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ORIGINAL

Curcumin promote autophagy via miR-582-5p and Akt/mTOR axis

La curcumina promueve la autofagia vía miR-582-5p y Akt/mTOR axis

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ABSTRACT

Objective: this study aimed to investigate the role of Curcumin in modulating miR-582-5p expression in cisplatin (DDP)-resistant cervical cancer cells.
Method: miR-582-5p expression levels were quantified by qPCR. Cell viability following DDP treatment was assessed using the CCK-8 assay. Colony formation ability was evaluated, and the expression of autophagy-related proteins (ATG7, Beclin-1, LC3-II/I) as well as the phosphorylation status of Akt and mTOR were analyzed by Western blotting.
Results: miR-582-5p expression was downregulated in DDP-resistant tissues and in Hela/DDP and SiHa/DDP cells. Curcumin treatment reduced the IC50 values of both cell lines and suppressed colony formation. Curcumin upregulated ATG7, Beclin-1, and LC3-II/I expression in DDP-resistant Hela and SiHa cells, while concurrently inhibiting the phosphorylation of Akt and mTOR. miR-582-5p modulated Akt phosphorylation and influenced Curcumin-induced autophagy in these resistant cell lines. Additionally, the phosphorylation status of Akt affected the autophagic response to Curcumin.
Conclusions: curcumin enhances autophagy in DDP-resistant cervical cancer cells, accompanied by downregulation of miR-582-5p and inhibition of Akt/mTOR phosphorylation.

Keywords: Curcumin; Mir-582-5p; DDP Resistance; Cervical Cancer, Autophagy.

RESUMEN

Objetivo: este estudio tuvo como objetivo investigar el papel de la curcumina en la modulación de la expresión de miR-582-5p en células de cáncer de cuello uterino resistentes al cisplatino (DDP).
Método: se cuantificaron los niveles de expresión de miR-582-5p mediante qPCR. La viabilidad celular después del tratamiento con DDP se evaluó utilizando el ensayo CCK-8. Se evaluó la capacidad de formación de colonias, y la expresión de proteínas relacionadas con la autofagia (ATG7, Beclin-1, LC3-II/I), así como el estado de fosforilación de Akt y mTOR se analizaron mediante Western blotting.
Resultados: la expresión de miR-582-5p se redujo en tejidos resistentes a DDP y en células Hela/DDP y SiHa/DDP. El tratamiento con curcumina redujo los valores de IC50 de ambas líneas celulares y suprimila formación

de colonias. Curcumin upregulated ATG7, Beclin-1, y LC3-II/I expresión en células Hela y SiHa resistentes a DDP, mientras que al mismo tiempo la inhibición de la fosforilación de Akt y mTOR. MiR-582-5p moduló la fosforilación de Akt e influyen la autofagia indujo la curcumina en estas líneas celulares resistentes. Además, el estado de fosforilación de Akt afectado la respuesta autofágica a la curcumina.
Conclusiones: la curcumina aumenta la autofagia en células de cáncer de cuello uterino resistentes al DDP, acompañada de una regulación negativa del miR-582-5p e inhibición de la fosforilación de Akt/mTOR.

Palabras clave: La Curcumina; Mir-582-5p; Resistencia al DDP; Cáncer Cervical, Autofagia.

INTRODUCTION

Cervical cancer is the fourth most prevalent gynecologic malignancy worldwide, with over 500,000 new cases and more than 300 000 deaths reported annually.[1,2] Although prophylactic vaccination against human papillomavirus (HPV) and early-stage treatment through surgery and radiotherapy offer a 5-year survival rate ranging from 70 % to 87 %, the prognosis for patients with advanced or recurrent disease remains poor.[3] For these individuals, platinum-based chemotherapy provides only a median overall survival of approximately 13,3 months. Current therapeutic strategies primarily include surgery, chemotherapy, and radiotherapy; however, the frequent emergence of chemoresistance—particularly to cisplatin (DDP)—limits their long-term efficacy. Consequently, the development of novel therapeutic agents and treatment modalities is urgently needed.[2]

Traditional Chinese Medicine (TCM), with a history spanning millennia, represents a multifaceted approach to health and disease management.[4,5] Curcumin, a bioactive polyphenolic compound derived from the rhizome of Curcuma longa (turmeric),[6,7] has demonstrated a wide range of pharmacological properties, including anti-inflammatory, antioxidant, and anticancer activities.[8,9] Its antitumor effects are mediated through the induction of cellular differentiation and apoptosis, as well as the inhibition of tumor growth at various stages.[10,11]

Our previous work identified miR-582-5p as a regulator of gastric cancer cell proliferation.[12] In the present study, the role of curcumin in modulating miR-582-5p expression and its impact on autophagy in DDP-resistant cervical cancer cells was investigated.

