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ORIGINAL ARTICLE

The Long Noncoding RNA HOST2 Promotes Gemcitabine Resistance in Human Pancreatic Cancer Cells

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Abstract

Our study was aimed to identify the fundamental role of lncRNA HOST2 in gemcitabine resistance regulation in human pancreatic cancer cells. The levels of HOST2 in pancreatic cancer cell lines were measured by quantitative real-time PCR (qRT-PCR). Due to high expression and strong gemcitabine resistance, Hs766T and AsPC-1 cell lines were selected to be knockdown the expression of HOST2 by transfection sh-HOST2. After manipulation of HOST2, the cell proliferation induced by gemcitabine was examined by CCK-8 assay. Next, colony formation ability of Hs766T and AsPC-1 cell lines was determined by clone-forming assay. At last, the relationship between HOST2 and cell apoptosis in Hs766T and AsPC-1 cell lines was evaluated by flow cytometry. QRT-PCR revealed that HOST2 was overexpressed in six pancreas neoplasm cell lines compared with normal cell lines HPDE6-C7. HOST2 expression levels in group resistant to gemcitabine were higher than the group sensitive to gemcitabine. Additionally, CCK-8 assay verified that cell proliferation was inhibited by sh-HOST2 with or without gemcitabine treatment. Furthermore, clone-forming assay revealed that colony formation ability was weakened by down-regulated HOST2 with or without gemcitabine treatment. Flow cytometry revealed that cell apoptosis induced by gemcitabine was promoted by sh-HOST2. In conclusion, down-regulated HOST2 inhibited proliferation and promoted apoptosis of pancreas cancer cells with or without gemcitabine treatment. Thus, HOST2 is a potential therapeutic target for gemcitabine chemoresistance in pancreatic neoplasms.

Keywords Pancreatic neoplasms · LncRNA · HOST2 · Gemcitabine

Introduction

World Health Organization classifies pancreas as the root of various innocent tumor and malignancy [1]. Pancreatic carcinoma is a hardly detectable cancer with a high fatality rate and low subsistence rate [2, 3]. Thereinto, the most common type of pancreatic neoplasms is Pancreatic Ductal Adenocarcinoma which takes up probably 85% morbidity [4]. Despite immunotherapy and other active treatments, the curative effects for pancreatic cancer are not so desirable [5, 6]. Furthermore, merely 10 and 20% patients diagnosed as pancreatic cancer can be carried out a surgical operation with poor prognosis [7, 8]. More functional cures of pancreatic carcinoma are yet to be clarified.

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Gemcitabine is a principal drug treatment for pancreatic carcinoma in early or advanced stage [9]. Moreover, gemcitabine is a cytotoxic therapy with 5-month median survival time offered and 5 weeks in general to live lengthened [10, 11]. But cases resistant to gemcitabine take place in succession, leading to low cancer response rate and poor therapeutic efficacy [12]. No more than 23.8% patients benefited from gemcitabine treatment according to clinical evidence [13]. Hence, to exam the fundamental rule of the gemcitabine resistance would give a profound insight into the cancer of pancreas.

Long noncoding RNA(≥ 200 nts)is unable to encode proteins but plays an extremely significant role in cell mobility such as cell proliferation, migration and apoptosis [14]. LincRNAs have also shown feasibility in several diseases and cancers including bladder cancer, stomach cancer, pancreatic cancer and many other human malignant tumors [15]. However, little is known about lincRNAs recently and a myriad of lncRNAs and corresponding effects is still poorly documented.

Human ovarian cancer-specific transcript 2 (HOST2) is one of a member of five human ovarian cancer-specific

transcripts (HOSTs). Except HOST2, other members in HOSTs family have ability to encode protein [16]. Thus, without an distinct open reading frame, HOST2, 2.9 kb in length, is a novel lnc RNA containing a myriad of copies of retroviral-related sequences [16]. LncRNA-HOST2 functions as cell biological function regulator in epithelial ovarian carcinoma by microRNA let-7b [17]. Besides, in spite of effects on human hepatocellular carcinoma, osteosarcoma as well as breast cancer, lncRNA-HOST2 is yet to be studied in pancreatic carcinoma [18–20].

