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Original Article

Silencing CDH17 reverses cisplatin resistance in gastric cancer cells by regulating the Warburg effect mediated by the Wnt/β-catenin pathway

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Abstract: Objective: To investigate the role of CDH17 in cisplatin (DDP) resistance in gastric cancer (GC) and to elucidate the potential molecular mechanisms. Methods: DDP-resistant GC cell lines were established, and CDH17 expression was silenced in these cells. Cell proliferation was assessed using the MTT assay. Cellular glycolytic activity was quantified, and apoptosis was assessed using flow cytometry. The expression of CDH17, β-catenin, key Warburg-related effector proteins, and Cleaved-caspase-3 was determined through molecular experiments. The Warburg effect inhibitor 2-DG and the Wnt/β-catenin signaling pathway agonist CP21R7 were applied to investigate the underlying molecular mechanism. Results: CDH17 was significantly upregulated in the DDP-resistant GC cells. CDH17 knockdown increased the sensitivity of GC cells to DDP, suppressed the Warburg effect, and inhibited the activation of the Wnt/β-catenin signaling pathway. Treatment with 2-DG reduced the chemoresistance in resistant GC cells. However, CP21R7 treatment promoted the Warburg effect in the DDP-resistant GC cells and partially attenuated the effects of CDH17 silencing on both the Warburg effect and DDP sensitivity. Conclusion: CDH17 silencing reversed DDP resistance in GC cells, primarily through inhibition of the Warburg effect mediated by the Wnt/β-catenin signaling pathway.

Keywords: Gastric cancer, chemotherapy resistance, Warburg effect, cadherin 17, Wnt/β-catenin signaling pathway

Introduction

Gastric cancer (GC) is one of the most prevalent malignancies worldwide. Despite significant advancements in diagnostic techniques and therapeutic strategies, GC ranks fourth in cancer-related mortality, with a 5-year survival rate of only about 20% [1]. The absence of specific early symptoms and effective screening methods leads to most patients being diagnosed at intermediate or advanced stages, thereby missing the optimal therapeutic window [2]. The development and progression of GC are influenced by both genetic predisposition and environmental factors, including *Helicobacter pylori* infection, chronic atrophic gastritis, alcohol consumption, and smoking [1, 3]. In China, GC ranks third in both incidence and mortality among all cancer types, imposing a significant burden on the healthcare system [4]. Current treatment modalities include surgical resection, radiotherapy, chemotherapy, and targeted therapy [5]. The combination of surgery and perioperative chemotherapy reduces postoperative recurrence [6]. However, chemoresistance remains the primary cause of treatment failure and postoperative recurrence [7]. Therefore, investigating the mechanisms of chemotherapy resistance is crucial for improving clinical outcomes in GC.

To sustain rapid proliferation, resist stress, and evade immune surveillance, cancer cells undergo metabolic reprogramming [8]. A key hallmark of this process is the Warburg effect, first described by Otto Warburg in the 1920s [9]. This aberrant metabolic phenotype is characterized by a preference for glycolytic lactate production rather than complete glucose oxidation, even under normoxic conditions [10].

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Consequently, compared to normal cells, cancer cells exhibit increased aerobic glycolysis and significantly increased glucose uptake [11]. The Warburg effect creates an acidic microenvironment that facilitates angiogenesis, tumor progression, and immune escape in GC [12]. Importantly, it also represents a major mechanism contributing to chemoresistance in cancer cells [13, 14].

Activation of multiple signaling pathways, including the PI3K/AKT [15, 16], PPARγ/mTOR/PKM2 [17], and Wnt/β-catenin [18], has been shown to enhance the Warburg effect, thereby promoting resistance to both targeted therapies and chemotherapeutic agents. Among these, the Wnt/β-catenin signaling pathway plays a critical role in regulating cancer cell proliferation, differentiation, and stemness [19]. Aberrant activation of this pathway is closely associated with chemotherapy and targeted therapy resistance across various types of tumors [20-22]. Research suggests that persistent activation of the Wnt/β-catenin signaling pathway not only promotes the initiation and progression of GC [23] but also contributes to chemoresistance [24, 25]. Conversely, inhibition of the Wnt/β-catenin pathway can suppress the Warburg effect, attenuating tumor growth, stemness, and drug resistance [26]. Consequently, targeting the Wnt/β-catenin signaling pathway to inhibit the Warburg effect could be a promising strategy for overcoming chemoresistance in GC.

Cadherin 17 (CDH17), also known as hepatointestinal cadherin, is a member of the cadherin superfamily and contains seven extracellular cadherin domains and one cytoplasmic domain [27]. As a calcium-dependent transmembrane protein, CDH17 is essential for intercellular adhesion and signaling. Dysregulation of CDH17 expression has been closely associated with the malignant progression of various tumors, including GC [28-30]. Furthermore, CDH17 has been identified as a potential diagnostic marker for digestive system cancers [31, 32]. Recent studies suggest that targeting CDH17 suppresses Wnt/β-catenin signaling in GC cells, thereby inhibiting tumor cell proliferation, migration, adhesion, and other malignant biological behaviors [33]. Additionally, CDH17 knockdown has been shown to reduce tumor cell stemness and enhance their sensitivity to cisplatin (DDP) [34]. However, whether CDH17 promotes chemotherapy resistance in GC by modulating metabolic reprogramming remains largely unexplored.

Based on this rationale, DDP-resistant GC cell lines were first established in this study using a drug concentration escalation approach. Thereafter, loss- and gain-of-function experiments were conducted to investigate whether CDH17 regulates the Warburg effect to influence drug sensitivity, with a goal of identifying a potential therapeutic target for overcoming DDP resistance in GC.

Materials and methods

Establishment of DDP-resistant GC cell lines

The human GC cell lines HGC-27 and AGS were obtained from the Cell Resource Center, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences (Beijing, China). Cells were cultured in RPMI-1640 medium (Gibco, Carlsbad, USA) supplemented with 10% fetal bovine serum (FBS, Gibco, Carlsbad, USA). DDP-resistant GC cell lines were generated through stepwise escalation of drug concentration. Specifically, HGC-27 and AGS cells were initially cultured in a medium containing 0.2 mg/L DDP (Aladdin, Shanghai, China). Once cell confluence reached about 80%, the DDP concentration was gradually increased. This process was repeated until cells grew stably in the medium containing 1 μg/mL DDP [35], indicating successful establishment of DDP-resistant GC cell lines (designated as HGC-27/DDP and AGS/DDP).