METHOD

Cell culture

The HeLa and SiHa cell lines were maintained in Dulbecco's Modified Eagle Medium (DMEM) medium (Gibco, Shanghai, China) supplemented with 10 % fetal bovine serum (FBS, Gibco), 100 U/mL penicillin, and 0,1 mg/mL streptomycin at 37°C in a humidified atmosphere containing 5 % CO2. To induce DDP resistance, cells were exposed to progressively increasing concentrations of DDP (Sigma-Aldrich, Shanghai, China), ranging from 1 nM to 100 nM over a six-month period. The DDP-containing medium was refreshed every 48 hours.[13]

Cell counting

Cell proliferation was assessed using the Cell Counting Kit-8 (CCK-8; Biosharp, Shanghai, China). Cells were seeded in 96-well plates at a density of 1×104 cells per well in 100 µL of medium. After treatment with various drug concentrations, 10 µL of CCK-8 solution was added at 24, 48, and 72 hours. Plates were incubated at 37°C, and absorbance at 450 nm was measured using a microplate reader.

Reverse transcription-quantitative PCR (RT-qPCR)

Total RNA was extracted using TRIzol reagent (Invitrogen, USA) in accordance with the manufacturer's instructions. Reverse transcription was performed with the TIANScript RT Kit (Tiangen Biotech, China) using the following thermal protocol: 70°C for 5 min, 37°C for 5 min, and 42°C for 60 min. Relative gene expression was quantified using the SYBR Premix Ex TaqTM II Kit (Takara, Japan) under the following cycling conditions: initial denaturation at 95°C for 10 min; 40 cycles of 95°C for 15 s and 60°C for 1 min; followed by a final extension at 72°C for 10 min. Primer sequences were: miR-582-5p forward: 5'-GCGGTTACAGTTGTTCAACC-3'; reverse: 5'-CTCAACTGGTGTCGTGGA-3'. GAPDH forward: 5'-ACAACTTTGGTATCGTGGAAGG-3'; reverse: 5'-GCCATCACGCCACAGTTTC-3'. The miRNA expression level was normalized to GAPDH, which served as the internal control, and relative quantification was performed using the 2-ΔΔCt method.

Western blotting

For Western blotting analysis, total protein was extracted, and concentrations were determined using a bicinchoninic acid assay kit (Beyotime Biotechnology, Shanghai, China). Protein samples were separated by SDS-PAGE and transferred to polyvinylidene fluoride membranes (Millipore, Billerica, MA, USA). Membranes were blocked with 5 % bovine serum albumin (BSA) at room temperature for 1 hour and incubated overnight

at 4°C with primary antibodies: p-Akt (1:1000), Akt (1:1000), p-mTOR (1:1000), mTOR (1:1000), Beclin-1 (1:1000), LC3Ⅱ/Ⅰ (1:1000), ATG7 (1:1000), and GAPDH (1:2000). After washing, membranes were incubated with HRP-conjugated goat anti-rabbit IgG (ab205718, Abcam) at room temperature for 1,5 hours. Detection was performed using enhanced chemiluminescence reagent (Beyotime Biotechnology, Shanghai, China), and protein bands were quantified using ChemiScope 6000 software (Clinx, Shanghai, China).[13]

Cloning formation assay

DDP-resistant HeLa and SiHa cells in the logarithmic growth phase were diluted with Dulbecco's Modified Eagle Medium (DMEM) (Gibco, Shanghai, China) and cultured in 6-well cell plates at a density of 1,5×103 cells per well. After the cells adhered to the wall, only Dulbecco›s Modified Eagle Medium (DMEM) (Gibco, Shanghai, China) was added to the control group, and 8,5μM curcumin (Sigma-Aldrich, Shanghai, China) was added to the experimental group and cultured for 1 week. After the cells formed obvious colonies (cell number>50), they were stained with 0,1 % crystal violet (Solarbio, Beijing, China) and photographed and counted under a microscope.

Over-expression plasmid transfection

Transfection of the miR-582-5p mimic and negative control (NC) was performed using Lipofectamine 3000 in accordance with the manufacturer's protocol.