In this study, we inquired into the regulation of lincRNA-HOST2 on gemcitabine resistance of the cancer of pancreas. We observed that depleted HOST2 suppressed gemcitabine resistance to impair proliferation and induce apoptosis in pancreatic neoplasm. Furthermore, for the first time, HOST2 was found to play an important part in enhancing gemcitabine sensitivity for the cancer of pancreas. Therefore, Hs766T and AsPC-1 pancreatic cancer cell lines promoted gemcitabine resistance by the regulation of HOST2.

Methods

Cell Culture and Reagents

HPDE6-C7, normal human pancreatic ductal epithelial cells, was acquired from BeNa Culture collection (Beijing, China). According to Arumugam et al., BxPC-3, CFPAC-1 and SU.86.86 pancreatic cancer cells were sensitive to gemcitabine whereas PANC-1, Hs766T and AsPC-1 pancreatic cancer cells were resistant to gemcitabine [21]. The human cancer cell lines of pancreas such as BxPC-3, CFPAC-1, SU.86.86, PANC-1, Hs766T and AsPC-1 were also obtained from BeNa Culture collection (Beijing, China). HPDE6-C7, BxPC-3, PANC-1 and HS766T were placed in DMEM medium (including glutamine and sodium pyruvate) with fetal bovine serum (FBS) to a final concentration of 10%. CFPAC-1 was maintained in ATCC-formulated Iscove's Modified Dulbecco's Medium supplemented with 10% FBS. Then SU.86.86 and AsPC-1 cell lines were fixed in ATCC-formulated RPMI-1640 Medium containing 10% FBS. All the cells should be cultured in a humidified incubator at 37 °C under 5% CO_2. Gemcitabine was obtained from Sigma-Aldrich (St. Louis, MO, USA).

RNA Isolation and qRT-PCR Analysis

The total RNA isolation from cell lines was conducted by TRIzol® (Invitrogen, Carlsbad, CA, USA) in accordance with manufacturer's protocols. After quantifying total RAN levels by NanoDrop 2000 (Thermo Fisher Scientific Inc., USA), cDNAs were synthesized by the First Stand cDNA Synthesis kit (Roche, Basel, Switzerland). Applied Biosystems™ PowerUp™ SYBR™ Green Master Mix (Thermo Fisher Scientific, Waltham, MA, USA) was then performed to conduct quantitative PCR analysis in Applied Biosystems QuantStudio™ 12 K Flex Software (Thermo Fisher Scientific, Waltham, MA, USA). The reactions were initially denatured at 95 °C for 3 min, ensuing denatured at 95 °C for 15 s with 40 cycles and annealed and extended at 60 °C for 40 s. The primer sequences (synthetized by Shanghai Invitrogen Biotechnology Co., Ltd., Shanghai, China) were as follows: forward primer for lnc-HOST2, 5'-CTCAAATCAATCACGACCCT-3′, reverse primer for lnc-HOST2 was 5'-AATGTAGCAGGACGAGCC -3′; forward primer for the reference gene GAPDH 5'-CCACCCAT GGCAAATTCCATGGCA-3′, reverse primer for GAPDH, 5'-TCTAGACGGCAGGTCAGGTCCACC-3′. Each group was repeated in triplicate. Relative quantitative expression levels of lncRNAs were calculated by the $2^{(-\Delta\Delta Ct)}$ methods.

Cells Transfection

The pancreatic cancer Hs766T and AsPC-1 cells were respectively divided into sh-NC (negative control) and sh-HOST2 groups. ShRNA expression vectors were provided by Shanghai GenePharma Co., Ltd. (Shanghai, China). 24 h before transfection, the pancreas cancer cells Hs766T and AsPC-1 were respectively placed in 6-well plates until its confluence reached 60 to 70%. Then the cells were separately transfected with sh-NC and sh-HOST2 by Lipofectamine 2000 Reagent (Life technologies corporation, Gaithersburg, MD, USA). Total cells in 6-well plates were placed in the 5% CO_2 incubator at 37 °C. Transfected after 48 h, the relative expression levels can be measure by qRT-PCR analysis.

