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RESEARCH PAPER

HCP5 contributes to cisplatin resistance in gastric cancer through miR-128/HMGA2 axis

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ABSTRACT

The long non-coding RNA HLA complex P5 (HCP5) is extensively related to cancer chemoresistance, while its function in gastric cancer (GC) has not been well elucidated yet. Here, the role and mechanism of HCP5 in regulating the chemoresistance of GC to cisplatin (DDP) was investigated. Our results revealed that HCP5 was increased in GC patients and indicated a poor prognosis. HCP5 knockdown weakens DDP resistance and reduced apoptosis of GC cells. miR-128 was decreased in GC patients and sponged by HCP5. HMGA2 was targeted by miR-128 and was increased in GC patients. HCP5 aggravated the resistance of GC cells to DDP in vitro by elevating HMGA2 expression via sponging miR-128. HCP5 silencing inhibited GC cells growth, resistance to DDP, and Ki-67 expression *in vivo*. In summary, HCP5 contributed to DDP resistance in GC cells through miR-128/HMGA2 axis, providing a promising therapeutic target for GC chemoresistance.

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KEYWORDS
lncRNA HCP5; gastric cancer; DDP; miR-128; HMGA2

1. Introduction

Gastric cancer (GC) is the fourth most common malignancy with the second highest lethality around the world [1]. Following the latest worldwide cancer statistics, the deaths due to GC are up to 782,685 in 2018, taking up 8.2% among all cancer deceases in that year [2]. For GC patients at an early stage, surgical resection treatment is the first choice. However, a combination of surgical resection and chemotherapy and radiotherapy is utilized for patients with advanced-stage GC frequently [3,4]. The therapy effect of GC is usually unpleasant due to its metastasis rate and high recurrence [5]. Therefore, deeper exploration of the molecular mechanism of GC tumorigenesis is greatly urgent to improve the therapeutic outcomes.

Long non-coding RNAs (lncRNAs) are a category of non-protein-coding RNAs, with exceeding 200 nucleotides in length, the dysregulation of which have been involved in tumor formation and development [6,7]. Mounting lncRNAs have been reported to contribute to cancer diagnosis and drug resistance [8–11]. LncRNA HLA complex P5 (HCP5) has been reported to advance the development, metastasis, and drug resistance in diverse cancers, including lung cancer, pancreatic cancer, and breast cancer [12–14]. However, the mechanism and role of HCP5 in the DDP resistance of GC cells is still elusive.

MicroRNAs (miRNAs) are small non-coding RNAs with 19–24 nucleotides, participating in gene expression regulation at the post-transcriptional level [15,16]. In addition, an enormous amount of research shows that miRNAs become essential regulators in cellular processes, including tumorigenesis and chemoresistance [17]. miR-128 has been uncovered to act as a tumor suppressor in GC [18] and sensitize ovarian cancer cells to DDP [19]. Additionally, HMGA2 could confer DDP resistance in various tumors [20,21]. The bioinformatics analysis predicted HCP5 and HMGA2 could be targeted via miR-128. We therefore hypothesized that HCP5 might take part in DDP resistance via regulating miR-128 and HMGA2.

In this work, lncRNA HCP5's functional role in DDP-resistant cells was determined. Moreover, we investigated the potential ceRNA mechanism of HCP5/miR-128/HMGA2.

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Supplemental data for this article can be accessed here

2. Materials and methods

2.1. Sample collection

Tumor (n = 36) and adjacent normal (n = 36) tissues were collected from GC patients who suffered surgery at First Hospital of Shanxi Medical University. All subjects have provided the written informed consent, and this work was approved via the ethics committee of First Hospital of Shanxi Medical University.

2.2. Cell culture and transfection

Human fetal gastric epithelial cells (GES-1) from the American Type Culture Collection (ATCC; Rockville, MD, USA) and GC cell lines (SNU-1 and MKN-45) from Shanghai Cell Bank and DDP resistant SNU-1/DDP and MKN-45/DDP cells were cultured in DMEM (Gibco, Grand Island, USA) containing 10% FBS (HyClone, Logan, USA) in an incubator at 37°C with 5% CO_2.

To silence lncRNA HCP5, small interfering RNA specifically against it (si-HCP5#1, si-HCP5#2) and si-con were designed by GenePharma (Shanghai, China). miR-128 mimic (miR-128), miR-con, and miR-128 inhibitor (anti-miR-128) were purchased from GenePharma. The HCP5 or HMGA2 sequence was inserted into the pcDNA-3.1 vector (Invitrogen, Carlsbad, CA, USA) to synthesize pcDNA-HCP5 (oe-HCP5) or pcDNA-HMGA2 (oe-HMGA2). Cell transfection was executed utilizing Lipofectamine 2000 (Invitrogen) following the instructions.

2.3. Quantitative real-time PCR (qRT-PCR)

Total RNA extraction was conducted utilizing TRIzol Reagent (Beyotime, Shanghai, China). Afterward, 1 μg was reverse-transcribed into cDNA with the PrimeScript-RT Kit (Madison, WI, USA), and then the SYBR® Premix-Ex-Taq™ (Takara, TX, USA) and ABI7300 system were utilized to carry out PCR. The relative expression levels were computed using $2^{-\Delta\Delta Ct}$ quantification method, normalized to U6 for miRNA or GAPDH for mRNA.

2.4. Drug sensitivity assay

The GC cells were seeded in 96-well plates, followed by treatment with different doses of DDP (0.1, 1, 5, 10, 20, 40, 80, 160 μM). The cells were incubated with CCK-8 solution (Beyotime) for 2 h and then checked for the absorbance at 450 nm utilizing a microplate reader.