Luciferase assay

Cells were co-transfected with the pRL-TK vector and the pGL3-basic plasmid harboring the mutant miR-582-5p binding site (Mut) using Lipofectamine 3000. After 24 h of incubation at 37°C in a 5 % CO2 atmosphere, cells were lysed and luciferase activity was measured using a commercial detection system. Specifically, 50 μL of the lysate supernatant was added to each well of a 96-well plate. Firefly luciferase activity was measured first by adding the appropriate substrate, followed by luminescence detection with a luminometer. A stop solution was then added to terminate the firefly luciferase reaction, and Renilla luciferase substrate was introduced to quantify Renilla activity. Luminescence values for both luciferases were recorded, and relative luciferase activity was calculated.

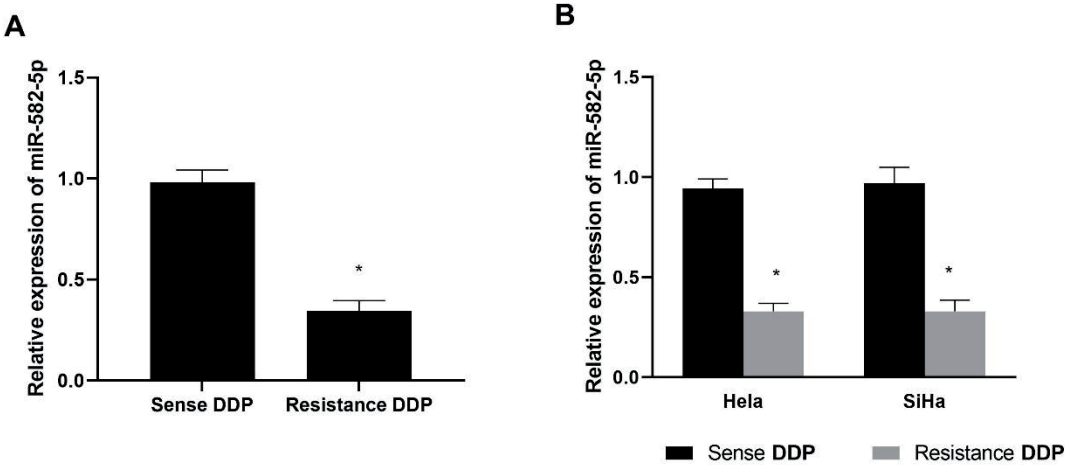
Statistical analysis

Statistical analysis was conducted using GraphPad Prism (La Jolla, CA, USA). Intergroup differences were evaluated using independent sample t-tests. All experiments included biological replicates, and significance was defined at $p < 0,05$. Data are presented as mean ± SD.

RESULTS

miR-582-5p was suppressed in cervical cancer cells exhibiting DDP resistance.

To investigate the role of miR-582-5p in DDP resistance in cervical cancer, its expression was quantified by qPCR. Results revealed that miR-582-5p was significantly downregulated in DDP-resistant HeLa and SiHa cells (figure 1).