Cell transfection and treatment

Based on the CDH17 mRNA reference sequence (NM_001144663) obtained from NCBI, three siRNAs targeting the coding region of CDH17 were designed and synthesized: si-CDH17-1, si-CDH17-2, and si-CDH17-3 (**Table 1**). These siRNAs were then transfected into HGC-27/DDP and AGS/DDP cells using the Lipofectamine™ 2000 reagent (Invitrogen, Carlsbad, USA). At 48 h post-transfection, CDH17 expression levels were assessed to determine the silencing efficiency, and the most effective siRNA was used in subsequent transfection experiments. Following the trans-

Table 1. The sequence of si-CDH17

Name	Sequence (5'-3')
si-CDH17-1	sense strand: GGAAUGUUACAGUUAGCUAAA
	antisense strand: UAGCUAACUGUAACAUUCCAG
si-CDH17-2	sense strand: GGUGUGAAGUACAAUGCAAGU
	antisense strand: UUGCAUUGUACUUCACACCAA
si-CDH17-3	sense strand: CGAUAGAGGUGUCUGACAAAG
	antisense strand: UUGUCAGACACCUCUAUCGUU

Note: CDH17: Cadherin 17.

fection experiments, the HGC-27/DDP and AGS/DDP cells were treated with the Wnt signaling pathway agonist CP21R7 (5 μM; Selleck, Houston, USA) [36] or the Warburg effect inhibitor 2-deoxyglucose (2-DG, 10 mM; Selleck, Houston, USA) [37] for 24 h.

MTT assay

The cells were seeded into 96-well plates and cultured for 24 h. Subsequently, various concentrations of DDP (0, 0.5, 1, 2, 4, 8, or 16 μg/mL) were added, followed by an additional 24-h incubation. Thereafter, 10 μL of MTT solution (5 mg/mL; Beyotime, Shanghai, China) was added to each well and incubated for 4 h at room temperature in the dark. To dissolve the formazan crystals, 100 μL of dimethyl sulfoxide (DMSO) was added. Absorbance was measured at 490 nm using a microplate reader. The half-maximal inhibitory concentration (IC_{50}), resistance index (RI), and resistance reversal fold-change were calculated.

Flow cytometry assay

After trypsin digestion, 1×10^5 cells were harvested, centrifuged, and resuspended in 195 μL of Annexin V-FITC binding solution. Subsequently, 5 μL of Annexin V-FITC and 10 μL of propidium iodide (PI) staining solution (Beyotime, Shanghai, China) were added sequentially, gently mixed, and incubated for 20 min at room temperature in the dark. Finally, the apoptosis rate was determined using flow cytometry.

Determination of lactic acid and adenosine triphosphate (ATP) levels

For lactate measurement, 4×10^6 cells were homogenized in 200 μL PBS, and the supernatant was collected following centrifugation. Protein concentration was subsequently determined, and lactate levels were quantified using a colorimetric assay kit (Elabscience, Wuhan, China). For ATP measurement, 2×10^6 cells were mixed with 0.3 mL of Reagent I from the ATP chemiluminescence assay kit (Elabscience, Wuhan, China), followed by a water bath at boiling temperature for 10 min. After centrifugation, the supernatant was collected, and intracellular ATP levels were measured according to the kit's protocol.

Determination of glucose uptake

Cells were seeded into 96-well plates at a density of 5×10^4 cells/mL (100 μL/well) and incubated for 24 h. Glucose uptake was then measured using a glucose uptake assay kit (Abnova, Taiwan, China) according to the manufacturer's protocol. Absorbance was recorded at 570 nm and 610 nm with a microplate reader, and the cellular glucose uptake was quantified as the ratio of the absorbance at 570 nm to that at 610 nm.

Quantitative real-time PCR (qRT-PCR)

Total RNA was extracted from the cells using TRIzol reagent (Beyotime, Shanghai, China). One-step qRT-PCR was performed with the BeyoFast™ Probe One-step qRT-PCR Kit (Beyotime, Shanghai, China) on a real-time fluorescence PCR system. The PCR program was as follows: reverse transcription at 50°C for 20 min, initial denaturation at 95°C for 2 min, followed by 40 cycles of denaturation at 95°C for 15 s and annealing/extension at 60°C for 30 s. The primer sequences were as follows: CDH17 forward primer 5'-AGGCC AAGAA CCGAGTCAAAT-3' and reverse primer 5'-GCAACCTGGAGATTGTGAG TAGA-3', β-actin forward primer 5'-CATGTACGTTGCTATCCAGGC-3' and reverse primer 5'-CTCCTTAATGTCACGCACGAT-3'. Relative CDH17 mRNA expression was calculated using the $2^{-\Delta\Delta Ct}$ method.

Immunofluorescence staining

The cells were seeded on coverslips placed in 6-well plates and cultured overnight. After fixation with 4% paraformaldehyde for 15 min, antigen retrieval, and permeabilization, cells

were blocked with bovine serum albumin for 30 min at room temperature. Cells were then incubated overnight at 4°C with a primary antibody against β-catenin (1:200; Abcam, Cambridge, UK), followed by incubation with a CY3-conjugated secondary antibody (1:100; Servicebio, Wuhan, China) for 1 h at room temperature in the dark. Nuclei were counterstained with DAPI and mounted with an anti-fluorescence quenching capping agent (Servicebio, Wuhan, China). Finally, the localization of β-catenin in the cells were visualized by laser confocal microscopy, and nuclear accumulation was quantified by measuring the optical density of positive signals using Image-Pro Plus software (6.0).

Western blot analysis

RIPA lysis buffer (Beyotime, Shanghai, China) was used for the extraction of total cellular proteins, and the protein concentration was quantified. Equal amounts of protein were separated by SDS-PAGE, transferred to membranes, and blocked with 5% skim milk powder for 1 h at room temperature. Membranes were then incubated overnight with primary antibodies at 4°C, followed by incubation with secondary antibodies (1:10,000; Abcam, Cambridge, UK) for 1 h at room temperature. The primary antibodies used were as follows: anti-CDH17 (1:1,000; Abcam, Cambridge, UK), anti-glucose transporter 1 (GLUT1, 1:500; Abcam, Cambridge, UK), anti-lactate dehydrogenase A (LDHA, 1:1,000; CST, Danvers, USA), anti-hexokinase II (HK2, 1:1,000; Abcam, Cambridge, UK), anti-pyruvate kinase M2 isoform (PKM2, 1:1000; CST, Danvers, USA), anti-β-catenin (1:1,000; Abcam, Cambridge, UK), anti-Cleaved-caspase-3 (1:500; Abcam, Cambridge, UK), and anti-β-actin (1:1,000; Abcam, Cambridge, UK). Protein bands were visualized using a chemiluminescence reagent, and band intensities were quantified using ImageJ software.

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Statistical analyses and graphical representations were performed using the GraphPad Prism 8 software. Comparisons of CDH17 and β-catenin expression, glucose uptake, lactate and ATP levels, and glycolysis-related protein expression between the parental and drug-resistant cells were performed using unpaired *t* tests. Differences in cell proliferation, glycolytic activity, and protein expression among drug-resistant cell groups following CDH17 silencing and/or CP21R7 treatment were analyzed using one-way analysis of variance (ANOVA) along with Tukey's post hoc test. A p value < 0.05 was considered statistically significant.

