paclitaxel-resistant CC cell lines in HeLa and SiHa cells (HeLa/PTX and SiHa/PTX). Subsequent western blot analysis confirmed the upregulated expression of CENPU in these resistant cells. High CENPU expression has been observed in various cancer types, including CC [18], hepatocellular carcinoma [19], and gastric cancer [20], suggesting a potential role in driving tumorigenesis. Additionally, previous research has linked CENPU to cell proliferation, migration and apoptosis [18–20]. Consistent with these findings, in our present study, we conducted CCK8, colony formation and flow cytometry assays, which collectively demonstrated enhanced cell growth and reduced cell apoptosis in HeLa/PTX and SiHa/PTX cells with elevated CENPU levels, thereby suggesting that paclitaxel-resistant CC cells exhibit increased tumor cell viability, a characteristic potentially associated with CENPU levels. To further investigate the role of CENPU in paclitaxel-resistant cells, we used si-CENPU to silence CENPU expression, and the results indicated that the silencing of CENPU led to a significant decrease in cell proliferation and an increase in cell apoptosis in HeLa/PTX and SiHa/PTX cells; providing strong evidence that si-CENPU may effectively mitigate the degree of paclitaxel resistance in CC cells.

Numerous studies have highlighted the pivotal role of the FOXM1/ABCC5 axis in multiple types of cancer [7, 16, 17]. Furthermore, ABCC5, functioning as a drug efflux pump, has been implicated in drug resistance across various cancer types [10]. Herein, we aimed to elucidate the impact of CENPU on the FOXM1/ABCC5 pathway and uncover the specific mechanisms involved. Western blot analysis was conducted to assess the expression levels of FOXM1 and