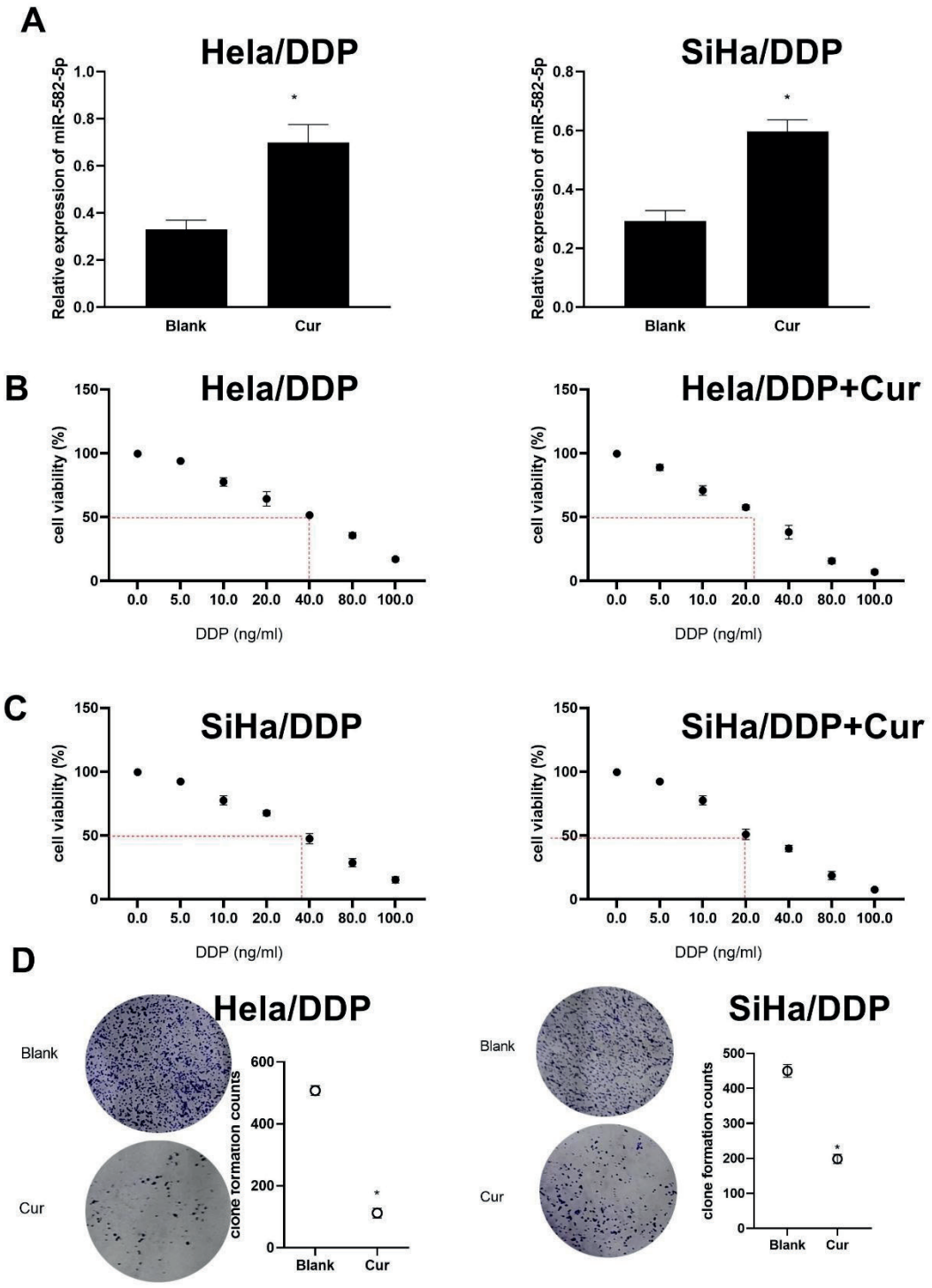


Note: $p < 0,05$. Comparisons between groups were performed using independent sample *t*-tests. All experiments were conducted in triplicate. All data are presented as mean ± SD

Figure 1. Relative expression of miR-582-5p in DDP-resistant cervical carcinoma. (A) Cervical carcinoma tissues. (B) DDP-resistant cervical cancer cell lines HeLa and SiHa

Curcumin promoted the miR-582-5p and susceptibility with DDP and inhibited clone formation

Treatment of HeLa and SiHa cells with curcumin in combination with DDP led to a marked upregulation of miR-582-5p. The enhancement of DDP sensitivity was reflected in reduced IC50 values in the curcumin-treated groups (figure 2A–C). Additionally, curcumin significantly suppressed colony formation in HeLa/DDP and SiHa/DDP cells (figure 2D). These findings indicate that curcumin enhances DDP sensitivity through upregulation of miR-582-5p.

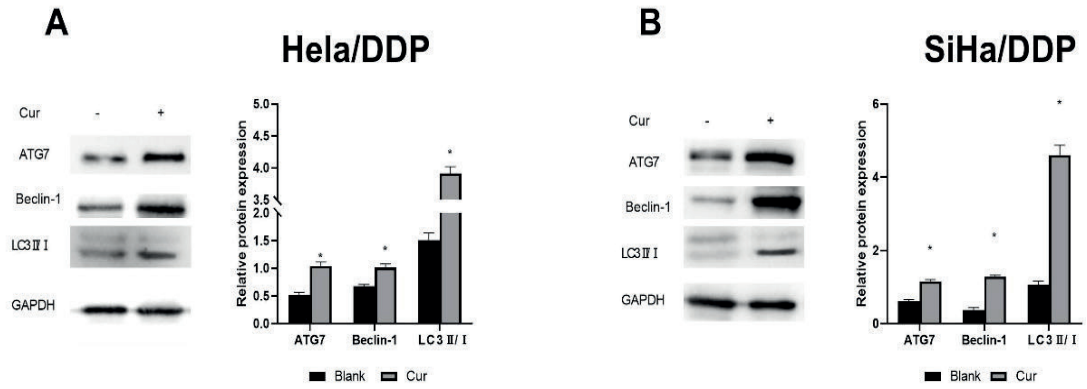


Note: p < 0,05. Independent sample *t*-tests were used for group comparisons. All experiments were conducted in triplicate. All data are presented as mean ± SD