CCK-8 Assay

Cell Counting Kit-8(CCK-8) was provided by Beyotime Biotechnology (Shanghai, China) to evaluate cell viability in accordance with recommendations of manufacturer. Transfected cells were incubated in 96-well plates (1×10^4 cells/well) for 72 h when simultaneously treated with diverse concentration of Gemcitabine ranging from 0 to 100 μM. Cell viability was detected by the microplate reader.

Clone-Forming Assay

Hs766T and AsPC-1 cells under logarithmic growth phase were harvested and evenly dispersed for cell suspension with administration of 0 and 10 μM concentrations of Gemcitabine. After being added into RPMI1640 medium, cells in six-well plate were inoculated in petri dish and subsequently were washed with PBS. Paraformaldehyde (PA) was

used to fix transfected cells for 15 min and GIMSA was employed to stain cells followed by dehydration in the air. This experiment was conducted in triplicate.

Flow Cytometry

Annexin V-FITC/PI Apoptosis Detection Kit (Sigma-Aldrich, St. Louis, MO, USA) and flow cytometry were used after 72 h of transfection in order to detect cell apoptosis rate. After 24 h of transfection, the transfected cells were treated with 0 and 10 μM Gemcitabine. Cells were rinsed with ice-cold PBS 3 times and centrifuged before the supernatant was discarded. Every tube of cells was added to 150 μl Binding buffer and 5 μl Annexin-V-FITC and evenly mixed. After incubation in the dark at room temperature for 15 min, another 100 μl of Binding buffer and 5 μl PI stain was added to each tube, which was then shaken. During the staining stage for 1 h, flow cytometry should be conducted immediately to evaluate cell apoptosis rate. This experiment was repeated in triplicate.

Statistical Analysis

GraphPad Prism 6.0 (GraphPad Prism,Version X, La Jolla, CA, USA) was used to conduct statistical analyses. Data were expressed as mean ± SD. Unpaired student's t test was adopted to assess differences between two groups while One-Way ANOVA was used to compare multiple groups. Statistical significance is reasonable when $P < 0.05$.

Results

LncRNA HOST2 Was Higher in Pancreatic Cancer Cell Lines

The qRT-PCR was adopted to evaluate HOST2 expression levels in 7 cell lines divided into one normal cell line HPDE6-C7 and the rest six tumor cell lines. Thereinto, tumor cell lines fell into two groups containing cell lines group sensitive to gemcitabine and resistant to gemcitabine. We demonstrated that HOST2 levels were overexpressed in six pancreatic neoplasm cell lines compared with HPDE6-C7 (Fig. 1). Besides, among the tumor cell lines, expression levels of AsPC-1, Hs766T and PANC-1 groups were found to be remarkably higher than SU.86.86, CFPAC-1 and BxPC-3 groups. In other words, HOST2 was overexpressed in groups resistant to gemcitabine in comparison with groups sensitive to gemcitabine (Fig. 1). In addition, as two highest expressed cell lines, AsPC-1 and Hs766T was selected for further research.

Down-Regulated HOST2 Improved Sensibility of Gemcitabine in Pancreatic Cancer Cell Lines

After transfection with sh-HOST2, HOST2 levels was significantly knockdown in comparison with sh-NC group in both Hs766T and AsPC-1 cell lines (Fig. 2a, b). Then, cell viability was detected under 0, 0.01, 0.1, 1, 10 and 100 μM gemcitabine by CCK-8 assay after sh-HOST2 and sh-NC transfection. We observed that cell proliferation of Hs766T and AsPC-1 was remarkably inhibited along with the concentration increases of gemcitabine and down-regulated HOST2 was more sensitive to gemcitabine in Hs766T and AsPC-1 cells (Fig. 2c, d). Therefore, down-expression of HOST2 observably enhanced sensibility of pancreatic cancer cell lines to gemcitabine.