2.5. Flow cytometry

For cell apoptosis analysis, the present assay was executed with Annexin V-FITC/PI Apoptosis Detection Kit (KeyGEN Biotech, Nanjing, China). Briefly, cells were harvested after transfection. Then, 5 μL Annexin V-FITC and 5 μL PI were added to stain the cells in the dark place for 15 min. Finally, apoptotic cells were determined using a flow cytometer.

2.6. Luciferase reporter assay

The partial sequence of HCP5 or HMGA2 3'UTR containing binding sites with miR-128 was inserted into pGL3 luciferase promoter vector (Promega, Madison, WI, USA) to generate wild-type luciferase reporter plasmid HCP5-WT or 3'UTR of HMGA2-WT. The mutant-type reporters were synthesized using Quick Change Site-Directed Mutagenesis kit (Agilent Technologies, Santa Clara, CA, USA). Later, constructed vectors and miR-con or miR-128 were co-transfected into SNU-1/DDP and MKN-45/DDP cells, respectively. 48 h later, luciferase density was determined using a dual luciferase assay system kit (Promega).

2.7. Xenograft model

Nude mice (n = 20, 4–5 weeks old) were provided by Slac Laboratory (Shanghai, China). Animal experiments have been approved by the animal ethics committee of First Hospital of Shanxi Medical University. Mice were randomly divided into 4 groups: sh-con + PBS group, sh-con + DDP group, sh-HCP5 + PBS group and sh-HCP5 + DDP group. There were 5 nude mice in each group. SNU-1/DDP cells transfected by HCP5 sh-

con were injected subcutaneously into the dorsal flanks of mice in sh-con + PBS group and sh-con + DDP group. SNU-1/DDP cells transfected by HCP5 shRNA were injected into the dorsal flanks of mice in sh-HCP5 + PBS group and sh-HCP5 + DDP group. Then, the mice were given an intraperitoneal injection of DDP (5 mg/kg) in sh-con + DDP group and sh-HCP5 + DDP group or equal volume of PBS in sh-con + PBS group and sh-HCP5 + PBS group every day. The tumor size was measured every 7 days. The xenograft tumor volume was calculated with the following formula: tumor volume = 0.5 * tumor width^2 * length. On 28th day, mice were killed by rapid neck dislocation and subcutaneous xenograft tumor was then obtained and weighed.

2.8. Immunohistochemical staining

Paraffin sections of xenograft tumors were dewaxing to water in xylene and descending series of ethanol. We penetrated sections using 0.5% Triton X-100. After 3 times wash, we blocked sections with 50% goat serum. The sections were then incubated with Mouse anti-human Ki-67 monoclonal antibody (Cell Signaling Technology, Danvers, MA, USA) overnight. We incubated the sections using secondary antibody followed by diaminobenzidine (DAB) solution and hematoxylin staining. The sections were photographed by light scope under an IX73 fluorescence microscope (Olympus, Valley, PA) and analyzed by Image J software.

2.9. Statistical analysis

All data were derived from at least 3threebiological repetitions and were exhibited as mean ± SD. Difference analysis was determined by t-test for two groups or one-way ANOVA for 3 or more groups. When P value < 0.05, it was deemed significant.

3. Results

3.1. HCP5 was overexpressed in DDP-resistant GC tissues and cells

To investigate HCP5's functional role in GC, analysis of the normalized RNA-seq data of Stomach Adenocarcinoma (STAD) from TCGA revealed that HCP5 was remarkably increased in GC tumor tissues compared with normal tissues (Figure 1(a)). qRT-PCR analysis further confirmed that lncRNA HCP5 was increased in GC tumor tissues as compared to their adjacent normal tissues in our clinical specimens (Figure 1(b)). Moreover, the expression of HCP5 was greatly higher in the GC tissues of DDP-resistant patients than that in the GC tissues of DDP-sensitive patients (Figure 1(c)). Similarly, the same upregulation trends were discovered in DDP-resistant GC cell lines (SNU-1/DDP and MKN-45/DDP) (Figure 1(d,e). In addition, we found that the upregulation of HCP5 was positively associated with the shorter overall survival rate in GC patients (Figure 1(f)). Together, HCP5 upregulation may be involved in GC DDP resistance.

3.2. HCP5 silencing re-sensitized DDP-resistant GC cells to DDP

To confirm the chemoresistance of SNU-1/DDP and MKN-45/DDP cells compared to SNU-1 and MKN-45 cells, the cells were treated with increasing doses (0.1, 1, 5, 10, 20, 40, 80, 160 μM) of DDP and then subject to CCK-8 assay. As shown in Figure 2(a,b), SNU-1/DDP and MKN-45/DDP cells had enhanced resistance to DDP relative to SNU-1 and MKN-45 cells, as evidenced by increased cell viability and IC50 of DDP. To analyze the functional role of HCP5 in DDP resistance, SNU-1 and MKN-45 cells were transfected with si-con, si-HCP5#1 or si-HCP5#2. qRT-PCR analysis revealed that the expression of HCP5 was distinctly decreased in si-HCP5 group (Figure 2(c,d). Furthermore, a CCK-8 assay showed that the knockdown of HCP5 sensitized SNU-1/DDP and MKN-45/DDP to DDP, as indicated by reduced IC50 of DDP (Figure 2(e,f)). Besides, HCP5 silencing enhanced the apoptosis of SNU-1/DDP and MKN-45/DDP cells with DDP exposure (Figure 2(g,h). Collectively, the knockdown of HCP5 could enhance the DDP sensitivity of DDP-resistant GC cells.