Figure 2. Effects of curcumin on DDP-resistant HeLa and SiHa cells. (A) Relative expression of miR-582-5p. (B, C) IC_{50} values of DDP. (D) Colony formation assay

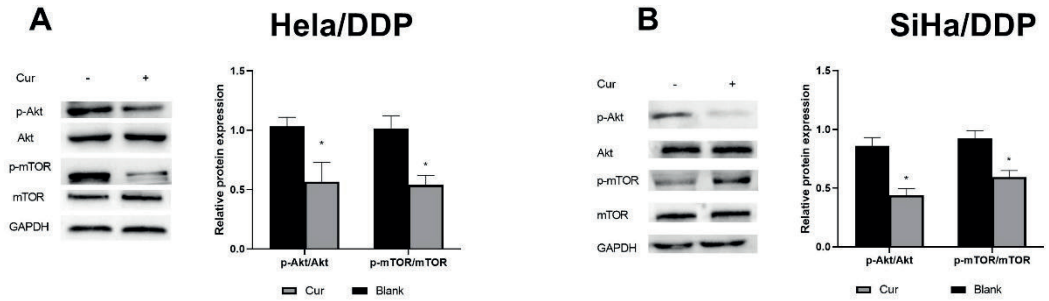
Curcumin promoted autophagy

The impact of curcumin on autophagy was further assessed by examining the expression of autophagy-related proteins, including ATG7, Beclin-1, and LC3Ⅱ/I. Expression of all three proteins was elevated in DDP-resistant HeLa and SiHa cells following curcumin treatment. To elucidate the underlying mechanism, the Akt/mTOR signaling pathway was analyzed. Curcumin markedly suppressed the phosphorylation levels of Akt and mTOR in DDP-resistant cells (figure 3 and figure 4), suggesting that curcumin induces autophagy via inhibition of the Akt/mTOR pathway.



Note: p < 0,05. Independent sample *t*-tests were used for comparisons. All experiments were conducted in triplicate. All data are presented as mean ± SD

Figure 3. Curcumin-induced autophagy in DDP-resistant cells. (A) Expression levels of ATG7, Beclin-1, and LC3Ⅱ/I in HeLa cells. (B) Expression levels of ATG7, Beclin-1, and LC3Ⅱ/I in SiHa cells



F Note: p < 0,05. Independent sample *t*-tests were applied for group comparisons. All experiments were conducted in triplicate. All data are presented as mean ± SD