Sh-HOST2 Inhibits Colony Formation Ability of Hs766T and AsPC-1 Cell Lines with or without Gemcitabine Treatment

Next, a clone-forming assay was executed in order to investigate the influence of HOST2 on colony formation in Hs766T and AsPC-1 cell lines treated respectively with and without 10 μM gemcitabine. The results showed that the cloned number of Hs766T and AsPC-1 cells was sharply attenuated after sh-HOST2 performed with or without gemcitabine treatment (Fig. 3a, c). What's more, the cloning numbers of Hs766T and AsPC-1 transfected sh-HOST2 and with gemcitabine treatment were least (Fig.3b, c). It was demonstrated that si-HOST2 observably inhibited resistance of pancreatic cancer cell lines to gemcitabine.

Sh-HOST2 Induces Hs766T and AsPC-1 Cell Lines Apoptosis after Treatment with Gemcitabine

To further examine the resistance effects of HOST2, flow cytometry assay was used to detect cell apoptosis after gemcitabine treatment in HOST2 down-regulation Hs766T and AsPC-1 cells. Down-regulated HOST2 weakened apoptosis rate in both Hs766T and AsPC-1 cells (Fig. 4a, c). We also detected that knockdown of HOST2 promoted apoptosis rate induced by gemcitabine in Hs766T and AsPC-1 cell lines compared with sh-NC (Fig. 4b, d). Therefore, depletion of HOST2 played a crucial role in pancreas cancer cells apoptosis and enhanced sensibility to gemcitabine.

Discussion

Muller et al. revealed that LncRNA was reported to serve vital roles in pancreatic cancer progression [22]. According to Moschovis et al., tumorigenesis in many cancers resulted from altered lncRNA relative expression levels [1]. At the earliest,

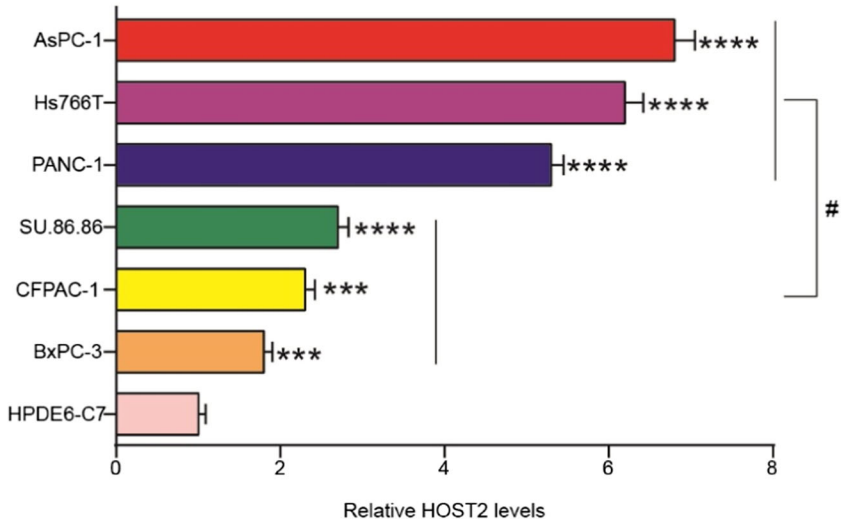

Fig. 1 HOST2 levels are up-regulated in pancreatic neoplasm cell lines, particularly among cell lines resistant to gemcitabine including AaPC-1, Hs766T and PANC-1. LncRNA HOST2 expression levels were evaluated in 6 pancreatic cancer cell lines including Bxpc-3, CFPAC-1, SU.86.86, PANC-1, Hs766T and AsPC-1 cell lines compared with normal human pancreatic ductal epithelial cell lines HPDE6-C7 using quantitative reverse transcription-PCR. Among the rest, Bxpc-3, CFPAC-1 and SU.86.86 are pancreatic cancer cells sensitive to gemcitabine while AaPC-1, Hs766T and PANC-1 are pancreatic cancer cells resistant to gemcitabine. $^{***}P < 0.001$, $^{****}P < 0.0001$ and $^{\#}P < 0.05$ revealed that there is marked statistical difference. Data are demonstrated as mean ± SD