Results

CDH17 knockdown enhanced the sensitivity of DDP-resistant GC cells to DDP

DDP-resistant GC cell lines were successfully established through stepwise exposure to increasing concentrations of DDP. MTT assays showed that the IC_{50} values of DDP in the resistant GC cell lines were significantly greater than those in the parental cells. Specifically, the RI was 5.74 in HGC-27/DDP cells and 6.42 in AGS/DDP cells (**Figure 1A**). Additionally, both CDH17 mRNA and protein expression levels were markedly upregulated in DDP-resistant GC cells relative to parental cells (**Figure 1B** and **1C**).

To investigate the role of CDH17 in chemoresistance, CDH17 was silenced in HGC-27/DDP and AGS/DDP cells using three siRNAs. Among them, siCDH17-1 exhibited the highest interference efficiency and was selected for subsequent experiments (**Figure 1D** and **1E**). Silencing CDH17 in HGC-27/DDP and AGS/DDP cells significantly decreased the IC_{50} value of DDP, with the resistance reversal rates of 3.30-fold in HGC-27/DDP cells and 2.97-fold in AGS/DDP cells (**Figure 2A**). Furthermore, CDH17 knockdown significantly increased apoptosis in both cell lines, and enhanced the sensitivity of resistant cells to 1 μg/mL DDP, leading to increased apoptosis (**Figure 2B**). Together, these findings indicate that CDH17 silencing enhances the sensitivity of DDP-resistant GC cells to DDP.

CDH17 knockdown suppressed the Warburg effect and Wnt/β-catenin signaling in DDP-resistant GC cells

Following CDH17 knockdown, glucose uptake and the production of lactate acid and ATP

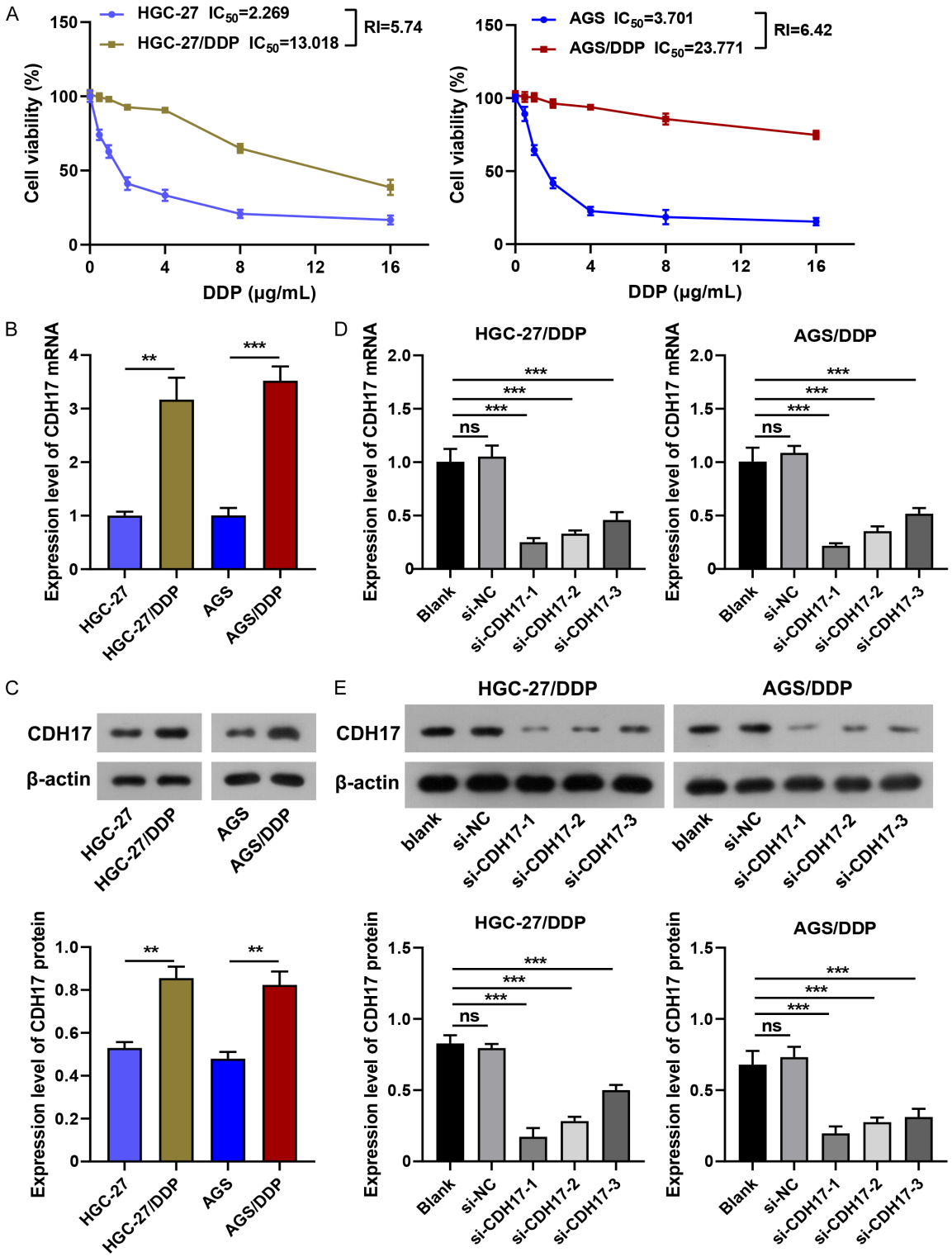


Figure 1. CDH17 is highly expressed in DDP-resistant GC cells. A. Cell viability was assessed by MTT assay in cisplatin (DDP)-resistant cells (HGC-27/DDP and AGS/DDP) and parental cells (HGC-27 and AGS) treated with varying concentrations (0, 0.5, 1, 2, 4, 8, and 16 μg/mL) of DDP for 24 h. IC_{50} values and resistance indices (RI) were calculated. B, C. qRT-PCR and Western blot analyses were performed to quantify CDH17 mRNA and protein expression in DDP-resistant cells (HGC-27/DDP and AGS/DDP) and parental cells (HGC-27 and AGS). D, E. After transfection with si-CDH17 and si-NC, CDH17 mRNA and protein expression levels were determined using qRT-PCR and Western blot analysis in DDP-resistant GC cells. Note: IC_{50}: half-maximal inhibitory concentration; RI: resistance index. ns: not significant; $^{**}P < 0.01$, $^{***}P < 0.001$.