3.3. HCP5 acts as a sponge of miR-128 in GC cells

LncRNAs were well known to exert regulatory roles through serving as ceRNAs to interact with miRNAs. Here, we searched the target miRNA of

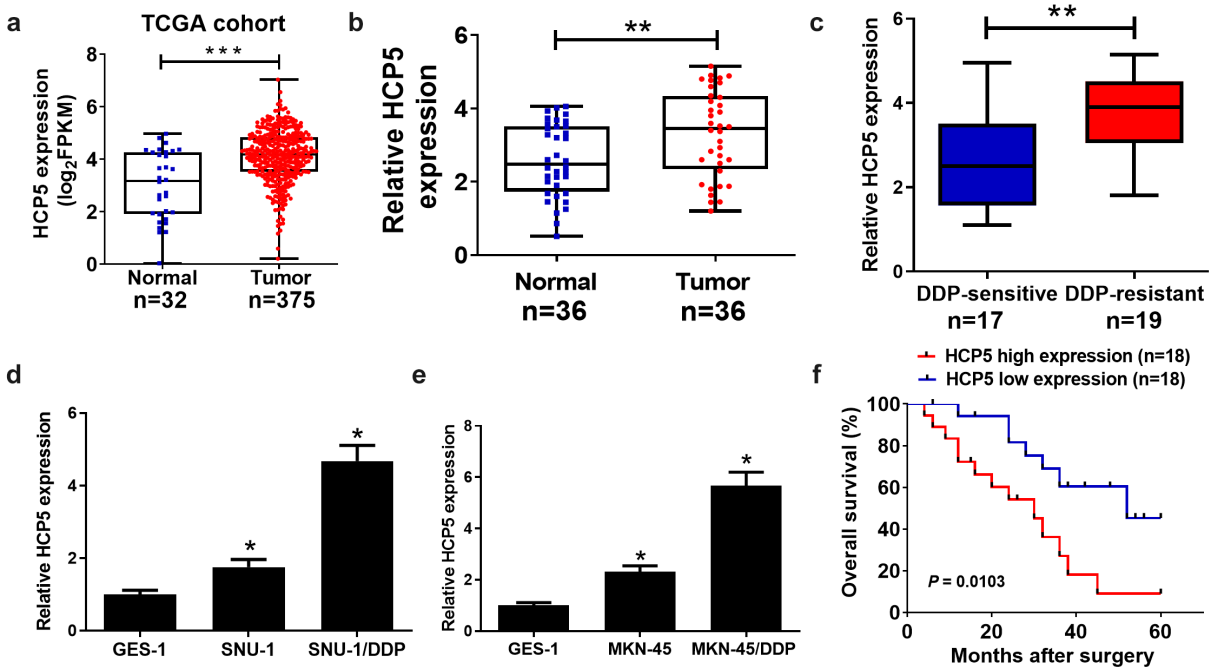

Figure 1. HCP5 was increased in GC tissues and cells. (a) TCGA dataset analysis of HCP5 expression in GC tumor or normal tissues. qRT-PCR was used to determine the expression of HCP5 in GC tumor (n = 36) or adjacent normal (n = 36) tissues (b), DDP-sensitive or DDP-resistant GC tissues (c), and GC cells or normal cell line GES-1 (d,e). Overall survival was evaluated through Kaplan-Meier analysis between low and high HCP5 expression groups in our clinical samples (f). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

HCP5 for better understanding its action mechanism. As forecasted by Starbase 3.0, HCP5 had binding sites with miR-128 (Figure 3(a)). Dual-luciferase reporter assay indicated that miR-128 overexpression obviously reduced the luciferase activity of HCP5-WT, while it had no significant effect on that of HCP5-MUT (Figure 3(b,c). To investigate the effect of HCP5 on miR-128 expression, we transfected SNU-1/DDP and MKN-45/DDP cells with si-HCP5, oe-HCP5 or oe-HCP5-MUT. Our qRT-PCR results indicated that HCP5 expression was dramatically down-regulated by si-HCP5 and remarkably up-regulated by oe-HCP5 or oe-HCP5-MUT (Supplement Figure S1). Additionally, HCP5 overexpression down-regulated miR-128 expression, while HCP5 knockdown increased its expression (Figure 3(d,e)). However, the overexpression of HCP5-MUT did not affect miR-128 expression (Figure 3(d,e)). Afterward, we found miR-128 was down-regulated in GC tissues, especially in DDP-resistant GC tissues (Figure 3(f,g)), and miR-128 expression was negatively correlated with HCP5 expression (Figure 3(h)). In sum, HCP5 could target miR-128 in GC.

3.4. HCP5 knockdown improved the sensitivity of GC cells toward DDP through adsorbing miR-128

To investigate whether HCP5 regulated DDP sensitivity through sponging miR-128, DDP resistant GC cells were transfected with si-HCP5 or si-HCP5+ anti-miR-128, followed by DDP exposure for 48 h. Moreover, qRT-PCR confirmed the success of the transfection (Figure 4(a,b)). Subsequently, CCK-8 assay and flow cytometry results manifested that miR-128 inhibition weakened the promotional effect of si-HCP5 on DDP sensitivity and apoptosis (Figure 4(c,f)–). Taken together, HCP5 knockdown overcame GC DDP resistance through regulating miR-128 expression.