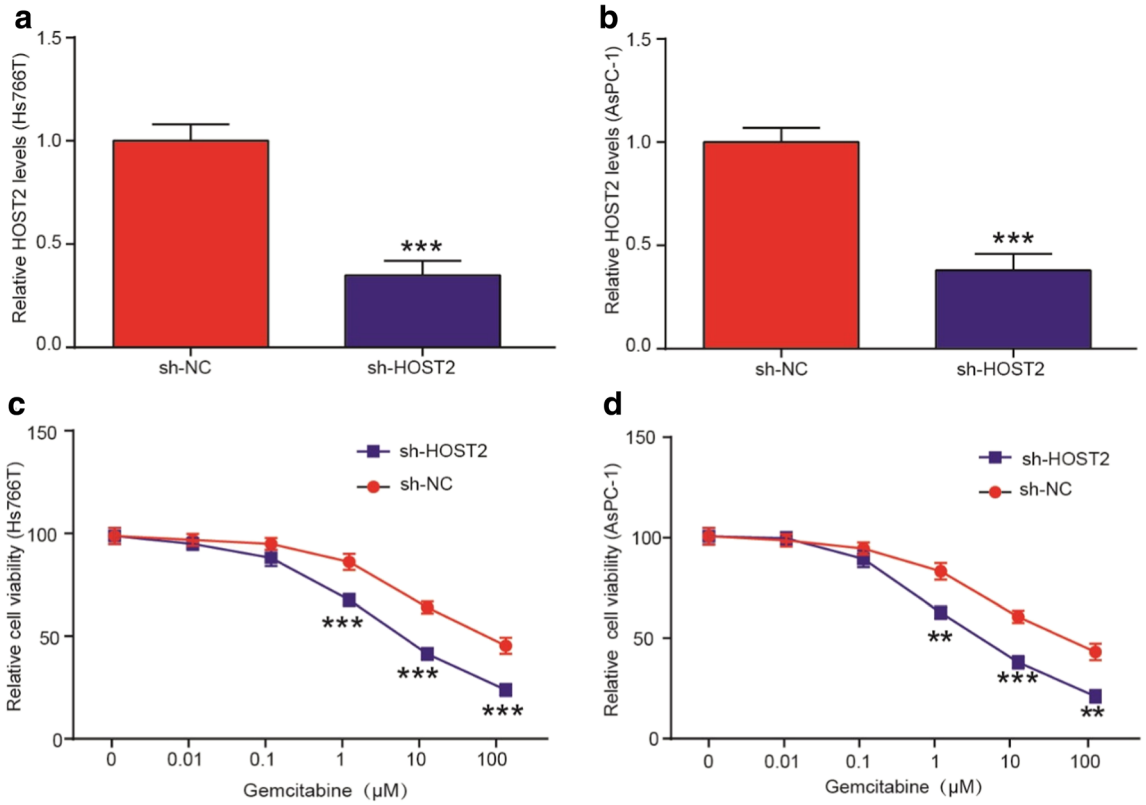

Fig. 2 HOST2 silencing suppressed cell growth in pancreatic cancer cells. (a-b) Hs766T and AsPC-1 cells were transfected with negative control (NC) shRNA and shRNA against HOST2 as demonstrated. Relative HOST2 expression levels after transfection for 48 h were observed using quantitative reverse transcription-PCR analysis in Hs766T and AsPC-1 cell lines among the two groups. **(c-d)** After HOST2 transfection and downregulation by sh-HOST2, the marked inhibition of cell viability by gemcitabine was found via CCK-8 assay in comparison with the sh-NC group. $^{**}P < 0.01$ and $^{***}P < 0.001$ demonstrated that significant difference emerged between sh-NC and sh-HOST2 groups