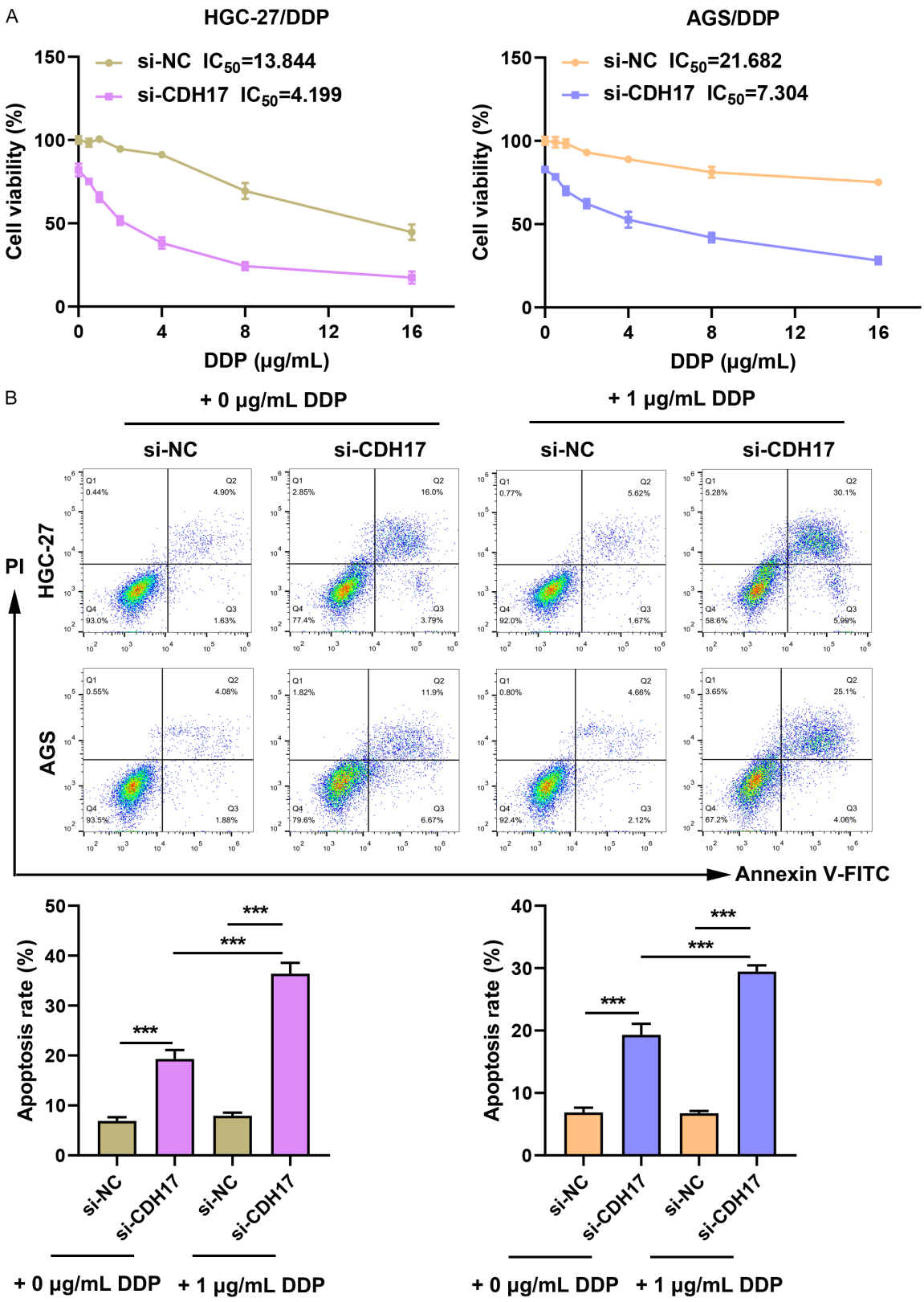


Figure 2. Silencing CDH17 reversed DDP resistance in GC cells. A. Cell viability of DDP-resistant GC cells transfected with si-CDH17 or si-NC was assessed using the MTT assay. B. Apoptosis was evaluated by Flow cytometry in DDP-resistant cells treated with or without 1 μg/mL DDP for 24 h. Note: PI: propidium iodide. ***$P < 0.001$.