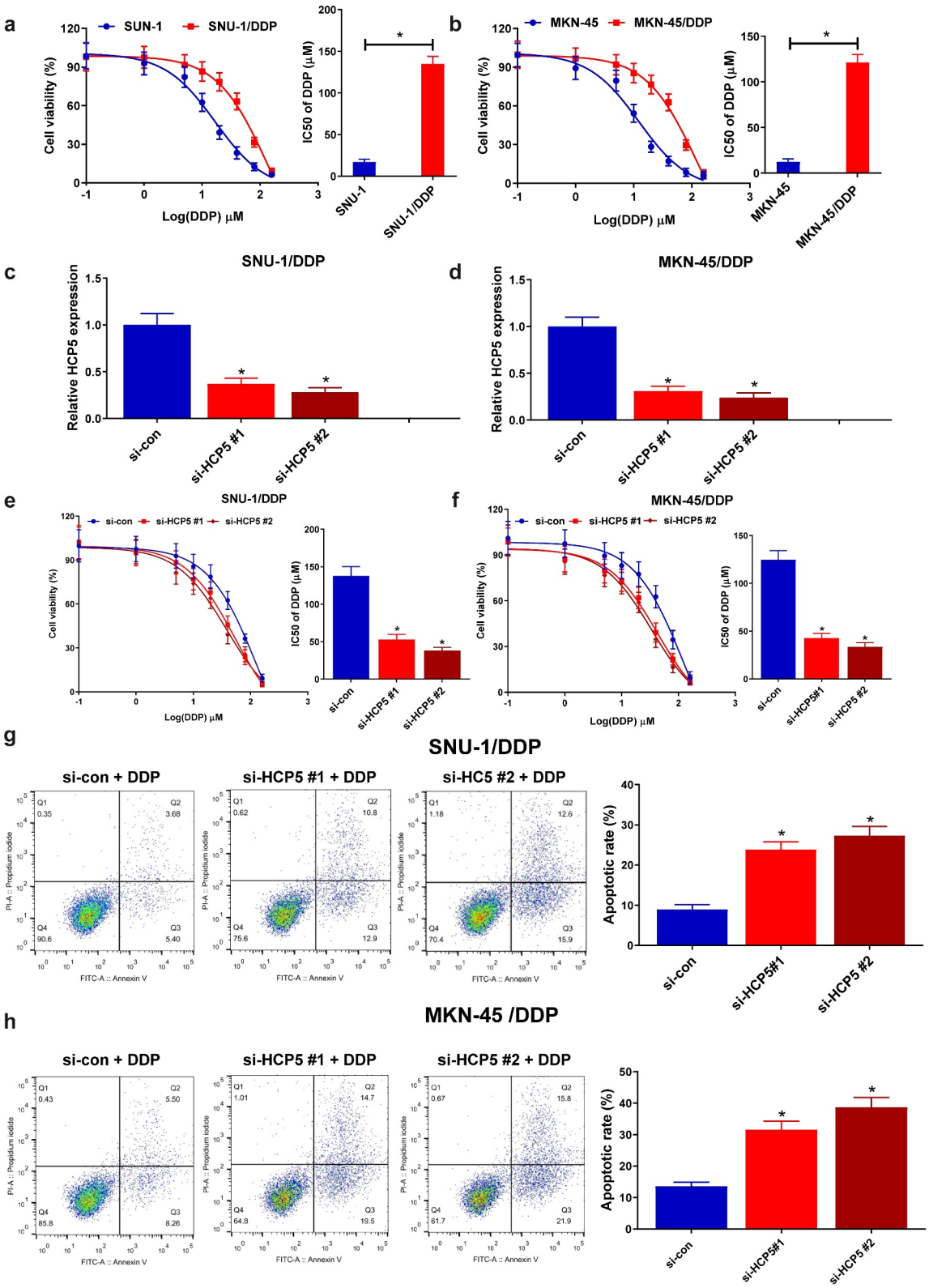

Figure 2. HCP5 knockdown enhanced DDP sensitivity of DDP-resistant GC cells. (a,b) Cell viability was determined by CCK-8 assays in SNU-1/DDP and MKN-45/DDP and SNU-1 and MKN-45 cells treated with different concentrations of DDP (0.1, 1, 5, 10, 20, 40, 80, 160 μM) for 48 h. (c,d) qRT-PCR analysis was carried out in SNU-1/DDP and MKN-45/DDP cells transfected with HCP5 siRNAs (si-HCP5 #1, si-HCP5 #2) or si-con. (e,f) SNU-1/DDP and MKN-45/DDP cells were transfected with si-HCP5 #1, si-HCP5 #2 or si-con and exposed to various doses of DDP (0.1, 1, 5, 10, 20, 40, 80, 160 μM) for 48 h. Cell viability was determined through CCK-8 assays. (g,h) Flow cytometry was performed to determine the apoptotic rate of si-HCP5 #1, si-HCP5 #2 or si-con transfected SNU-1/DDP and MKN-45/DDP cells treated with DDP. *$P < 0.05$.

