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ORIGINAL ARTICLE

Long non-coding RNA GHET1 contributes to chemotherapeutic resistance to Gemcitabine in bladder cancer

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Abstract

Purpose Bladder cancer (BC) ranks first in the incidence of urogenital tumors in China and second only to prostate cancer in the West. This study will clarify the roles and mechanism of lncRNA GHET1 in chemotherapeutic resistance of BC to Gemcitabine.

Methods The expression of GHET1 was examined using real-time quantitative PCR. Cell Counting Kit-8 assay was applied to analyze cell proliferation and Gemcitabine sensitivity. Cell apoptosis was detected using Annexin V-FITC/PI double-stained flow cytometry. The expression of ABCC1 protein was examined using Western blotting.

Results Firstly, the expression of GHET1 was up-regulated in BC, its high expression was relevant to high grade and muscle invasion of BC patients. Secondly, high expression of GHET1 was related to low Gemcitabine sensitivity of BC patients, and GHET1 was highly expressed in Gemcitabine-resistant BC cell lines. Thirdly, knockdown of GHET1 decreased the IC50 of Gemcitabine in Gemcitabine-resistant BC cell lines and advanced the Gemcitabine-induced cytotoxicity; GHET1 promoted Gemcitabine resistance in BC. Finally, knockdown of GHET1 also inhibited the expression of ABCC1 protein in Gemcitabine-resistant BC cells.

Conclusions High expression of GHET1 was related with the low sensitivity to Gemcitabine of BC; GHET1 contributed to chemotherapeutic resistance to Gemcitabine in BC through up-regulating ABCC1 expression. Our findings are helpful to expound the molecular mechanism of chemotherapeutic resistance in BC.

Keywords Bladder cancer · Long noncoding RNA · GHET1 · Chemotherapeutic resistance · Gemcitabine

Introduction

Bladder cancer (BC) is a disease caused by the uncontrolled malignant proliferation of some cells in the bladder. It ranks first in the incidence of urogenital tumors in China and second only to prostate cancer in the West [1, 2]. With the continuous progress of comprehensive treatment based on radical resection of BC, the clinical therapeutic effects have been greatly improved, but 5-year survival rate of advanced BC is still hovering around 45% due to recurrence and metastasis after operation [3, 4].

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Chemotherapy can effectively inhibit the recurrence and metastasis of BC, but drug resistance restricts its clinical application and seriously affects the clinical efficacy [5]. It is well known that the mechanisms of chemotherapeutic resistance for BC mainly include abnormal efflux pump function, DNA repair deregulation and unbalanced signaling pathways, etc. [6, 7].

Long noncoding RNAs (lncRNAs) have been a hotspot in cancer etiology and treatment in recent years. Recent studies have shown that some lncRNAs may be biomarkers and therapeutic targets for cancer prognosis and diagnosis [8–11]. The growing evidences proved that some lncRNAs participate in the genesis and progression of chemotherapeutic resistance a variety of malignant tumors, including BC [12–14]. Our previous literature reported growth arrest-specific 5 (GAS5) restrained chemotherapeutic resistance to doxorubicin and malignant proliferation in bladder urothelial carcinoma [15]; nuclear-enriched abundant transcript 1 (NEAT1) could active Wnt/β-catenin

signaling pathway, and then promote chemotherapeutic resistance to doxorubicin of bladder urothelial carcinoma [16].

Gastric carcinoma proliferation-enhancing transcript 1 (GHET1) gene was first identified by Yang F in gastric cancer tissues in 2014, which contains 1913 nucleotides and is located at chromosome 7q36.1 [17]. Recent literature reported that the GHET1 gene was highly expressed and played the roles of oncogene in various malignant tumors, including breast cancer, glioma and gastric cancer, etc. [18–20]. So far, only one literature reported that GHET1 was up-regulated in BC and its high expression was relevant to poor survival, bigger tumor size and high grade of BC patients; knockdown of GHET1 inhibited invasion and proliferation ability of BC cells [21]. Zhang et al. reported that GHET1 promoted chemotherapeutic resistance to cisplatin in gastric cancer [22]. However, there are no reports of abnormal expression and function of GHET1 related to chemotherapeutic resistance in BC.