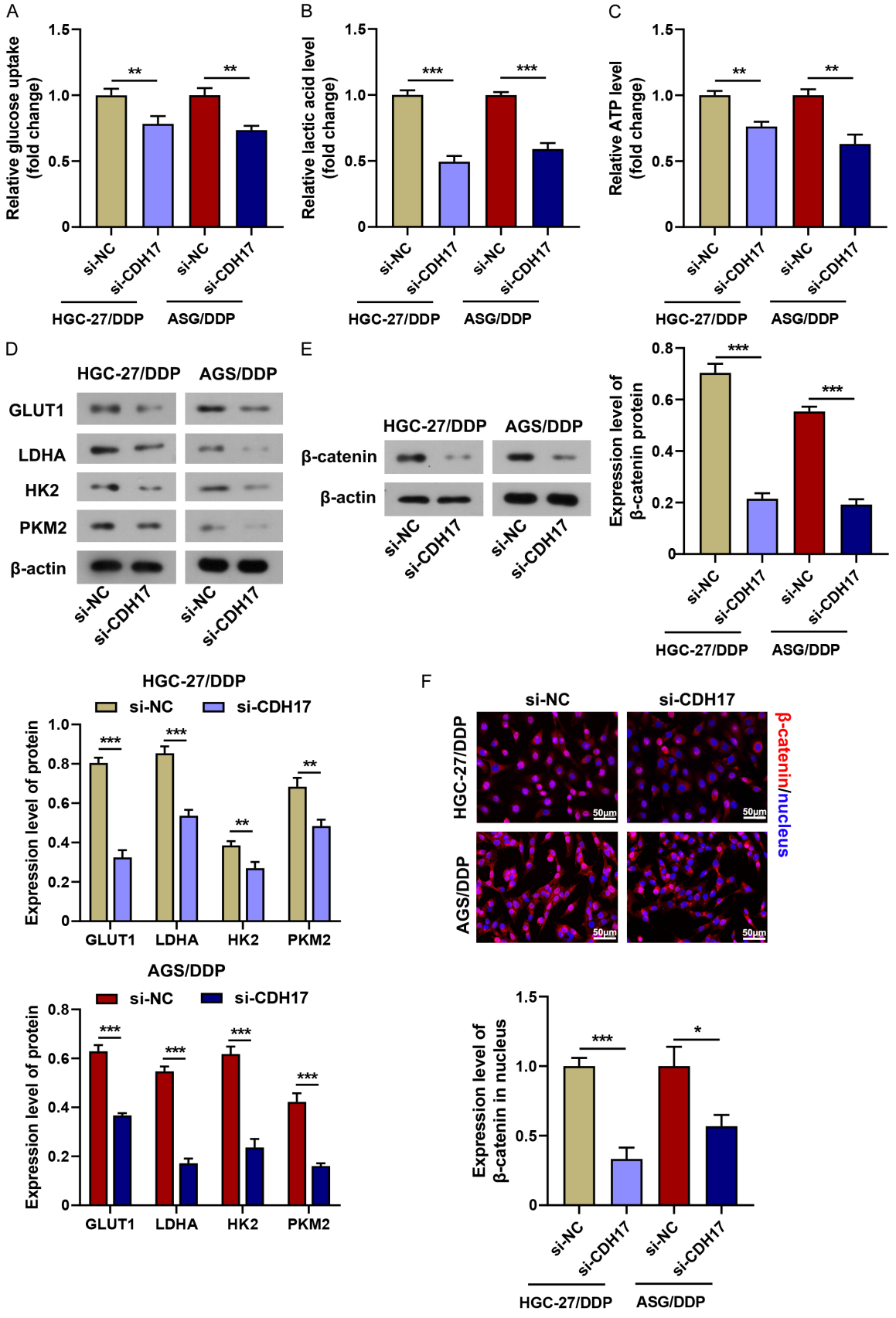

A
Relative glucose uptake (fold change)
B
Relative lactic acid level (fold change)
C
Relative ATP level (fold change)
si-NC
si-CDH17
HGC-27/DDP
ASG/DDP
D
HGC-27/DDP
AGS/DDP
GLUT1
LDHA
HK2
PKM2
β-actin
E
β-catenin
Expression level of β-catenin protein
F
si-NC
si-CDH17
HGC-27/DDP
AGS/DDP
β-catenin/nucleus
50μm
Expression level of protein
Expression level of β-catenin in nucleus

Figure 3. Silencing CDH17 suppressed the Warburg effect and inhibited Wnt/β-catenin signaling in DDP-resistant GC cells. (A-C) After transfection with si-CDH17 or si-NC, the glucose uptake (A), lactate production (B), and adenosine triphosphate (ATP) (C) levels were measured in DDP-resistant GC cells. (D, E) Protein expression of glucose transporter 1 (GLUT1), lactate dehydrogenase A (LDHA), hexokinase II (HK2), pyruvate kinase M2 isoform (PKM2), and β-catenin in the DDP-resistant GC cells was assessed using Western blot. (F) Subcellular localization and expression of β-catenin in DDP-resistant GC cells were examined using immunofluorescence staining (400×). Note: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

were significantly reduced in both HGC-27/DDP and AGS/DDP cells (**Figure 3A-C**). Consistently, the expression levels of glycolysis-related proteins, including GLUT1, LDHA, HK2, and PKM2, were markedly decreased (**Figure 3D**). Notably, β-catenin expression was also downregulated in these cells, with a pronounced reduction in its nuclear accumulation (**Figure 3E**, **3F**). These findings suggest that CDH17 silencing suppressed the Warburg effect and attenuated the activation of the Wnt/β-catenin signaling pathway in DDP-resistant GC cells. Given the established role of Wnt/β-catenin signaling in regulating glycolysis in cancer cells [26, 38], we hypothesized that CDH17 may influence the Warburg effect in DDP-resistant cells through the modulation of this pathway.

CDH17 knockdown suppressed the Warburg effect in DDP-resistant GC cells by blocking the Wnt/β-catenin pathway

To validate this hypothesis, DDP-resistant GC cells were treated with CP21R7, a Wnt/β-catenin signaling pathway agonist, for a gain-of-function analysis. CDH17 knockdown significantly reduced the viability of both HGC-27/DDP and AGS/DDP cells, whereas CP21R7 treatment increased viability. Furthermore, CP21R7 partially counteracted the inhibitory effect of CDH17 knockdown on the proliferation of DDP-resistant GC cells (**Figure 4A**). In addition, CP21R7 treatment increased glucose uptake, lactate production, and ATP synthesis in both HGC-27/DDP and AGS/DDP cells (**Figure 4B-D**), while upregulating the expression of β-catenin, GLUT1, LDHA, HK2, and PKM2. Further, co-treatment with CP21R7 partially attenuated the inhibitory effect of CDH17 silencing on the Warburg effect in DDP-resistant GC cells (**Figure 4E**). Collectively, these findings indicate that CDH17 silencing suppresses the Warburg effect in DDP-resistant GC cells through blocking Wnt/β-catenin signaling pathway.

Activating the Wnt/β-catenin pathway counteracted the effect of CDH17 silencing on DDP resistance

The Warburg effect has been shown to contribute to chemoresistance in cancer cells [39-41]. In this study, treatment of DDP-resistant GC cells with 2-DG, a Warburg effector inhibitor, reduced the IC_{50} of DDP, increased apoptosis, and upregulated the expression of Cleaved-caspase-3 (**Figures 5**, **6**). These findings confirmed that inhibition of the Warburg effect can reverse drug resistance in DDP-resistant GC cells. Based on these findings, we hypothesized that the sensitizing effect of CDH17 silencing involves suppression of the Warburg effect through regulation of the Wnt/β-catenin signaling pathway. Consistent with this hypothesis, combined treatment with CP21R7, an agonist of the Wnt/β-catenin signaling pathway, increased the IC_{50} of DDP in both HGC-27/DDP and AGS/DDP cells compared to CDH17 silencing alone (**Figure 5**), reduced apoptosis (**Figure 6A**), and downregulated the expression of Cleaved-caspase-3 protein (**Figure 6B**). These findings indicate that activation of Wnt/β-catenin signaling attenuates the sensitizing effect of CDH17 silencing on DDP-resistant GC cells, thereby reducing their drug sensitivity.

Discussion

While many chemotherapeutic agents, such as DDP and 5-fluorouracil, have demonstrated favorable efficacy in combination therapy for early-stage GC following surgical resection [42, 43], the emergence of drug resistance often leads to treatment failure. Therefore, strategies to delay or reverse chemoresistance are therefore critical to improving the prognosis of GC patients. In this study, we demonstrated that CDH17 contributes to the development of chemoresistance in GC cells through the regulation of the Warburg effect. Functional gain- and loss-of-function experiments confirmed that silencing CDH17 reversed DDP resistance in