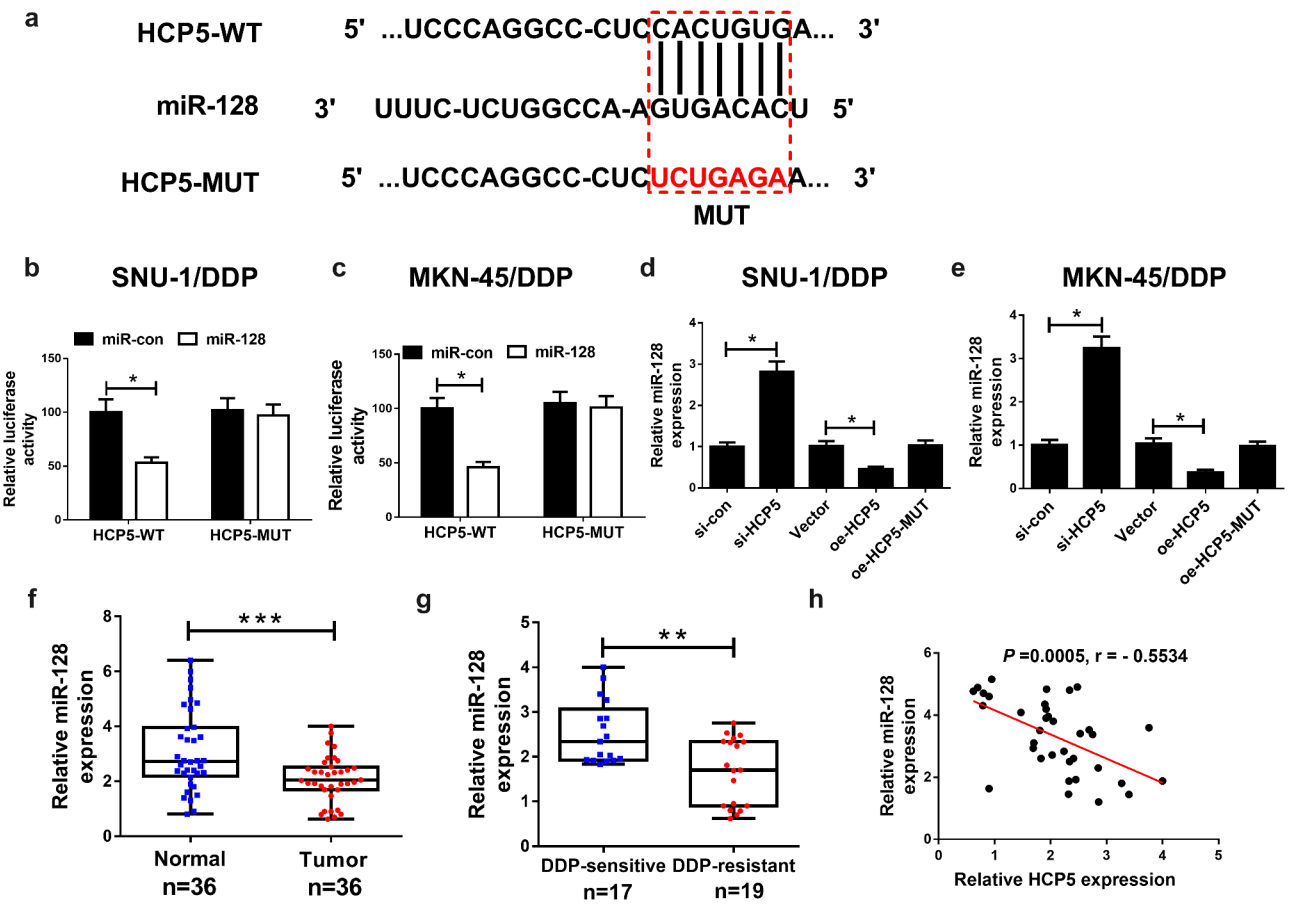

Figure 3. HCP5 acted as a sponge of miR-128 in GC cells. (a) The predicted binding sites between lncRNA HCP5 and miR-128 predicted by Starbase 3.0. (b,c) Dual luciferase reporter assay for the luciferase activity of HCP5-WT and HCP5-MUT in GC cells co-transfected with miR-128 or miR-con. (d,e) qRT-PCR was performed to measure miR-128 expression in GC cells transfected with si-HCP5, oe-HCP5 and oe-HCP5-MUT. qRT-PCR assay detected the expression of miR-128 in GC tissues (f,g), and the correlation between the miR-128 and HCP5 was calculated (h). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

3.5. HCP5 confers DDP resistance in GC cells through regulating miR-128/HMGA2 axis

The public databases Targetscan 7.0, microRNA.org, and miRanda prediction showed the binding site between miR-128 and HMGA2 (Figure 5(a)). Consistently, the luciferase activity of HMGA2-WT vector was dramatically reduced after miR-128 overexpression, which was abolished by upregulation of HCP5. However, no significant change in the luciferase activity of HMGA2-MUT was found in all groups (Figure 5(b,c)). miR-128 overexpression or HCP5 knockdown inhibited HMGA2 expression, while miR-128 inhibition reversed si-HCP5-mediated HMGA2 down-regulation (Figure 5(d,e)). In addition, HMGA2 expression was obviously elevated in GC tissues (Figure 5(f,g,h)) and positively correlated with HCP5 expression in GC samples .To further investigate whether HCP5 affected DDP sensitivity of GC cells through regulating HMGA2 expression, SNU-1/DDP and MKN-45/DDP cells were transfected with si-con, si-HCP5, si-HCP5 + oe-HMGA2. Our qRT-PCR results showed that HCP5 knockdown decreased HMGA2 expression, which could be reversed by oe-HMGA2 transfection (Supplement Figure S2). Additionally, HMGA2 overexpression declined the promotional effect of si-HCP5 on DDP sensitivity and apoptosis (Figure 5(i,l)–). Collectively, HCP5 conferred DDP resistance in GC cells through up-regulating HMGA2 expression by adsorbing miR-128.