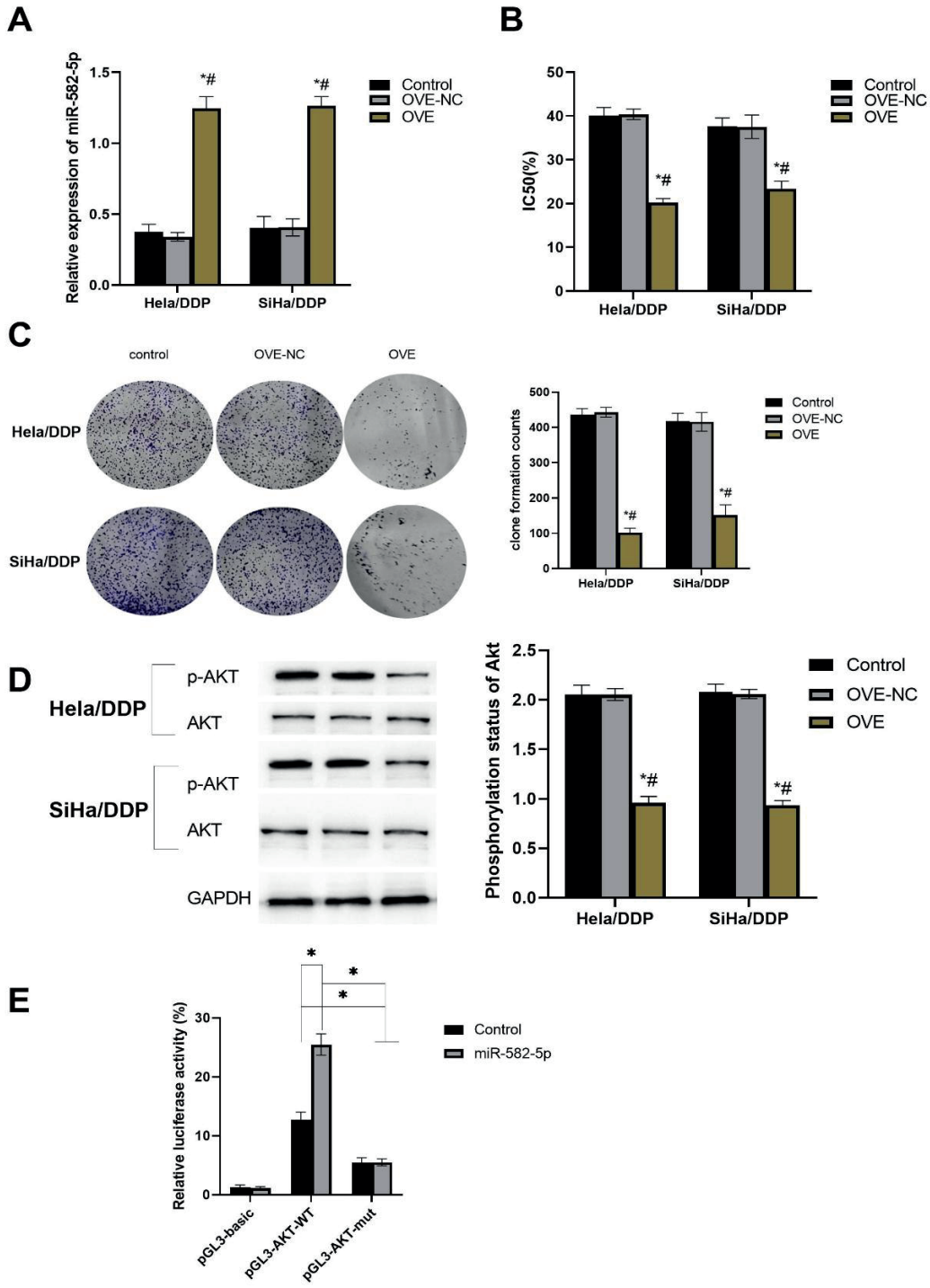
igure 4. Effects of curcumin on Akt/mTOR signaling in DDP-resistant cells. (A) Phosphorylation levels of Akt and mTOR in HeLa cells. (B) Phosphorylation levels of Akt and mTOR in SiHa cells.

miR-582-5p regulated autophagy via Akt

To further examine the relationship between miR-582-5p and Akt signaling, miR-582-5p was overexpressed using synthetic mimics in DDP-resistant HeLa and SiHa cells (figure 5A). Overexpression of miR-582-5p reduced the IC50 of DDP (figure 5B), inhibited colony formation (figure 5C), and significantly decreased the phosphorylation level of Akt (figure 5D–E). These results demonstrate that miR-582-5p promotes DDP sensitivity by suppressing Akt phosphorylation.

The influence of Curcumin on Hela and SiHa with DDP resistance after miR-582-5p overexpression.

To further assess the role of miR-582-5p during the Curcumin was added, miR-582-5p was overexpressed in DDP-resistant HeLa and SiHa cells prior to curcumin treatment. Neither IC50 values nor colony formation capacity showed significant differences between curcumin-treated and untreated groups under miR-582-5p overexpression (figure 6A-B). Similarly, the expression levels of autophagy-related proteins ATG7, Beclin-1, and LC3Ⅱ/I remained unchanged with or without curcumin, as did the phosphorylation status of Akt and mTOR (figure 6C-D). These findings suggest that miR-582-5p mediates the pro-autophagic and sensitizing effects of curcumin in DDP-resistant HeLa and SiHa cells.