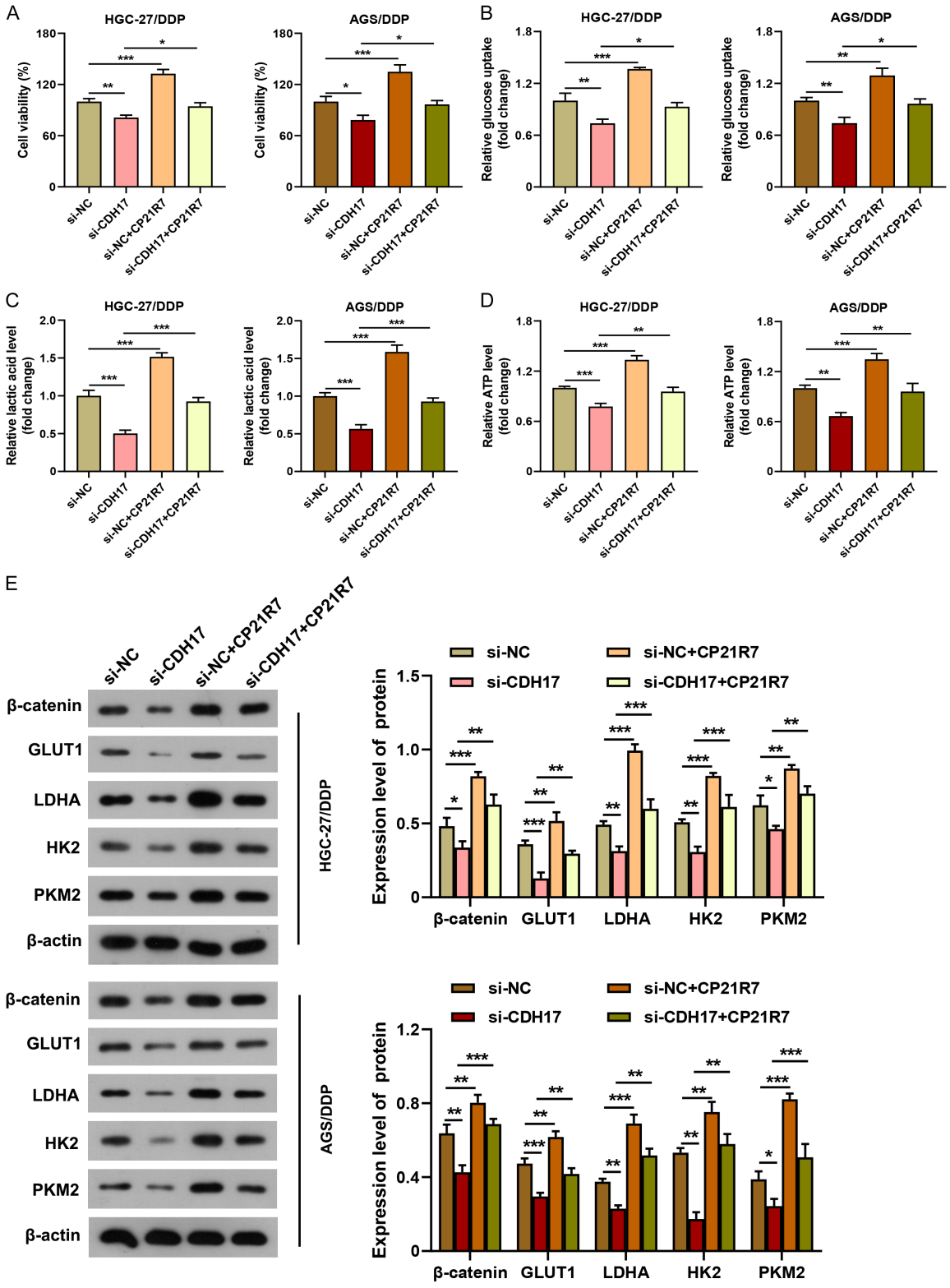


Figure 4. The Wnt/β-catenin agonist CP21R7 reversed the inhibitory effect of CDH17 silencing on the Warburg effect in DDP-resistant GC cells. After transfection with si-CDH17 and si-NC, HGC-27/DDP and AGS/DDP cells were treated with 5 μM CP21R7 for 24 h. (A) Cell viability of DDP-resistant GC cells was assessed using the MTT assay. (B-D) Glucose uptake (B), lactate production (C), and ATP synthesis (D) in the DDP-resistant GC cells were quantified. (E) Protein expression of β-catenin, GLUT1, LDHA, HK2, and PKM2 were determined using Western blot analysis. Note: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