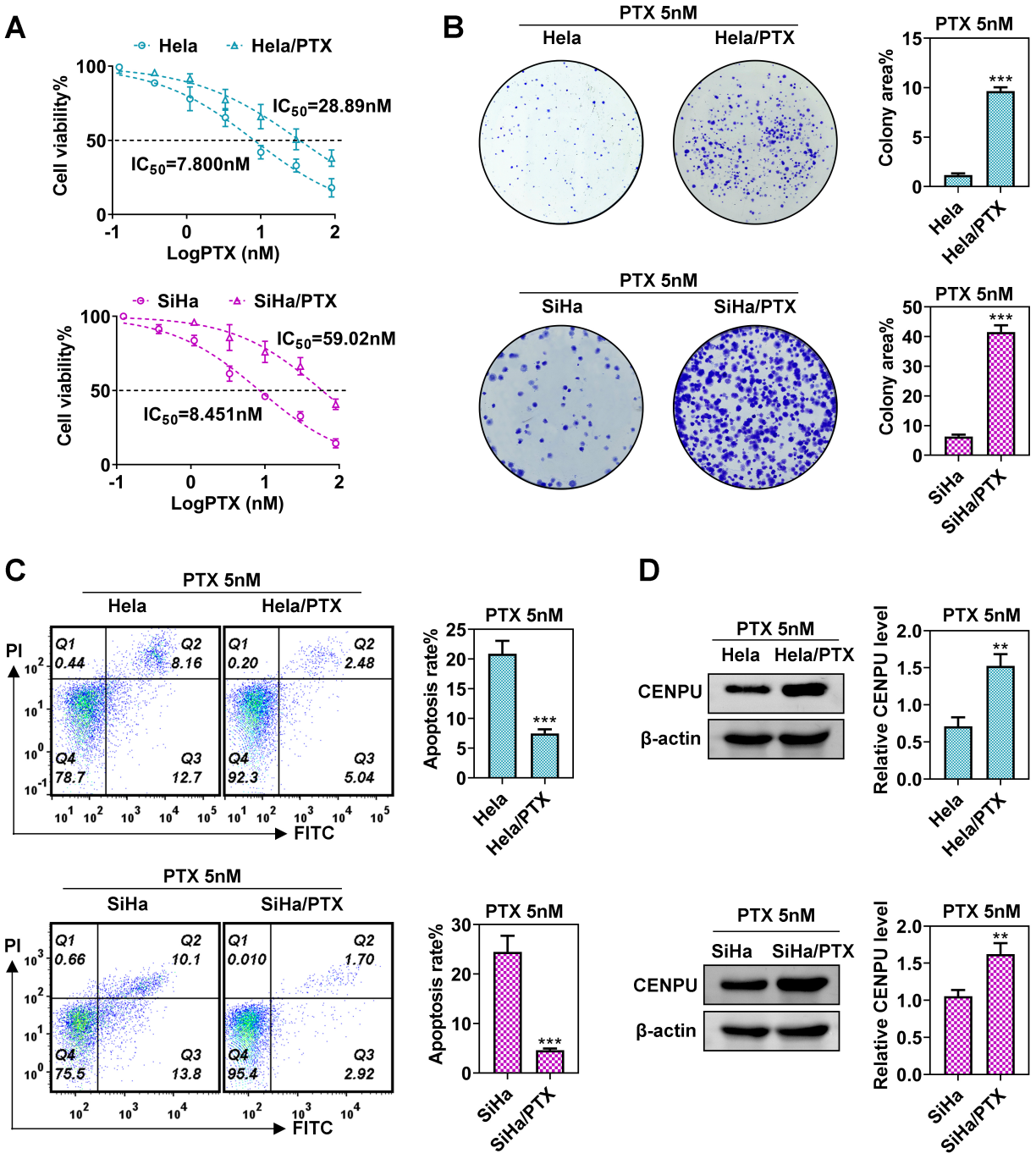

FIGURE 1. Upregulation of CENPU expression in paclitaxel-resistant cervical cancer cells. Paclitaxel-resistant HeLa (HeLa/PTX) and SiHa (SiHa/PTX) cells were generated by exposing HeLa and SiHa cells to stepwise escalating paclitaxel doses over several months. (A) Half-maximal inhibitory concentration (IC_{50}) values of paclitaxel were calculated, and cell viability was assessed using the Cell Counting Kit-8 (CCK8) assay. (B) Cell proliferation was measured by colony formation assay. (C) Flow cytometry analysis was performed to determine the apoptosis rate in HeLa/PTX and SiHa/PTX cells. (D) Western blot analysis was conducted to evaluate the expression of centromeric protein U (CENPU) in HeLa/PTX and SiHa/PTX cells. Data are presented as the mean ± SD. $^{**}p < 0.01$, $^{***}p < 0.001$ *vs*. Hela or SiHa cells.