Note: p < 0,05 vs. control group; #p < 0,05 vs. OVE-NC group. Independent sample *t*-tests were used for comparisons. All experiments were conducted in triplicate. All data are presented as mean ± SD

Figure 5. Effects of miR-582-5p overexpression in DDP-resistant HeLa and SiHa cells. (A) Relative expression of miR-582-5p. (B) IC_{50} values of DDP. (C) Colony formation. (D) Phosphorylation levels of Akt. (E) Relative luciferase activity

To investigate whether Akt activation modulates the response to curcumin, Akt signaling was artificially activated in DDP-resistant HeLa and SiHa cells. Despite curcumin treatment resulting in elevated miR-582-5p expression compared to control (figure 7A), neither IC50 values nor colony formation capacity were affected (figure 7B-C). Furthermore, expression of ATG7, Beclin-1, and LC3Ⅱ/Ⅰ remained unchanged, as did the phosphorylation levels of Akt and mTOR (figure 7D-E). These results indicate that Akt phosphorylation counteracts the ability of curcumin to induce autophagy and enhance chemosensitivity in DDP-resistant HeLa and SiHa cells.

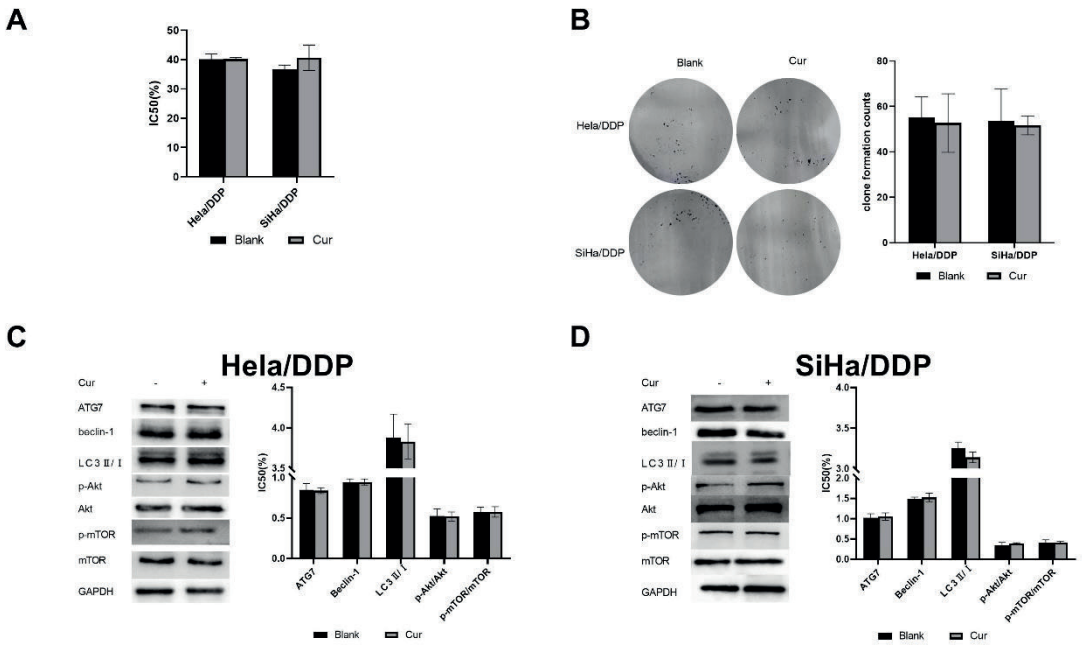


Figure 6. Effects of curcumin on DDP-resistant HeLa and SiHa cells after miR-582-5p overexpression. (A) IC_{50} values of DDP. (B) Colony formation. (C, D) Expression of ATG7, Beclin-1, and LC3Ⅱ/I, and phosphorylation levels of Akt and mTOR. All data are presented as mean ± SD