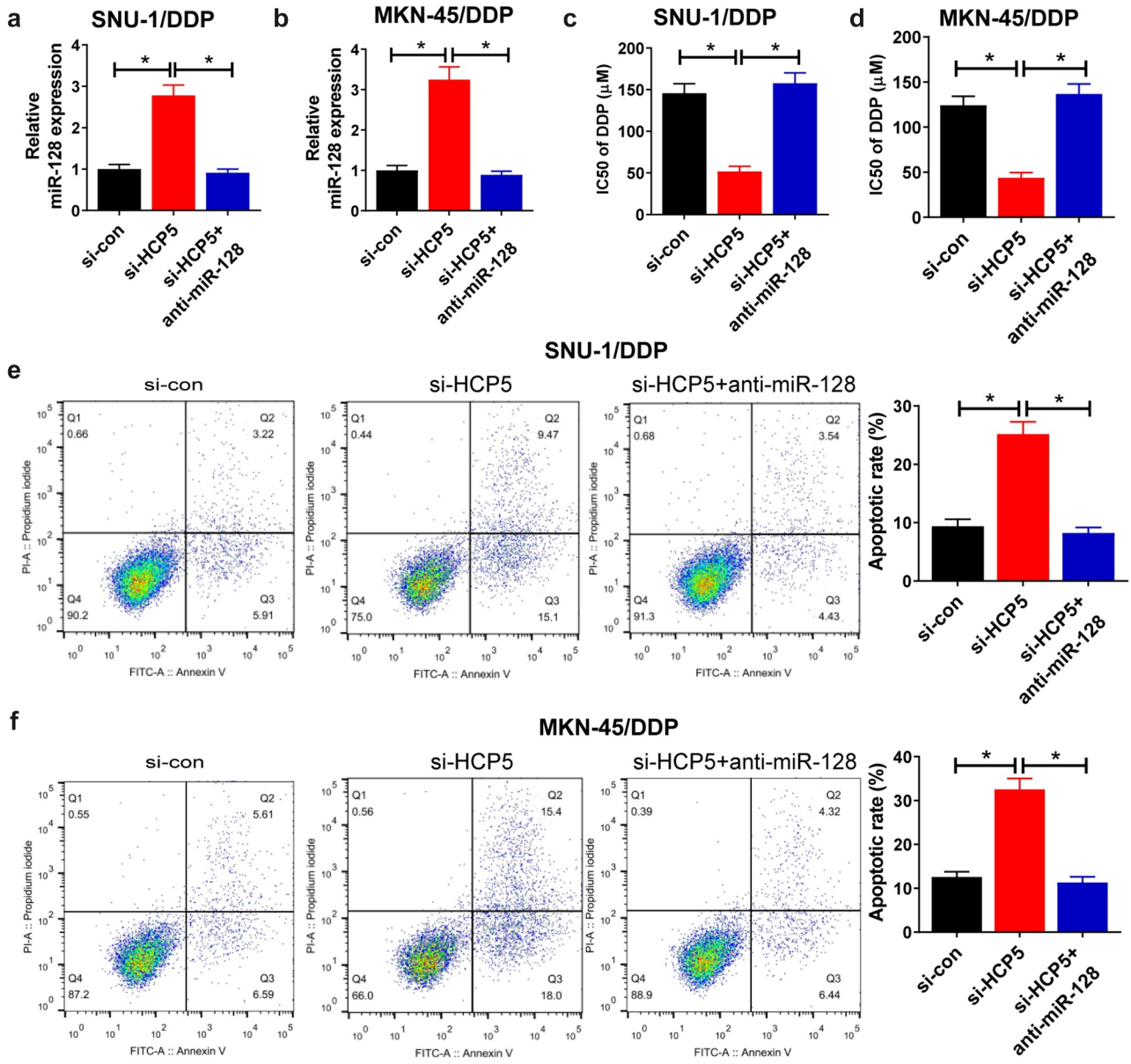

Figure 4. HCP5 knockdown overcame DDP resistance in GC cells through adsorbing miR-128. GC cells (SNU-1/DDP and MKN-45/DDP) were transfected with si-con, si-HCP5 or si-HCP5 + anti-miR-128. (a,b) qRT-PCR assay for the expression of miR-128 in treated cells. CCK-8 assay (c,d) and flow cytometry analysis (e,f) were performed for detecting IC50 of DDP and apoptosis of GC cells after co-transfection. * $P < 0.05$.

3.6. HCP5 knockdown enhances DDP sensitivity in tumors in vivo

The tumorigenicity and sensitivity to DDP of SNU-1/DDP cells was investigated. As shown in Figure 6 (a,b), seriously lower volume and weight of xenograft tumor was found in sh-con + DDP group and sh-HCP5 + PBS group when compared with sh-con + PBS group. At the same time, relative to sh-HCP5 + PBS group, prominently lower xenograft tumor volume and weight was observed in sh-HCP5 + DDP group. Moreover, decreased HMGA2 and increased miR-128 expression was observed after DDP treatment and HCP5 silencing, especially after DDP exposure along with sh-HCP5 treatment (Figure 6(c)). The results of immunohistochemical tests of xenograft tumors showed that the Ki-76 positive cells in sh-con + DDP group and sh-HCP5 group were less than that in the sh-con group. Meanwhile, xenograft tumors of sh-HCP5 + DDP group presented less Ki-76 positive cells than that of sh-HCP5 + PBS group (Figure 6(d)).