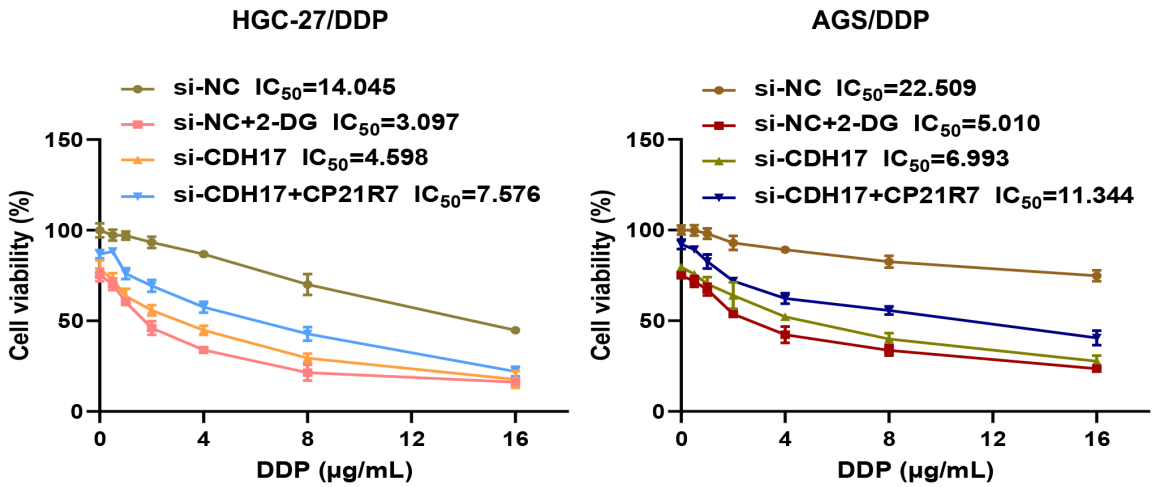


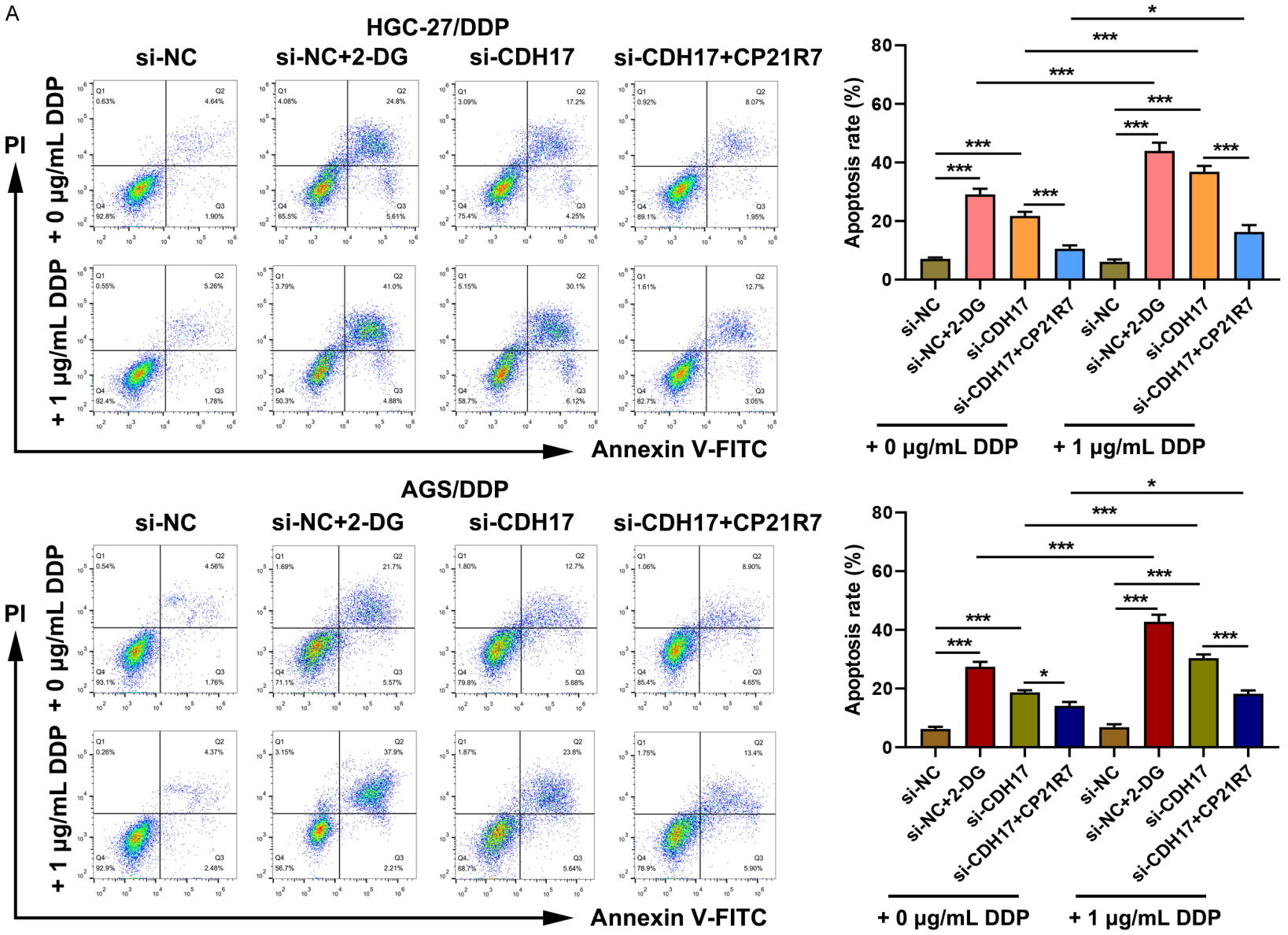
Figure 5. The Wnt/β-catenin agonist CP21R7 reversed the sensitizing effect of CDH17 silencing in DDP-resistant GC cells. After transfection with si-CDH17 and si-NC, HGC-27/DDP and AGS/DDP cells were exposed to 5 μM CP21R7 or 10 mM 2-DG for 24 h. Cell viability was assessed using the MTT assay to calculate the IC_{50} value of DDP.

GC cells, an effect associated with suppression of the Warburg effect through inhibition of Wnt/β-catenin signaling. These findings may offer potential therapeutic targets for overcoming clinical chemoresistance in GC patients.

The aberrant expression of CDH17 and its associated tumor-promoting functions in GC have garnered increasing interest from the research community in recent years. Clinical evidence shows that CDH17 levels are markedly elevated in the plasma of patients with stage II-III GC [44]. Furthermore, high CDH17 expression in GC tissues is correlated with lymph node metastasis and advanced clinical stages [30, 45]. Experimental studies have confirmed that CDH17 knockdown can suppress GC cell proliferation, metastasis, and tumorigenicity, while promoting apoptosis [46-48]. Therefore, CDH17 has been considered a promising diagnostic and therapeutic target in GC. Evidence also suggests that silencing CDH17 enhances the sensitivity of GC cells to DDP [49]. However, its precise role in chemoresistance remains unclear. In this study, we revealed that CDH17 expression was significantly upregulated in DDP-resistant GC cells, and suppression of CDH17 expression increased their sensitivity to DDP, suggesting that CDH17 may play a pivotal role in the development of DDP resistance in GC cells.

GLUT1 is the primary transporter responsible for glucose uptake in cancer cells, mediating glucose uptake from the extracellular to the intracellular environment [50]. Its high expression in tumors meets the increased glucose demand of the rapidly proliferating cancer cells [51]. HK2 is the first rate-limiting enzyme of glycolysis, catalyzing the phosphorylation of glucose to glucose-6-phosphate [52]. PKM2 functions in the final step of glycolysis, converting phosphoenolpyruvate to pyruvate, which leads to ATP production [53]. LDHA facilitates the reduction of pyruvate to lactate while simultaneously oxidizing NADH, thereby sustaining glycolytic flux [54]. Collectively, during the Warburg effect, GLUT1 and HK2 facilitate glucose uptake and utilization, PKM2 regulates metabolic flux, and LDHA sustains glycolysis and contributes to microenvironment acidification. Therefore, these enzymes represent critical therapeutic targets, and inhibition of GLUT1 [55], HK2 [56], PKM2 [57], or LDHA [58] has been proposed as a promising therapeutic strategy for GC.

These proteins constitute a central axis of tumor-associated aerobic glycolysis, supplying energy and promoting tumor progression, metastasis, and chemoresistance through metabolic reprogramming [13, 14]. The Warburg effect plays a significant role in the development of chemoresistance in GC, involving multiple mechanisms. Cancer cells utilize glycolysis as a primary source of energy, which reduces their reliance on mitochondrial oxidative phosphorylation, thereby avoiding chemo-


A
HGC-27/DDP
si-NC
si-NC+2-DG
si-CDH17
si-CDH17+CP21R7
PI
+ 0 μg/mL DDP
+ 1 μg/mL DDP
Annexin V-FITC
Apoptosis rate (%)
+ 0 μg/mL DDP
+ 1 μg/mL DDP
AGS/DDP
si-NC
si-NC+2-DG
si-CDH17
si-CDH17+CP21R7
PI
+ 0 μg/mL DDP
+ 1 μg/mL DDP
Annexin V-FITC
Apoptosis rate (%)
+ 0 μg/mL DDP
+ 1 μg/mL DDP