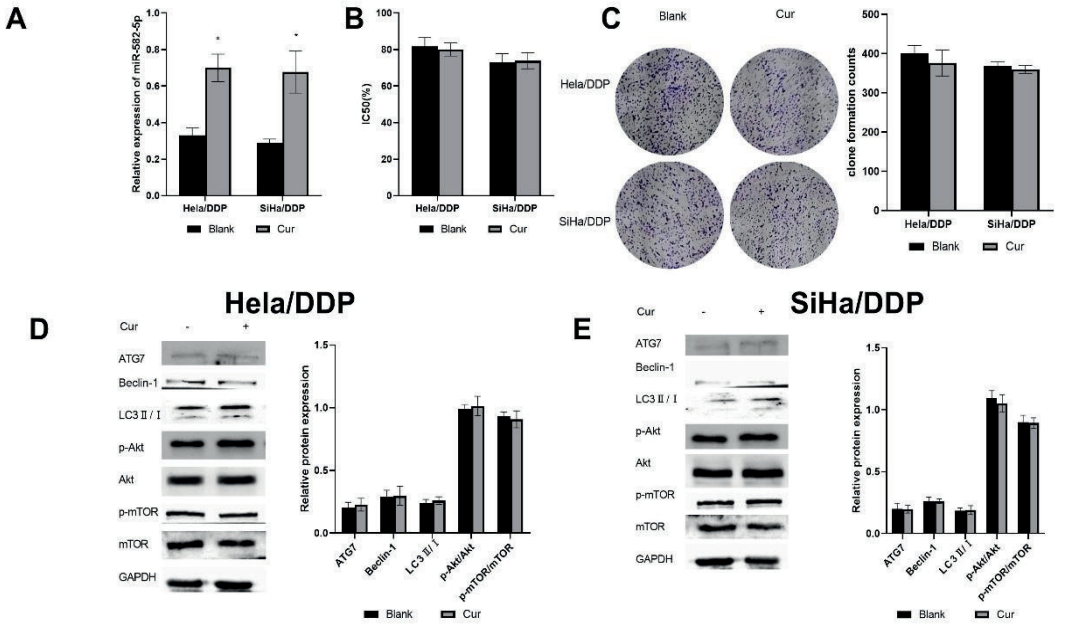


Figure 7. Effects of curcumin on DDP-resistant HeLa and SiHa cells following Akt activation. (A) Relative expression of miR-582-5p. (B) IC_{50} values of DDP. (C) Colony formation. (D, E) Expression of ATG7, Beclin-1, and LC3Ⅱ/I, and phosphorylation levels of Akt and mTOR. All data are presented as mean ± SD

DISCUSSION

Cervical cancer remains one of the most prevalent malignancies among women, with over 300,000 deaths reported annually worldwide. Standard treatment options include surgery, chemotherapy, and radiotherapy; however, the emergence of chemotherapy resistance, particularly to DDP, poses a significant challenge. Therefore, the development of novel therapeutic strategies and agents is imperative. In this study, curcumin was found to alleviate DDP resistance in cervical cancer cells.

Curcumin, a bioactive compound extracted from turmeric—a key component in TCM,[11,12,13,14] exhibits a broad spectrum of pharmacological activities, including anticancer, anti-inflammatory, and antioxidant effects.[10,15]

Notably, curcumin has demonstrated inhibitory effects against multiple tumor types, such as hepatocellular carcinoma, gastric cancer, colorectal cancer, esophageal cancer, breast cancer, prostate cancer, skin cancer, lymphoma, and leukemia.[8,11,16,17,18,19,20] Its antitumor mechanisms include induction of apoptosis, suppression of oncogene expression, inhibition of tumor invasion and metastasis, anti-angiogenic activity, and enhancement of chemosensitivity.[14,21,22,23,24] In the present study, curcumin was shown to reverse DDP resistance in cervical cancer cells, potentially through the induction of autophagy mediated by miR-582-5p.

miR-582-5p exhibits context-dependent functions across various tumor types, acting either as a tumor suppressor or an oncogene through distinct molecular pathways.[25,26] In ovarian cancer, low levels of miR-582-3p have been associated with poor overall survival. In colorectal cancer, miR-582 expression is linked to tumor progression and may regulate targets such as PTEN.[27,28,29] In non-small cell lung cancer, miR-582-3p correlates with survival outcomes and exhibits tumor-promoting activity. Furthermore, in oral cancer, exosomal miR-582-3p modulates malignancy by targeting SFRP1.[30,31] In this study, miR-582-5p was found to regulate autophagy through modulation of Akt phosphorylation in DDP-resistant cervical cancer cells. Curcumin enhanced autophagy via the miR-582-5p/Akt axis.

CONCLUSIONS

In conclusion, the findings demonstrate that curcumin enhances autophagy in DDP-resistant cervical cancer cells by upregulating miR-582-5p and inhibiting the phosphorylation of Akt and mTOR. These results suggest that curcumin exerts its chemosensitizing effect through the miR-582-5p-mediated suppression of the Akt/mTOR signaling pathway. This study was limited to in vitro experiments at the cellular level. Further investigation at the in vivo level is necessary to validate these findings and assess their translational potential.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the Mongolian National University of Medical Sciences.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Research: Dandan Huang, Erdenezaya Odkhuu.

Methodology: Dandan Huang.

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Drafting - original draft: Dandan Huang.

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