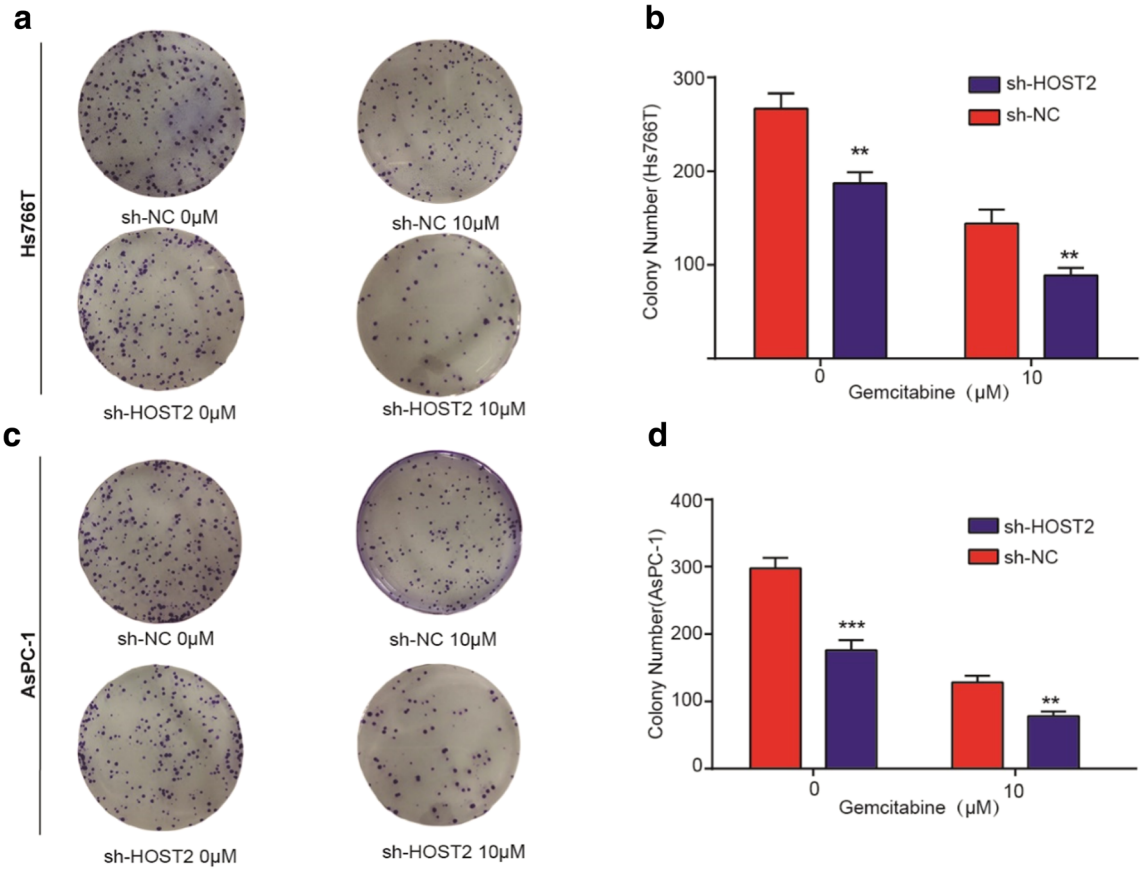

Fig. 3 Knockdown HOST2 in Hs766T and AsPC-1 cells led to the attenuated clone formation ability with or without gemcitabine. (a-b) Down-expression of HOST2 reduced colony number of Hs766T with or without gemcitabine. **(c-d)** Down-expression of HOST2 reduced colony number of AsPC-1 with or without gemcitabine. ** $P < 0.01$, *** $P < 0.001$ compared with sh-NC group

lncRNA-HOST2 gene was found by Rangel et al. to merely have a high expression in epithelial ovarian cancer cell lines while there is depleted or hardly any HOST levels in other tumors [16]. Nevertheless this is not exactly the case. According to later studies, HOST2 gene was revealed to be significantly regulated in epithelial ovarian cancer cell lines [17], human hepatocellular carcinoma cell [20], breast cancer [18] and osteosarcoma tissues [19]. However, little is known about the correlation between HOST2 gene and pancreatic cancer progression. This aroused our great attention in the expression of HOST2 in pancreatic cancer cells sensitivity and resistance to gemcitabine. Then our studies found that lncRNA HOST2 expression levels were elevated in pancreatic carcinoma cells compared with normal pancreas cells HPDE6-C7, which was similar to above findings.

