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Review

# Long noncoding RNA GHET1 in human cancer

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ABSTRACT

LncRNAs are a group of noncoding RNAs that are > 200 nucleotides in length. These RNAs have no significant protein-coding potential due to the lack of obvious open reading frames. To date, accumulating evidence has demonstrated that dysregulation of lncRNAs exhibits indispensable roles in the pathological processes of human cancers. These RNAs function as either oncogenes or tumor suppressor genes to regulate proliferation, migration and invasion of cancer cells. GHET1, a prominent oncogenic lncRNA, is highly expressed in diverse malignancies. Furthermore, GHET1 performs key functions in carcinogenesis and progression, suggesting that GHET1 is expected to be a prospective biomarker or therapeutic target for cancers. In this review, we provide a summary of the current evidence concerning the biological functions, underlying mechanisms and clinical significance of GHET1 during tumor development.

## 1. Introduction

Thanks to remarkable progress in genome sequencing technologies, increasing numbers of lncRNAs, which were originally regarded as transcriptional noise, have been widely reported in recent years [1–3]. LncRNAs, which are mainly transcribed by RNA polymerase II, have emerged as a novel class of ncRNAs > 200 nucleotides in length [4,5]. LncRNAs have no or limited protein-coding capacity as a result of lacking obvious open reading frames [6]. LncRNAs regulate gene expression and pathophysiological processes at the epigenetic, transcriptional and posttranscriptional levels generally *via* gene imprinting, histone modification, chromatin remodeling, transcriptional interference, alternative splicing and cell cycle control [7–14]. Numerous investigations have indicated that aberrant expression of lncRNAs is involved in the occurrence and development of various malignancies through promoting proliferation, invasion and metastasis or inhibiting apoptosis of cancer cells [15–17]. The molecular mechanisms by which lncRNAs impact cellular biological behavior are exceedingly sophisticated. LncRNAs can serve as guides to induce regulatory molecules to the promoters of target genes or can act as decoys to prevent regulatory molecules from binding with promoter regions. LncRNAs also work as scaffolds to recruit protein complexes or function as ceRNAs to competitively bind to target miRNAs [18–22]. Notably, lncRNAs likely represent viable biomarkers or therapeutic targets for the diagnosis and treatment of tumors.

Among the cancer-related lncRNAs, GHET1 is a promising candidate that exhibits high stability, efficiency and specificity. GHET1 is located at chromosome 7q36.1 and has a length of 1913 bp. GHET1 was originally determined to be overexpressed in gastric carcinoma by Yang in 2013, and upregulated GHET1 significantly contributes to cancer progression [23,24]. Subsequently, GHET1 has gradually drawn widespread attention. Increasing studies have reported that GHET1 was overexpressed and predicted a poor prognosis in diverse carcinomas, including gastric carcinoma, bladder cancer, colorectal cancer, hepatocellular carcinoma, esophageal squamous cell carcinoma, pancreatic cancer, non-small cell lung cancer, head and neck cancer, breast cancer, and glioma [25,26]. These findings elucidate the potential clinical value of GHET1 in the research and therapy of cancer. The present review summarizes current studies regarding the expression, function, mechanism and clinical significance of GHET1 in the initiation and progression of cancers (Tables 1 and 2).

*Abbreviations:* GHET1, gastric carcinoma high expressed transcript 1; lncRNAs, long non-coding RNAs; ncRNAs, non-coding RNAs; ceRNA, competing endogenous RNA; miRNAs, microRNAs; GC, gastric cancer; HCC, hepatocellular carcinoma; EMT, epithelial-mesenchymal transition; NSCLC, non-small cell lung cancer; BC, breast cancer; CRC, colorectal cancer; qRT-PCR, quantitative real-time polymerase chain reaction; ESCC, esophageal squamous cell carcinoma; HNC, head and neck cancer; IGF2BP1, insulin-like growth factor-2 mRNA-binding protein 1; KLF2, kruppel-like factor 2; EZH2, enhancer of zeste homolog 2; LATS1, large tumor suppressor 1; YAP1, yes-associated protein 1; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; MDR1, multi-drug resistance protein 1; MRP1, multidrug resistance-related protein 1; ATF1, activating transcription factor 1; PCA3, prostate cancer antigen 3

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**Table 1**
Functional characterization of GHET1 in cancers.