ATP binding cassette subfamily C member 1 (ABCC1), also named multidrug resistance-associated protein 1 (MRP1), belongs to the superfamily of ATP-binding cassette (ABC) transporters, which mainly participates in the transport of various intracellular and extracellular complexes, regulates the distribution of intracellular substances. ABCC1 acts as an efflux pump to expel chemotherapeutic drugs out of cells, which can reduce intracellular drug concentration and contribute to the formation of chemotherapeutic resistance. Li et al. found that emodin sensitized J82 and T24 cells to cisplatin through silencing ABCC1 expression and elevating the cellular reactive oxygen species (ROS) level [23]. Our previous study reported that knockdown of lncRNA plasmacytoma variant translocation 1 (PVT1) down-regulated the ABCC1 expression and promoted cisplatin and doxorubicin resistance in BC [24].

Therefore, this study explores the roles and mechanism of GHET1 in regulating the chemotherapeutic resistance in BC.

Materials and methods

Cell lines and cell culture

Human BC cell lines (J82, T24) and bladder epithelial immortalized cell line SV-HUC-1 were stored in our laboratory. Gemcitabine-resistant J82/Gem and T24/Gem cell lines were previously established and stored in our laboratory [25]. All cells were cultured in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum (ExCell Bio, Shanghai, China) in a 37 °C incubator.

Clinical specimens

Seventy-four cases of BC patients were hospitalized in Shengjing Hospital between March 2017 and August 2018. The Ethics Committee of Shengjing Hospital approved this study, and all patients signed informed consent. The cystoscopy was used to obtain normal bladder urothelial tissue (NBUT) and BC tissue specimens. All patients were pathologically diagnosed as BC, and did not receive chemotherapy or radiotherapy before diagnosis.

After diagnosis, all 74 BC patients were treated with neoadjuvant chemotherapy using Gemcitabine. The chemotherapeutic effects were evaluated based on the results of enhancement CT scanning and cystoscopy after three chemotherapy cycles. According with evaluation results, Gemcitabine-sensitive patients were 41 cases and Gemcitabine-insensitive patients were 33 cases.

Real-time quantitative PCR (qRT-PCR)

TRNzol reagent (TIANGEN, Beijing, China) was applied to extract total RNA from cell line and tissue specimens. The A260/A280 ratio of purified RNA was typically between 1.8 and 2.4 and the yield between 80 and 120 μg. RNA samples were stored at − 80 °C. RNA integrity was assessed by gel electrophoresis. The RNA was reverse transcribed to cDNA. According to instructions, lnRcute lncRNA qPCR Kit (TIANGEN, Beijing, China) was used to detect the relative expression of GHET1 on a 7500 PCR System (Applied Biosystems, ThermoFisher, Foster City, CA, USA). Each reaction contained 2 × lnR lncRNA Premix (25 μL), 50 × ROX Reference Dye (1 μL), Forward Primer (1.25 μL), Reverse Primer (1.25 μL), RNA template (2 μL) and RNase-Free ddH2O (19.5 μL). The cycling condition is as follows: stage 1: 42 °C for 20 min, 95 °C for 3 min,1 cycle; stage 2: 94 °C for 30 s, 60 °C for 30 s, 72 °C for 30 s, 40 cycles; stage 3: 72 °C for 50 min. The GHET1′s primers were 5′-GAACAA AGCAGGTAAACATTGG-3′ and 5′-GCAAAGGCAGAG TGAAAGGT-3′. After normalization with reference gene, $2^{-\Delta\Delta CT}$ method was used to calculate the relative expression level of GHET1.

Cells transfection

Knockdown plasmid of GHET1 (sh-GHET1) and negative control plasmid (sh-NC) (Ribobio, Guangzhou, Guangdong, China) were transfected into Gemcitabine-resistant BC cells using riboFECT reagent (Ribobio, Guangzhou, Guangdong, China) according to instructions. qRT-PCR was applied to examine the knockdown efficiency.

Cell proliferation assay

Cell proliferation ability was detected with Cell Counting Kit-8 (APEcBIO, Houston, TX, USA). In detail, 2×10^3 Gemcitabine-resistant BC cells were suspended with 100-µl culture medium in 96-well plates; then 10-µl CCK-8 solution was added and mixed gently; the cell mixtures reacted for 1 h in the absence of light and at room temperature. The Synergy HTX Microplate Reader (BioTek, Winooski, VT, USA) was used to detect the value of optical density at 450 nm.