It was found that gemcitabine was characterized by cell apoptosis induction through interference with DNA replication in pancreatic cancer patients [23]. However, human pancreatic carcinoma is typical chemotherapy drug resistance cancer, which is detrimental to therapeutic efficacy of gemcitabine [23]. Thus, we aimed to examine whether the expression of lncRNA HOST2 varies in pancreatic tumor cells sensitive and resistant to gemcitabine. Predictably, gemcitabine resistance was observed to be resulted in overexpression of lncRNA-HOST2 gene in Hs766T and AsPC-1 pancreatic cancer cell lines in contrast with cell lines which sensitive to gemcitabine. This is in agreement with early findings that elevation of lnc-ROR expression levels was correlated with the gemcitabine resistance to pancreatic carcinoma [24].In addition to that, significantly upregulated lncRNA HOTTIP was also reported to be connected with gemcitabine sensitivity in Pancreatic Ductal Adenocarcinoma by Li et al. [25]. In the end, according to You et al., overexpressed LncRNA PVT1 was identified as a regulator of gemcitabine resistance in the cancer of pancreas [23].

Moreover, to determine the effects of HOST2 gene on biological function of gemcitabine-resistant pancreatic cancer cells, we examined the proliferation and apoptosis of Hs766T and AsPC-1 cells after depleting HOST2 gene expression. Our findings indicated that sh-HOST2 under administration of gemcitabine attenuated proliferation and promoted apoptosis of Hs766T and AsPC-1 cells. The silencing of lnc-RNA HOTTIP was reported to impair cell proliferation in gemcitabine-resistant pancreatic carcinoma [25]. Zhang et al. reported in 2016 that lincRNA MALAT1 reduced cell apoptosis rate induced by gemcitabine in the pancreatic neoplasm cells [26].

In the current study, in vitro experiments confirmed the roles of lncRNA-HOST2 expression on occurrence and