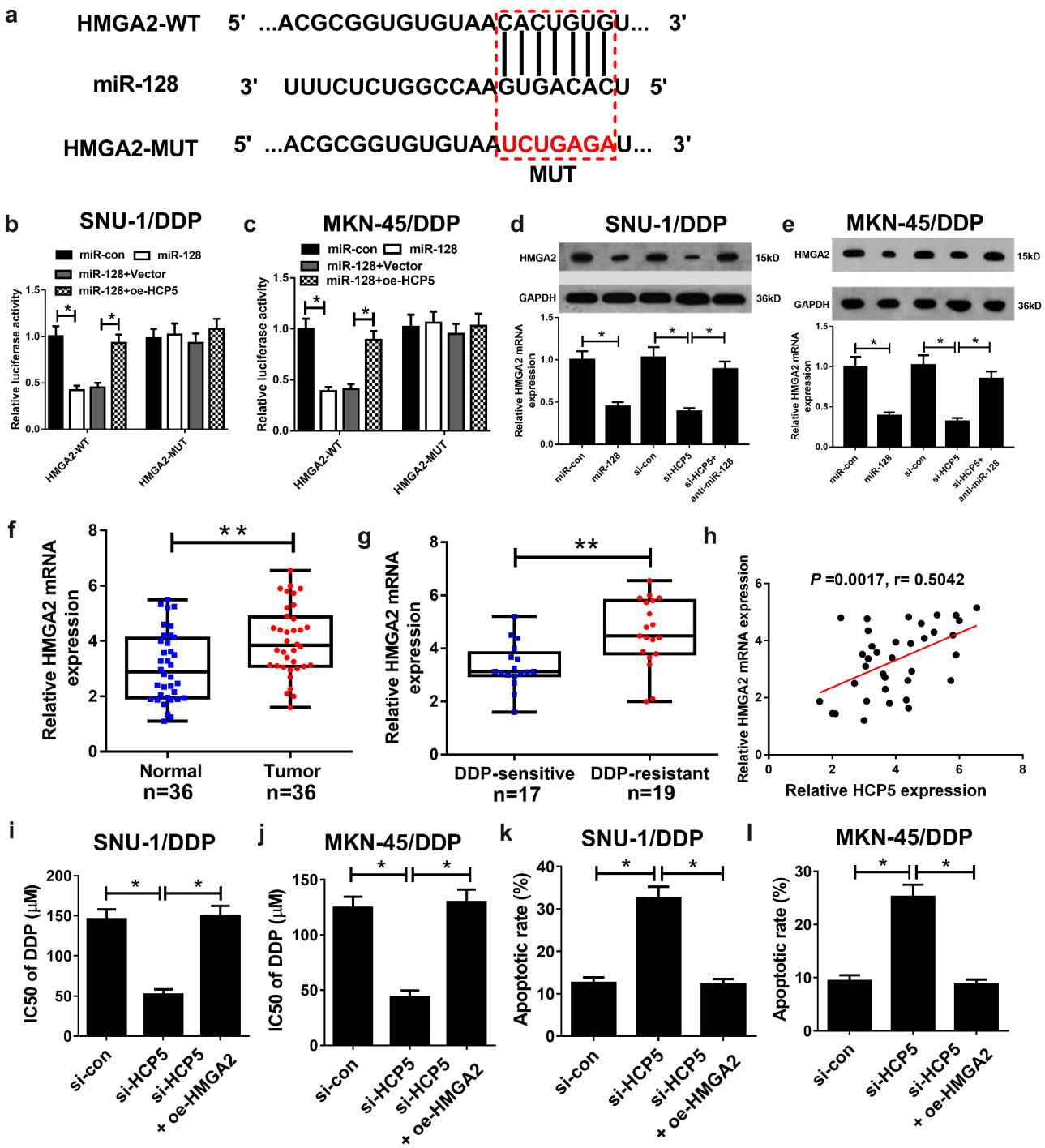

Figure 5. HCP5 conferred DDP resistance in GC cells through miR-128/HMGA2 axis. (a) The predicted binding sites between 3'UTR of HMGA2 and miR-128. (b,c) Dual-luciferase reporter assay for the luciferase activity of 3'UTR of HMGA2-WT and 3'UTR of HMGA2-MUT in GC cells. (d,e) The effect of miR-128, si-HCP5, or si-HCP5 + anti-miR-128 on HMGA2 expression level. qRT-PCR was used to detect HMGA2 expression in GC tissues (f,g), and the correlation between the HMGA2 and HCP5 was calculated (h). CCK-8 assay (i,j) and flow cytometry analysis (k,l) were performed for detecting IC50 of DDP and apoptosis of GC cells after si-HCP5 alone or along with oe-HMGA2 transfection. * $P < 0.05$, ** $P < 0.01$.