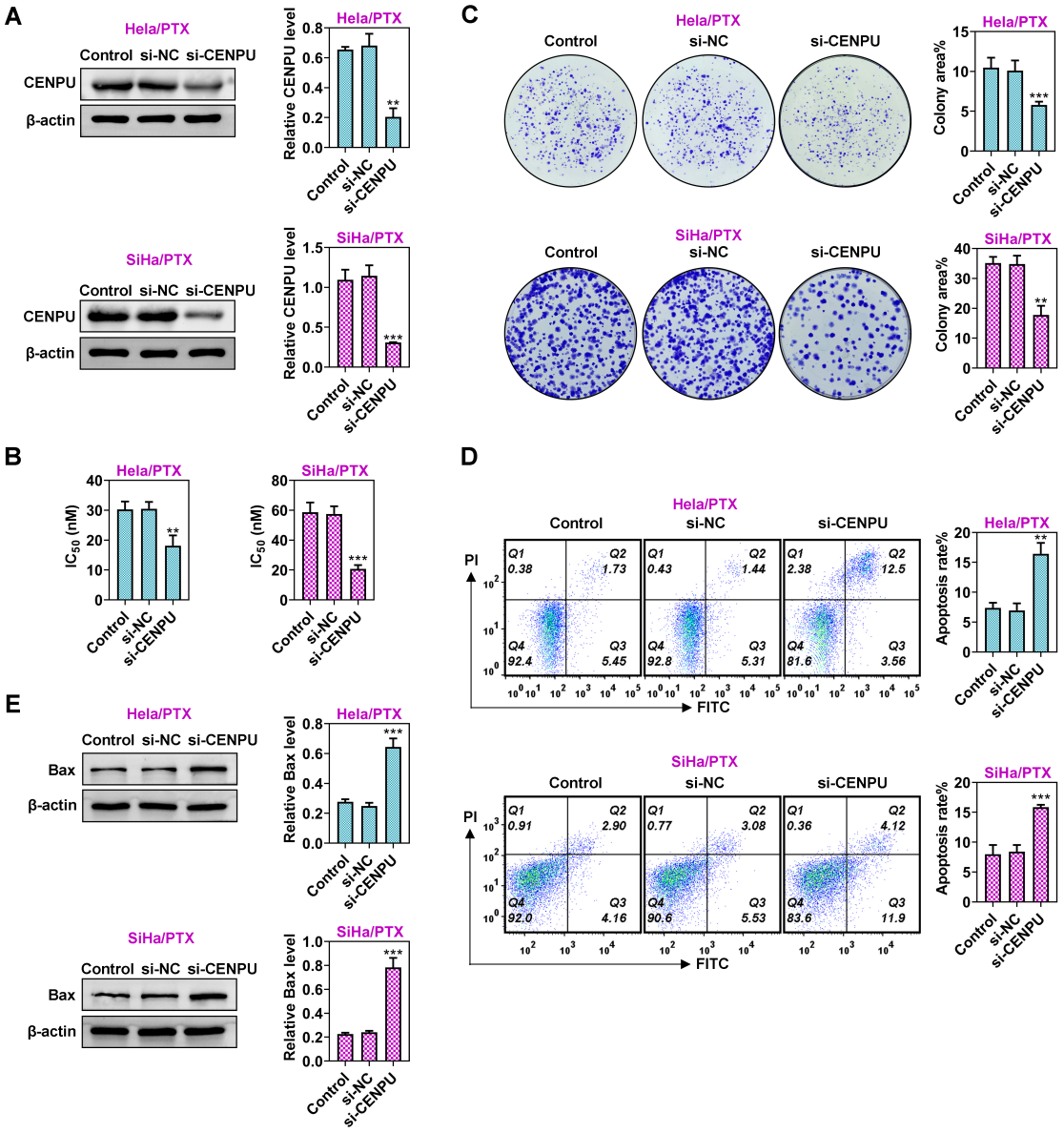

FIGURE 2. CENPU knockdown mitigates paclitaxel resistance in cervical cancer cells. CENPU expression was silenced through the transfection of si-CENPU into Hela/PTX and SiHa/PTX cells. (A) Western blot analysis confirmed the reduction in CENPU levels in si-CENPU-treated cells. (B) The IC_{50} for paclitaxel was determined. (C) Colony formation assays were employed to assess cell proliferation in si-CENPU-treated cells. (D) Flow cytometry was used to quantify apoptotic cell numbers. (E) Western blot analysis evaluated the expression of Bax. Data are presented as the mean ± SD. $^{**}p < 0.01$, $^{***}p < 0.001$ *vs.* control.

ABCC5 in si-CENPU-treated cells, revealing that the silencing of CENPU effectively suppressed the expression of both FOXM1 and ABCC5. As anticipated, the introduction of exogenous FOXM1 into si-CENPU-treated cells counteracted the effects of CENPU knockdown, strongly indicating that the downregulation of CENPU alleviates paclitaxel resistance in cells by modulating the FOXM1 pathway.

5. Conclusions

In conclusion, this study revealed that CENPU exhibits specific upregulation in paclitaxel-resistant CC cells. The silencing of CENPU has been shown to effectively inhibit cell growth and proliferation while promoting apoptosis, ultimately mitigating paclitaxel resistance in CC cells. Furthermore, our findings suggest that the impact of CENPU on paclitaxel-resistant cells may be mediated through the deregulation of the FOXM1/ABCC5 signaling pathway. Consequently, CENPU could emerge as a potential therapeutic target for alleviating paclitaxel chemotherapeutic resistance.