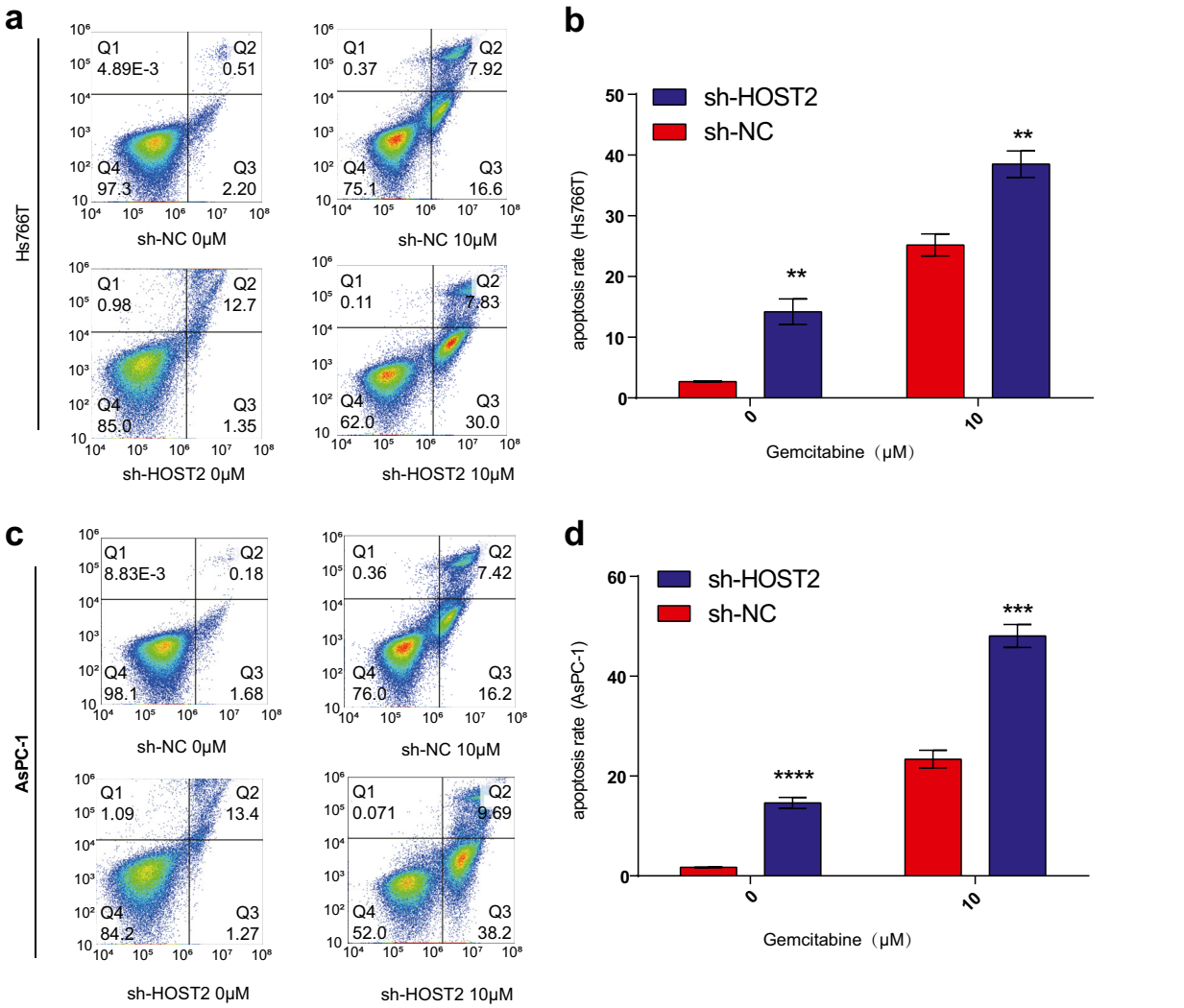

Fig. 4 Sh-HOST2 promoted pancreas cancer cells apoptosis treated with or without gemcitabine. (a-b) Flow cytometry with PI/Annexin V-FITC staining was used to evaluate apoptosis of Hs766T cell lines with or without gemcitabine treatment after sh-NC and sh-HOST2 transfection. **(c-d)** Apoptosis rates of AsPC-1 with or without gemcitabine treatment after sh-NC and sh-HOST2 transfection. ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ compared with sh-NC group

development of pancreatic carcinoma. Primarily, our results suggested that over-expressed HOST2 gene turned out to be in pancreatic cancer cells. Meanwhile, HOST2 expression levels were also high in human pancreatic carcinoma cell resistant to gemcitabine. This promotes us to center around the regulation of HOST2 after transfection and gemcitabine exposure on the proliferation and apoptosis of pancreatic cancer cells resistant to gemcitabine. As expected, our study indicated that sh-HOST2 plays a large role in pancreatic cancer cell proliferation inhibition and apoptosis induction by regulating gemcitabine sensitivity. This is the first time that the expression of HOST2 and the correlation of HOST2 and gemcitabine had been examined in pancreatic carcinoma.

Conclusions

In conclusion, the present study revealed that downregulated HOST2 inhibited cell growth and induced cell apoptosis after treatment with gemcitabine. Our results gave an insight into the expression and fractional biological activity of HOST2 in regulation of gemcitabine resistance and oncogenesis. However, further characterization of HOST2 gene remains explored.

Compliance with Ethical Standards

Ethics Approval and Consent to Participate This study was authorized by the Sichuan People's Hospital, and obtained written informed consents from all the participants.

Conflict of Interest The authors confirm that there are no conflicts of interest.

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