Drug sensitivity assay

Gemcitabine was used to treat Gemcitabine-resistant BC cells, the concentration gradient of Gemcitabine was 0.1 µg/ml, 0.5 µg/ml, 1 µg/ml, 5 µg/ml and 10 µg/ml [25]. After 24 h, the value of optical density was examined. Based on these dates, the dose–response curve was drawn and half maximal inhibitory concentration (IC50) was calculated.

Apoptosis rate detection

Annexin V-FITC/PI Double-stained cell apoptosis kit (KeyGEN, Nanjing, Jiangsu, China) was applied to examine apoptosis. In detail, 5×10^5 Gemcitabine-resistant BC cells were suspended with 500-µl binding buffer, 5-µl Annexin V-FITC was added and mixed gently; then, 5-µl PI was added and mixed gently; the cell mixtures reacted for 15 min in the absence of light and at room temperature. Flow cytometry was applied to examine apoptosis rate.

Western blotting

Protein Extraction Kit (Beyotime, Beijing, China) was applied to extract proteins from Gemcitabine-resistant BC cells. Protein specimens were separated by polyacrylamide gel electrophoresis, and then transferred to a polyvinylidene fluoride (PVDF) membrane. PVDF membrane was blocked using non-fat milk, hybridized with ABCC1 antibody (PAB068Hu01, Cloud-Clone, Wuhan, Hubei, China) and second antibody, then treated with ECL reagent (Engreen, Beijing, China). Image analysis software Image J (NIH, Bethesda, MD, USA) was used to examine and calculate relative expression of ABCC1 protein.

Statistical analysis

All data are analyzed with SPSS version 22.0 (IBM, Armonk, NY, USA) software. Student's *t* test and One-way ANOVA were applied to analyze the statistical differences. If *P* value is less than 0.05, the difference has statistical significance.

Results

GHET1 gene was highly expressed in BC

Compared with matched NBUT, the expression of GHET1 in BC specimens was up-regulated significantly (Fig. 1a). Similarly, the GHET1 expression in J82 and T24 cells was

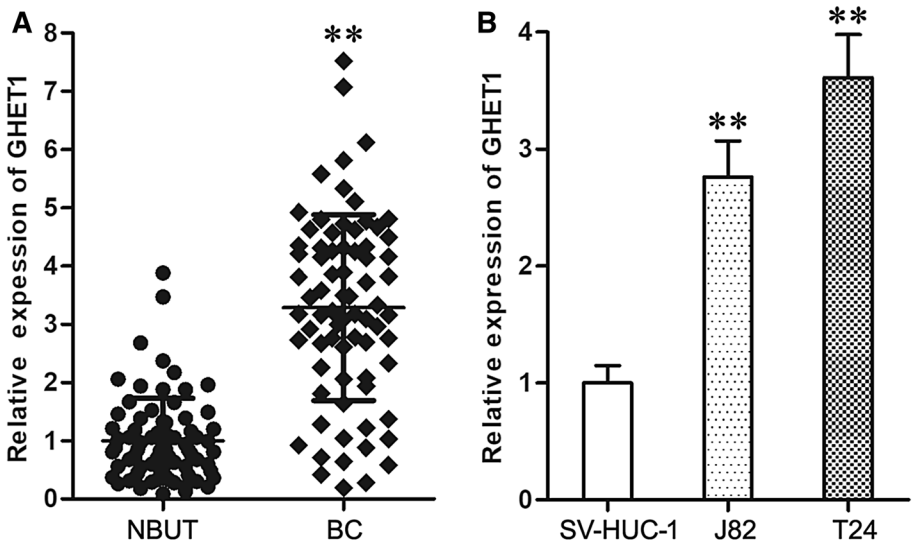

Fig. 1 GHET1 gene was highly expressed in BC in BC. **a** The expression of GHET1 in BC was up-regulated compared with NBUT. $^{**}P < 0.01$ vs. NBUT. **b** The expression of GHET1 in J82 and T24 cells was up-regulated in comparison with SV-HUC-1 cells. $^{**}P < 0.01$ vs. SV-HUC-1 cells

also up-regulated in comparison with SV-HUC-1 cells (Fig. 1b).