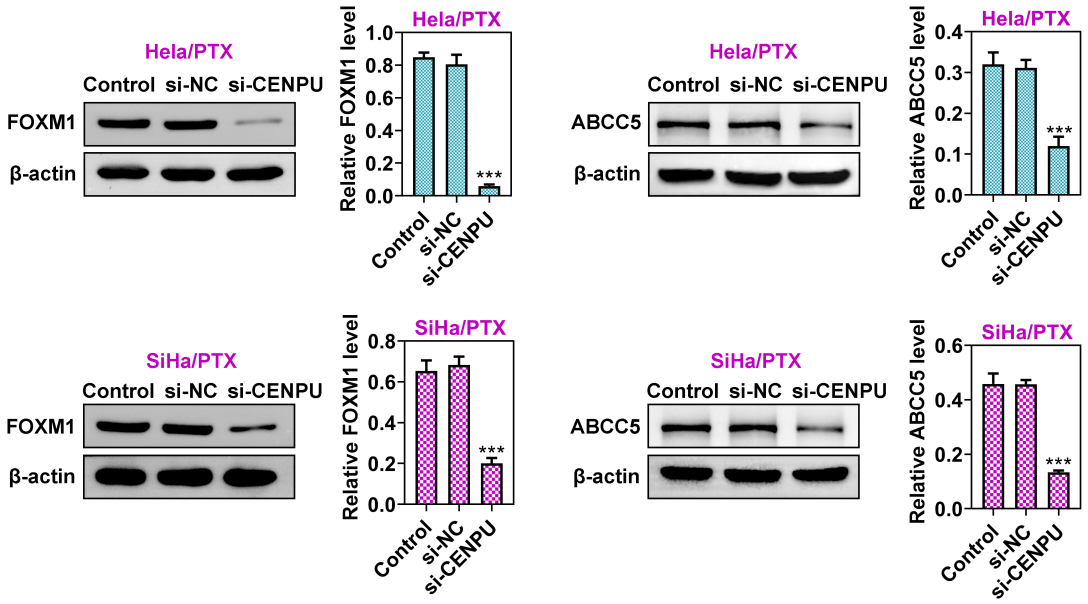

FIGURE 3. CENPU modulates the FOXM1/ABCC5 pathway. Western blot analysis was conducted to evaluate the expression levels of Forkhead box M1 (FOXM1) and Adenosine Triphosphate (ATP) binding cassette subfamily C member 5 (ABCC5) in HeLa/PTX and SiHa/PTX cells in the presence or absence of si-CENPU. Data are presented as the mean ± SD. ***$p < 0.001$ *vs.* control.

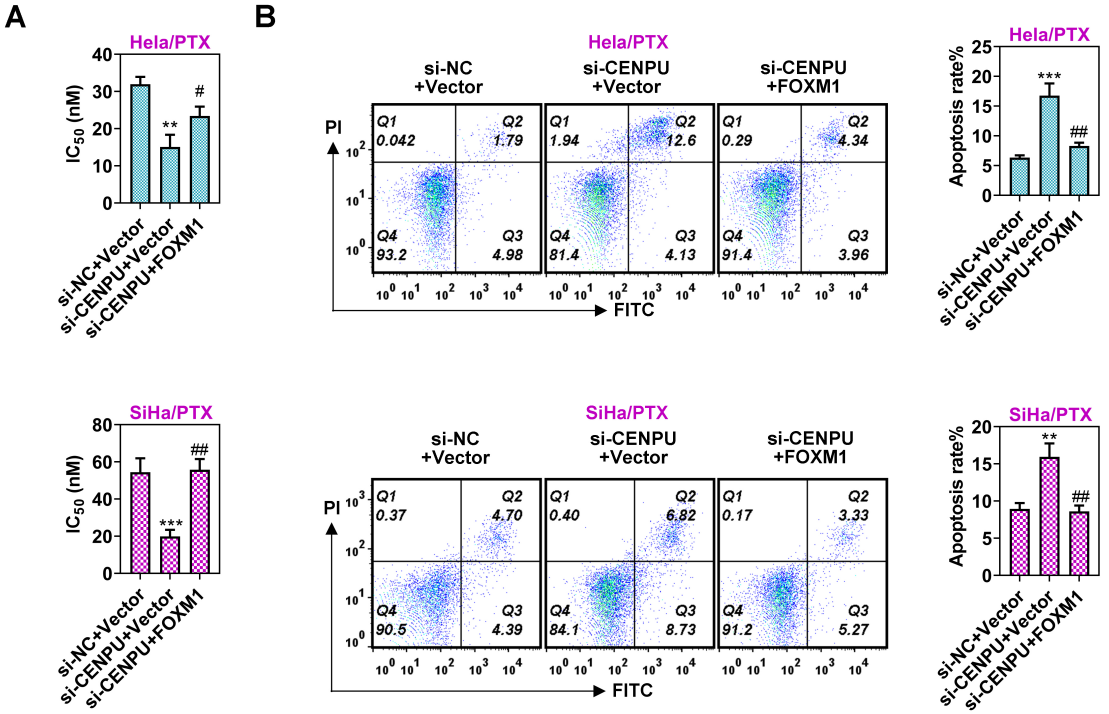

FIGURE 4. CENPU modulates paclitaxel resistance in cervical cancer cells by regulating FOXM1. (A) IC_{50} values were assessed in si-CENPU and si-CENPU + FOXM1 groups. (B) Apoptosis rates were assessed in si-CENPU and si-CENPU + FOXM1 groups. Data are expressed as the mean ± SD. **$p < 0.01$, ***$p < 0.001$ *vs.* si-NC + Vector. #$p < 0.05$, ##$p < 0.01$ *vs.* si-CENPU + Vector.

AVAILABILITY OF DATA AND MATERIALS

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

AUTHOR CONTRIBUTIONS

XZ, YYZ and MW—designed the study and carried them out; 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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