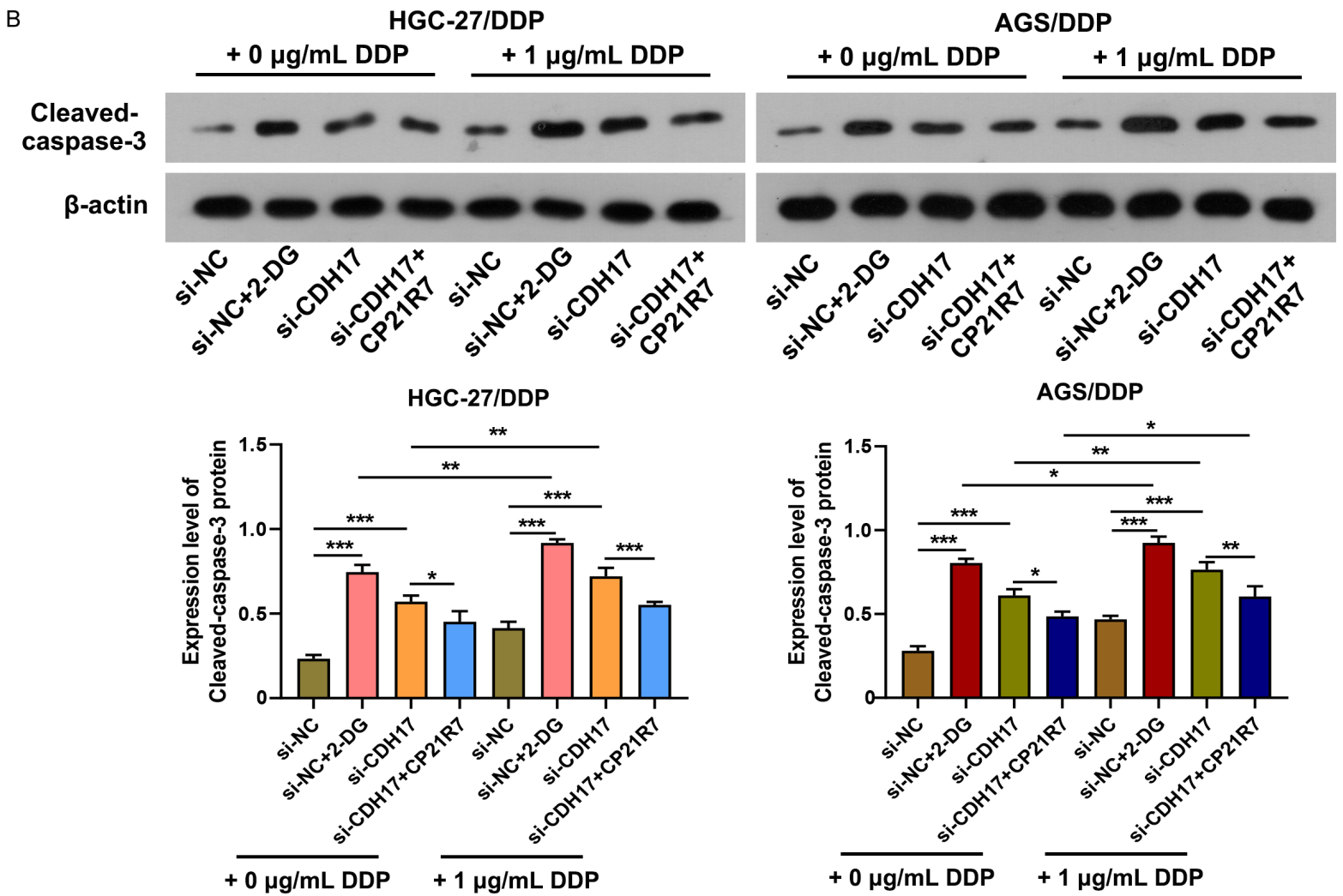


Figure 6. The Wnt/β-catenin agonist CP21R7 reversed the pro-apoptotic effect of CDH17 silencing in DDP-resistant GC cells. DDP-resistant GC cells were treated with or without 1 μg/mL DDP for 24 h. A. Apoptosis was evaluated by flow cytometry. B. Protein expression of cleaved-caspase-3 was determined using Western blot. Note: **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

therapy-induced mitochondrial apoptosis [59]. In addition, the Warburg effect contributes to reduced cancer apoptosis by sustaining NADPH production to mitigate the oxidative stress induced by chemotherapy drugs [60]. Moreover, glycolysis-induced acidification of the tumor microenvironment [61] and promotion of immune escape processes [62] contribute to treatment resistance.

In the present study, Warburg effect inhibitor 2-DG increased the sensitivity of DDP-resistant GC cells to DDP. CDH17-knockdown reduced glucose uptake, ATP synthesis, and lactate production in the DDP-resistant GC cells, accompanied by decreased expression of key glycolytic proteins including GLUT1, LDHA, HK2, and PKM2. These findings suggest that CDH17 silencing may enhance the chemosensitivity of DDP-resistant GC cells by suppressing Warburg effect. Nevertheless, further research is needed to elucidate the underlying regulatory mechanisms linking CDH17 to metabolic reprogramming in GC.

It was observed that CDH17 knockdown significantly downregulated β-catenin expression and reduced its nuclear accumulation in DDP-resistant GC cells. β-catenin is a key effector of the Wnt/β-catenin signaling pathway. In the absence of Wnt signals, β-catenin is phosphorylated and subsequently degraded through ubiquitination, maintaining its low cytoplasmic levels and preventing its nuclear translocation. Upon pathway activation, β-catenin escapes degradation, accumulates in the cytoplasm, and subsequently translocates into the nucleus, where it activates transcription of downstream target genes [63]. In GC cells, CDH17 silencing reduces β-catenin expression and thereby inactivates the Wnt/β-catenin signaling pathway [33, 64]. Studies have shown that this pathway is involved in regulating the Warburg effect in cancer cells [26, 65]. In this study, CP21R7, a Wnt/β-catenin signaling agonist, reversed the inhibitory effects of CDH17 silencing, restoring glycolysis and the expression of Warburg-associated proteins in DDP-resistant GC cells. More importantly, CP21R7 partially counteracted the sensitizing effect of CDH17 silencing on DDP treatment. These findings suggest that CDH17 promotes chemoresistance in GC by modulating the Warburg effect through Wnt/β-catenin signaling.

Conclusion

This study demonstrated that CDH17 contributes to cisplatin chemoresistance in GC cells by regulating the Warburg effect via the Wnt/β-catenin pathway. Silencing CDH17 suppressed glycolysis and reversed DDP resistance, highlighting CDH17 as a potential therapeutic target for overcoming chemoresistance in GC. This approach may serve as an adjunctive strategy to enhance the efficacy of chemotherapy in the treatment of GC.

The major limitation of this study is the lack of *in vivo* validation. Future research should incorporate animal models to confirm the role of CDH17 in chemoresistance and further delineate the downstream molecular mechanisms linking CDH17, Wnt/β-catenin signaling, and metabolic reprogramming. Such investigations will provide a more solid foundation for the potential clinical application of CDH17-targeted strategies to overcome chemotherapy resistance in GC.

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Disclosure of conflict of interest

None.

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