High expression of GHET1 displayed a positive correlation with high grade and muscle invasion of BC patients. On the contrary, the expression of A has no correlation with other pathological parameters, such as age, gender, smoking history and lymph node metastasis (Table 1). These results hinted that GHET1 gene took part in genesis and progress of BC.

Table 1 The correlation between the expression of GHET1 and the clinicopathological factors of 74 cases bladder cancer patients

Pathological factors	Case	Relative expression of GHET1	*P* value
Age (years)			0.832
< 54	37	3.316	
≥ 54	37	3.252	
Gender			0.908
Male	46	3.296	
Female	28	3.264	
Smoking history (more than 10 years)			0.269
No	43	3.142	
Yes	31	3.481	
Grade			0.014*
Low grade	34	2.885	
High grade	40	3.623	
Muscle invasion			0.002**
Negative	39	2.853	
Positive	35	3.764	
Lymph node metastasis			0.964
Negative	70	3.282	
Positive	4	3.319	
Gemcitabine chemotherapy			0.034*
Sensitive	41	2.924	
Insensitive	33	3.733	

*$P < 0.05$, **$P < 0.01$

High expression of GHET1 was related with low Gemcitabine sensitivity in BC

High expression of GHET1 was related with low Gemcitabine sensitivity of BC patients (Fig. 2a and Table 1). Moreover, the GHET1 expression in J82/Gem and T24/Gem cells was higher than that in the corresponding J82 and T24 cells (Fig. 2b). These findings preliminarily proved that the high expression of GHET1 was relevant to poor sensitivity to Gemcitabine in BC; GHET1 took part in the genesis of chemotherapeutic resistance in BC.

Knockdown of GHET1 inhibited Gemcitabine resistance in BC cells

To verify the roles of GHET1 on chemotherapeutic resistance, sh-GHET1 was transfected into J82/Gem and T24/Gem cells to knockdown the expression of GHET1 to carry out loss-of-function experiments (Fig. 3a).

Knockdown of GHET1 reduced IC50 of Gemcitabine from 4.88 ± 0.47 μg/ml and 5.64 ± 0.63 μg/ml to 1.94 ± 0.31 μg/ml and 2.23 ± 0.36 μg/ml in J82/Gem and T24/Gem cells, respectively (Fig. 3b), which certified GHET1 knockdown re-sensitized J82/Gem and T24/Gem cells to Gemcitabine. In addition, knockdown of GHET1 suppressed cell proliferation as well as promoted apoptosis in J82/Gem and T24/Gem cells treated with 0.5 μg/ml Gemcitabine (Fig. 3c, d). Together, GHET1 contributed to Gemcitabine resistance in BC.

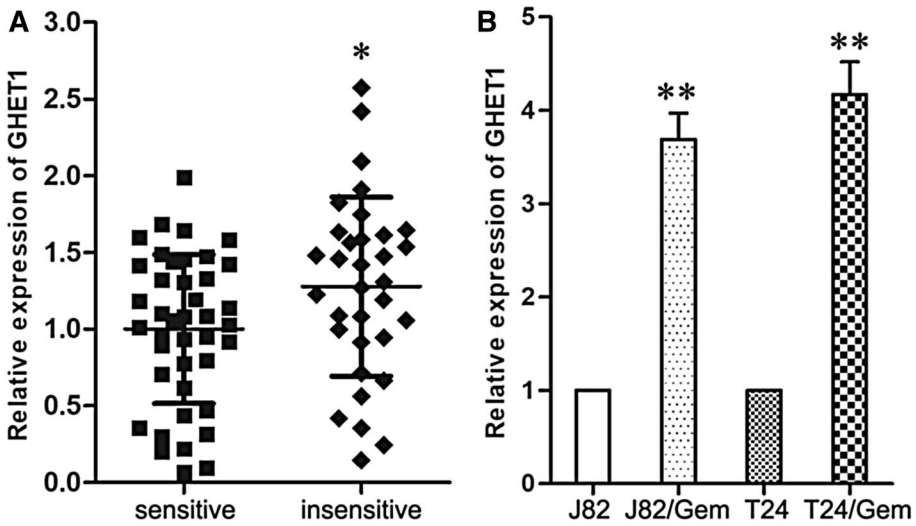

Fig. 2 High expression of GHET1 was related with low Gemcitabine sensitivity in BC. **a** The expression of GHET1 in Gemcitabine-insensitive BC was higher than that in Gemcitabine-sensitive BC. *$P < 0.05$ vs. Gemcitabine-insensitive BC. **b** The expression of GHET1 in J82/Gem and T24/Gem cells was much higher than that in the corresponding J82 and T24 cells. **$P < 0.01$ vs. J82 and T24 cells