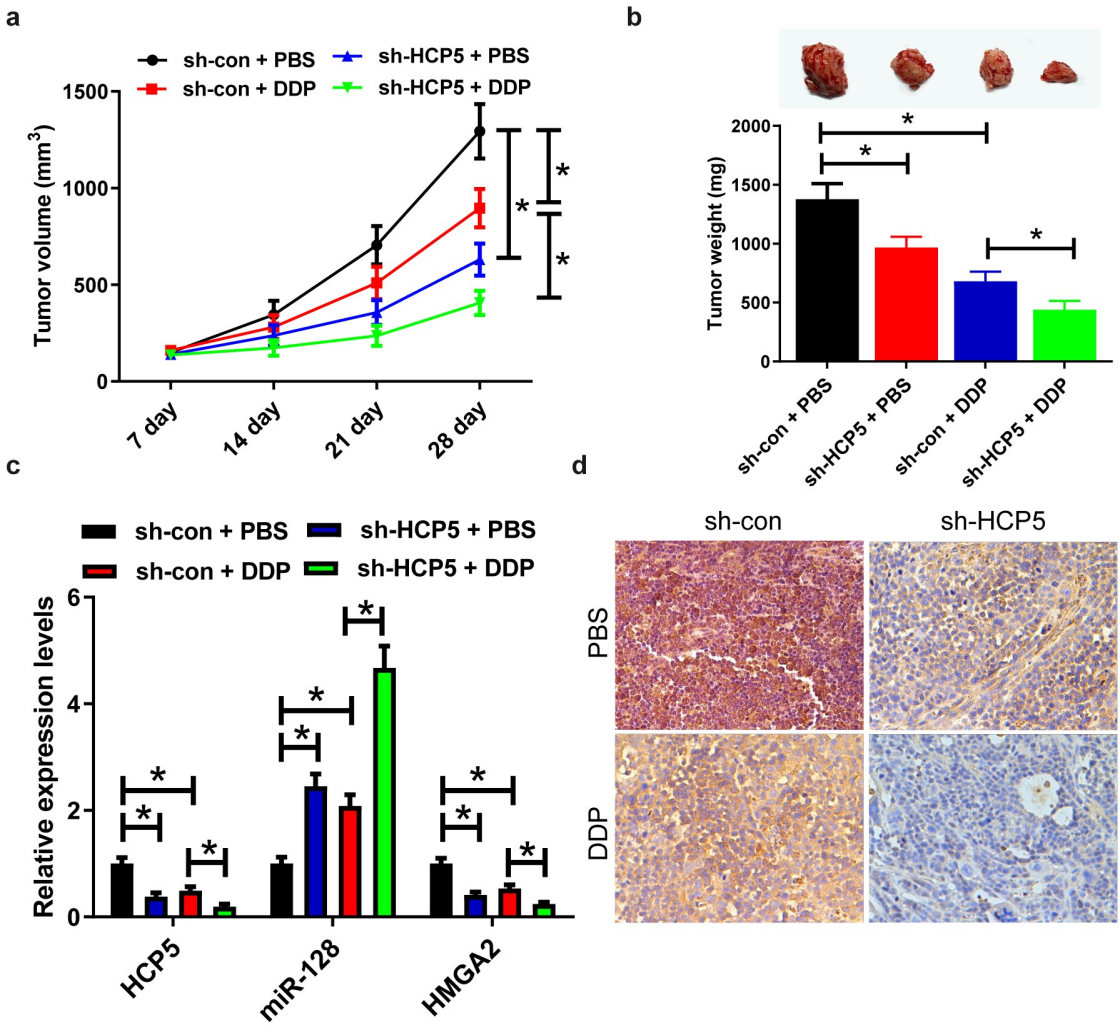

Figure 6. HCP5 knockdown enhanced DDP sensitivity in tumors *in vivo*. (a,b) Tumor volume and weight of xenograft tumors of mice inoculated with SNU-1/DDP cells stably expressing sh-HCP5 or sh-con and treated with DDP or PBS. (c) qRT-PCR analyzed HCP5, miR-128 and HMGA2 expression in xenograft tumors. (d) Representative image of Ki-67 IHC staining. *$P < 0.05$.

Collectively, the knockdown of HCP5 improved DDP sensitivity in tumors *in vivo*.

4. Discussion

DDP is one of the most active agents for GC therapy. Unfortunately, DDP resistance, whether primary or acquired, is the bottleneck of GC chemotherapy, leading to a poor prognosis of GC patients. Therefore, it is urgent to clarify the mechanism of DDP resistance and to elucidate how to combat DDP resistance in GC. In this study, we found that HCP5 expression was increased in GC and closely related to GC prognosis. Furthermore, in vitro experiments demonstrated that lncRNA HCP5 could promote DDP resistance of GC cells. These findings suggested that HCP5 exerted a tumor-promoting function in GC.

Dysregulated lncRNAs have been well known as central contributors to the development of chemoresistance. HCP5, a novel identified lncRNA, was revealed to be implicated in chemoresistance. For instance, HCP5 re-sensitized Gemcitabine-resistant pancreatic cancer cells toward Gemcitabine through suppressing proliferation, invasion, migration, and promoting apoptosis and autophagy by acting as a ceRNA to sponge miR-214-3p and elevate HDGF expression [13]. The up-regulation of lncRNA HCP5 induced by mesenchymal stem cell (MSC) facilitated stemness and oxaliplatin and 5-Fu chemoresistance in GC

cells through miR-3619-5p/AMPK/PGC1α/CEBPB axis [22]. Especially, HCP5 led to DDP resistance in DDP-resistant breast cancer cells through PTEN inhibition [23]. Nonetheless, the role of HCP5 in DDP resistance of GC cells has never been studied. Herein, we first analyzed RNA-seq data from TCGA STAD dataset and revealed HCP5 was up-regulated in GC tumor tissues. We further confirmed increased HCP5 expression in our GC tissue samples as well as DDP-resistant GC tissues and cell lines. The upregulation of HCP5 was positively associated with the shorter overall survival in GC patients, suggesting its potential prognostic value in GC patients. Moreover, HCP5 silencing overcame DDP resistance in GC cells, as indicated by a decline in cell viability and an increase in cell apoptosis, indicating the role of HCP5 as a promising target to restore chemosensitivity in GC.

Accumulating researches demonstrated that lncRNAs could competitively decoy miRNAs to reduce their availability and indirectly up-regulate downstream mRNAs' expressions [24]. Therefore, we tried to search the target miRNA of HCP5 using online database Starbase 3.0. Among the predicted targets, miR-128 was chosen for further research due to its tumor suppressive role in GC and its implication with DDP resistance in cancers [18,19]. Our target prediction and dual luciferase reporter assay confirmed that HCP5 was a molecular sponge for miR-128. Previous studies demonstrated the involvement of miR-128 in DDP resistance in cancers. For example, the sensitivity of SKOV3/CP cells to DDP was enhanced by miR-128 through suppression of ABCC5 and Bmi-1 expression [19]. miR-128 inhibition elevated JAG1 expression and eventually led to the DDP resistance in SHG-44/DDP cells [25]. Additionally, miR-128 could enhance the response of prostate cancer cells to DDP through inhibiting HMGA2 expression [26]. Consistently, our study revealed that miR-128 overexpression re-sensitized SNU-1/DDP and MKN-45/DDP cells to DDP. Down-regulation of miR-128 weakened si-HCP5-mediated enhancement of DDP sensitivity. All these findings suggested that HCP5 knockdown improved DDP sensitivity of GC cells through sponging miR-128. Then, the targets of miR-128 was further explored. Our public databases Targetscan 7.0, microRNA.org and miRanda predictions and dual luciferase reporter assay verified HMGA2 was a miR-128 target. Additionally, HCP5 silencing suppressed HMGA2 expression in GC cells, which could be reversed by miR-128 inhibition. These results demonstrated that HCP5 could up-regulate HMGA2 expression through sponging miR-128 in GC. HMGA2 has been reported to confer DDP resistance in many tumors [20,21]. In this study, consistently, HMGA2 up-regulation weakened the enhanced DDP sensitivity of SNU-1/DDP and MKN-45/DDP cells caused by HCP5 silencing. These demonstrations partially explicated the mechanism through which HCP5/miR-128 regulated GC DDP resistance.

In summary, this study demonstrated that HCP5 contributed to DDP resistance through miR-128/HMGA2 axis, providing a promising therapeutic target to overcome DDP resistance in GC.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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