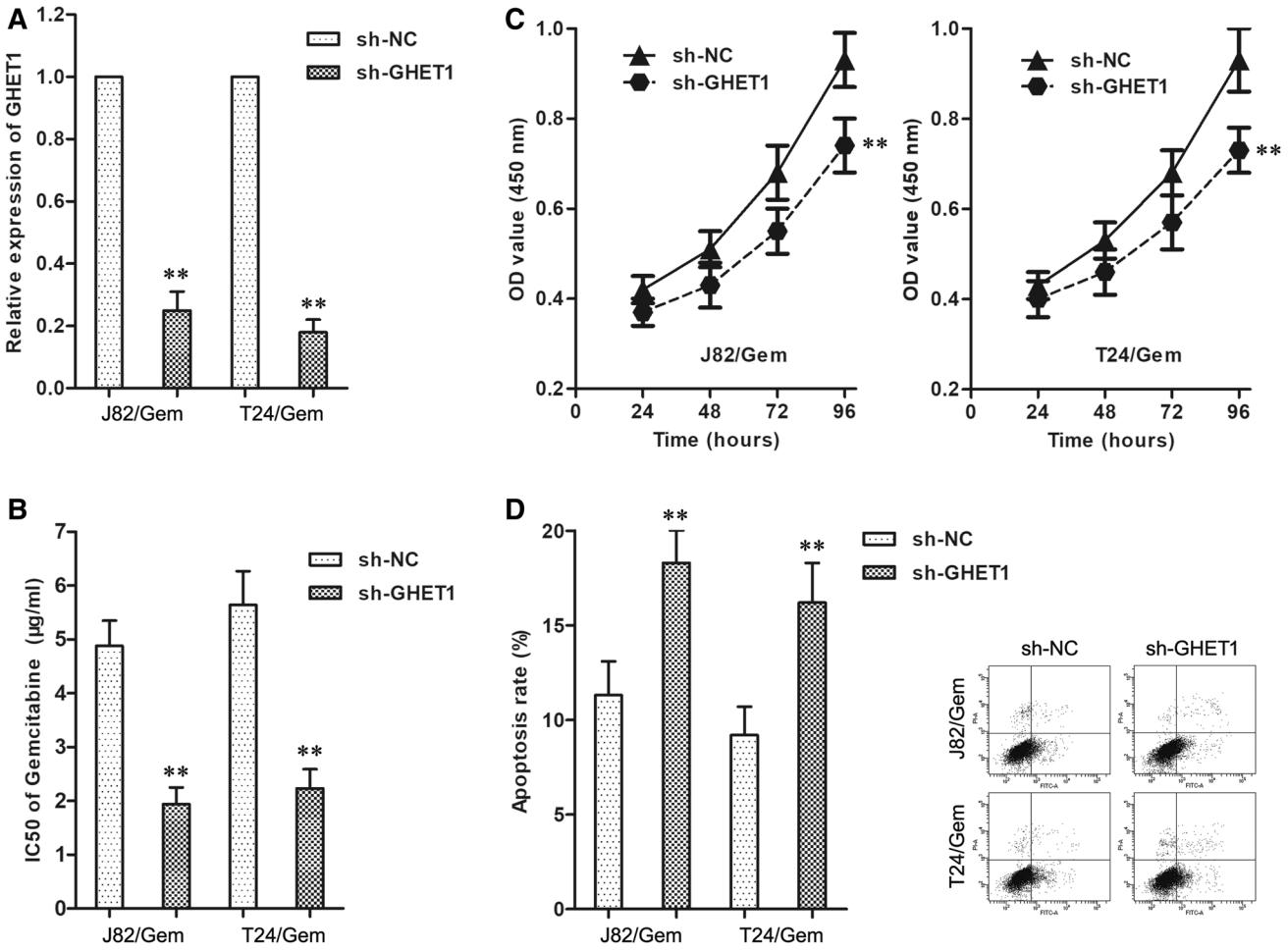

Fig. 3 Knockdown of GHET1 inhibited Gemcitabine resistance in BC cells. **a** Transfection of sh-GHET1 knockdown the expression ofGHET1 in J82/Gem and T24/Gem cells. **b** Knockdown of GHET1 reduced IC50 of Gemcitabine in J82/Gem and T24/Gem cells. **c** Knockdown of GHET1 suppressed cell proliferation in J82/Gem and T24/Gem cells treated with 0.5 μg/ml Gemcitabine. **d** Knockdown of GHET1 promoted apoptosis in J82/Gem and T24/Gem cells treating with 0.5 μg/ml Gemcitabine. $^{**}P < 0.01$ vs. sh-NC group

GHET1 up-regulated the expression of ABCC1 protein in BC cells

Based on TCGA Pan-Cancer (PANCAN) database, the co-expression analysis with 426 BC samples showed that the expression of GHET1 had significant positive correlation with the ABCC1 expression (Fig. 4a, $r = 0.128$, $P < 0.01$). In addition, in J82/Gem and T24/Gem cells, knockdown of GHET1 significantly inhibited the expression of ABCC1 protein (Fig. 4b).

Discussion

Increasing evidence pointed out that lncRNAs participated in the formation of chemotherapeutic resistance in almost all malignant tumors, including BC [12–14, 26]. Wang et al. reported that lncRNA H19 could promote SIRT1-mediated autophagy to advance the chemotherapeutic resistance to 5-Fluorouracil in colorectal cancer [27]. LncRNA NEAT1 was highly expressed in gastric cancer and functioned as an oncogene to regulate proliferation, apoptosis, invasion and chemotherapeutic resistance to Adriamycin in gastric cancer cells [28]. Our literature reported that CDKN2B-AS1 was highly expressed in BC and related to low Gemcitabine sensitivity of BC; CDKN2B-AS1 suppressed sensitivity of Gemcitabine-resistant BC cells to Gemcitabine through Wnt/β-catenin signaling pathway [25].

Gemcitabine is a first-line antineoplastic drug for BC, which is a new derivative of cytidine. It is activated by deoxycytosine kinase and metabolized by cytidine deaminase. Its main metabolite incorporates DNA to block DNA synthesis, arrest cells at G1/S stage, leading to cell death [29]. Nevertheless, Gemcitabine resistance often occurs in clinical practice, which can lead to chemotherapy failure.

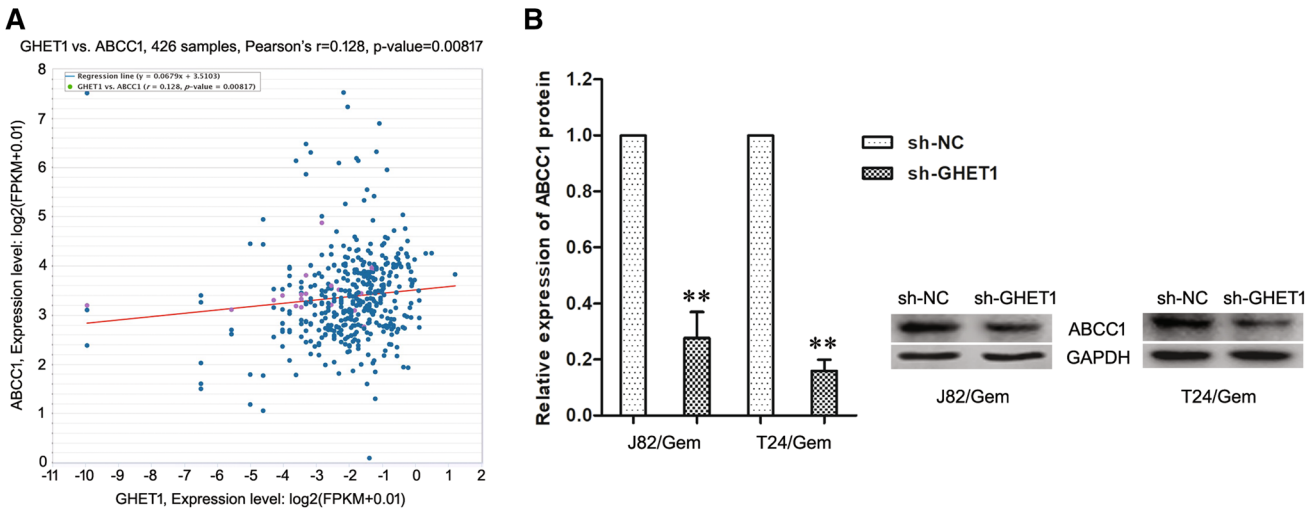

Fig. 4 GHET1 up-regulated the expression of ABCC1 protein in BC cells. **a** The co-expression analysis based on TCGA Pan-Cancer (PANCAN) database showed the expression of GHET1 was positive correlated with the ABCC1 expression ($r=0.128$, $P<0.01$). **b** Knockdown of GHET1 inhibited the expression of ABCC1 protein in J82/Gem and T24/Gem cells. $^{**}P<0.01$ vs. sh-NC group

In this study, GHET1 was confirmed to be highly expressed in BC; high expression of GHET1 was positively related to high grade and muscle invasion of BC, which hinted that GHET1 might be involved in tumorigenesis and progress of BC.

In addition, high expression of GHET1 was related to low Gemcitabine sensitivity of BC patients, which preliminarily proved that GHET1 took part in the genesis of chemotherapeutic resistance in BC. Zhang et al. reported that GHET1 promoted the development of chemotherapeutic resistance to cisplatin in gastric cancer [22]. However, there is no report on the study of Gemcitabine resistance in BC.

Therefore, loss-of-function assays were applied to explore the roles of GHET1 on chemotherapeutic resistance to Gemcitabine in BC. GHET1 knockdown reduced IC50 of Gemcitabine in Gemcitabine-resistant BC cells and advanced the Gemcitabine-induced cytotoxicity, which confirmed that GHET1 contributed to chemotherapeutic resistance to Gemcitabine in BC.

The statistical analysis based on TCGA Pan-Cancer (PANCAN) database showed a significant positive correlation between the expression of GHET1 and ABCC1. Furthermore, knockdown of GHET1 could significantly inhibit the expression of ABCC1 protein in Gemcitabine-resistant BC cells. As we all know, ABCC1 is an important multidrug resistance-related gene; abnormal expression and function of ABCC1 are involved in the occurrence of chemotherapeutic resistance in almost all malignant tumors, including BC [30–32]. The findings of this study proved that GHET1 could up-regulate the expression of ABCC1 to promote the Gemcitabine resistance in BC. Nevertheless, the underlying mechanism of GHET1 regulating the expression of ABCC1 is unknown.

There were increasing evidences to approve that lncRNAs could act as competitive endogenous RNAs (ceRNAs) and molecular sponges to microRNAs and change the expression or function of these microRNAs, thereby regulating the expression of the target genes of these microRNAs. For example, lncRNA CDKN2B-AS1 could bind and silence miR-125a-5p, and then promote the formation of chemotherapeutic resistance in gastric cancer by regulating the miR-125a-5p's target genes Multidrug Resistance-Associated Protein 4 (MRP4) and B cell lymphoma-2 (Bcl2) [33]; lncRNA TUSC7 inhibited chemotherapeutic resistance to temozolomide in glioblastoma by targeting miR-10a [34]. Recent research had found that GHET1 promoted the malignant biological behaviors of glioma U251 cells through down-regulation of miR-216a [35]. Based on the opinions of these researchers, we speculate that GHET1 might up-regulate the expression of ABCC1 protein by targeted regulating some microRNAs.

To sum up, lncRNA GHET1 was highly expressed in BC; the high expression of GHET1 was related with the poor sensitivity to Gemcitabine of BC; and GHET1 contributed to chemotherapeutic resistance to Gemcitabine in BC through up-regulating the multidrug resistance-related gene ABCC1. Our findings are helpful to elucidate the molecular mechanism of chemotherapeutic resistance in BC. However, we have not studied the regulatory mechanism of GHET1 in depth, which requires our follow-up studies.

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Author contributions ZL and DX carried out the experiments and performed the statistical analysis. HZ participated in the study design and drafted the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest to disclose.

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