| Cancer types | Expression | Functional role | Related gene | Role | Refs |
|---|---|---|---|---|---|
| Gastric cancer | Upregulated | Proliferation, migration, invasion, apoptosis, drug resistance | IGF2BP1, c-Myc, Bax, Bcl-2, MDR1, MRP1 | Oncogenic | 23,27,28 |
| Hepatocellular carcinoma | Upregulated | EMT, proliferation, migration, invasion, cell cycle arrest, apoptosis | EZH2, KLF2, ATF1, N-cadherin, Vimentin, E-cadherin | Oncogenic | 29,30 |
| Non-small cell lung cancer | Upregulated | EMT, proliferation, invasion | LATS1, YAP1, Twist1, N-cadherin, E-cadherin | Oncogenic | 31,32 |
| Breast cancer | Upregulated | EMT, proliferation, migration, invasion, cell cycle arrest, apoptosis | N-cadherin, Vimentin, E-cadherin | Oncogenic | 33 |
| Colorectal cancer | Upregulated | EMT, proliferation, migration, invasion, cell cycle arrest | E-cadherin, Vimentin, Fibronectin | Oncogenic | 34 |
| Bladder cancer | Upregulated | EMT, proliferation, invasion | E-cadherin, Vimentin, Fibronectin | Oncogenic | 35 |
| Esophageal squamous cell carcinoma | Upregulated | EMT, proliferation, migration, invasion, apoptosis | E-cadherin, Vimentin, N-cadherin | Oncogenic | 36 |
| Pancreatic cancer | Upregulated | Proliferation, apoptosis | – | Oncogenic | 24 |
| Head and neck cancer | Upregulated | Proliferation, migration, invasion, apoptosis, cell cycle arrest | – | Oncogenic | 37 |
| Glioma | Upregulated | Proliferation, migration, invasion, apoptosis | – | Oncogenic | 38 |

IGF2BP1, insulin-like growth factor-2 mRNA-binding protein 1; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; MDR1, multi-drug resistance protein 1; MRP1, multidrug resistance-related protein 1; EMT, epithelial-mesenchymal transition; EZH2, enhancer of zeste homolog 2; KLF2, kruppel-like factor 2; ATF1, activating transcription factor 1; LATS1, large tumor suppressor 1; YAP1, yes-associated protein 1.

## 2. GHET1 deregulation in human cancers

### 2.1. GHET1 in gastric cancer

GHET1 expression was markedly elevated in 42 GC tissues compared with that in paired adjacent nontumor tissues ($P < .001$). Moreover, increased GHET1 expression was significantly correlated with tumor size ($P = .011$) and tumor invasion ($P = .005$). The patients with upregulated GHET1 were indicated to have a worse overall survival by Kaplan-Meier analysis ($P = .039$). Functionally, gain- and loss-of-function analyses demonstrated that GHET1 overexpression contributed to cellular proliferation *in vitro* ($P < .05$) and *in vivo* ($P < .01$), but knockdown of GHET1 suppressed the proliferation of GC cells ($P < .05$) [23]. Subsequently, another study also uncovered that GHET1 was dramatically overexpressed in 20 GC tissues ($P < .001$) and 2 cell lines ($P < .001$) compared with expression in nontumor controls. Enforced GHET1 promoted proliferation ($P < .05$), invasion and migration ($P < .001$) of GC cells but inhibited cellular apoptosis ($P < .05$) [27]. Notably, GHET1 expression was higher in GC tissues from 20 cisplatin drug-resistant patients compared with tissue from 20 drug-sensitive patients ($P < .01$). The same result was also obtained in the cell experiment ($P < .01$), and silencing GHET1 reduced the drug resistance of cisplatin-resistant GC cell lines ($P < .01$) [28]. These findings suggest that GHET1 exhibits tremendous potentiality for the diagnosis and treatment of GC. GHET1 is likely to work as a novel diagnostic biomarker and intervention target.

### 2.2. GHET1 in hepatocellular carcinoma

GHET1 expression was significantly upregulated in 68 HCC tissues ($P < .01$) and 4 cell lines ($P < .01$) compared with corresponding adjacent nontumor tissues and a normal hepatic cell line, respectively. Furthermore, enhanced GHET1 was markedly related to vascular invasion ($P = .006$), cirrhosis ($P = .025$), tumor volume ($P = .001$), Edmindson grade ($P = .003$) and poor prognosis ($P < .05$). Proportional hazards method analysis further showed that GHET1 overexpression was an independent prognostic factor of worse survival ($P = .006$). Pertinent to biological function, knockdown of GHET1 not only inhibited cellular proliferation ($P < .01$) but also caused cell cycle arrest ($P < .01$) and induced apoptosis ($P < .01$) in HCC cell lines [29]. Ding et al. [30] similarly revealed elevated GHET1 expression in 20 HCC tissues ($P < .01$) and 3 cell lines ($P < .01$) in comparison with normal counterparts. Silencing GHET1 could depress the proliferation ($P < .01$), migration and invasion ($P < .01$) of HCC cells *in vitro*. More importantly, upregulated GHET1 induced the EMT of HCC cells by increasing the expression of N-cadherin ($P < .01$) and Vimentin ($P < .01$) but decreasing E-cadherin expression ($P < .01$). GHET1, which serves as an oncogene in cancer progression, may provide a golden opportunity for prognosis evaluation and molecular targeting therapy in HCC patients.

### 2.3. GHET1 in non-small cell lung cancer

GHET1 expression was obviously increased in 52 NSCLC tissues ($P < .001$) and 3 human NSCLC cell lines ($P < .05$) compared with that in adjacent normal tissues and a human bronchial epithelial cell line. The correlation between GHET1 expression and clinicopathological characteristics of NSCLC patients was also analyzed, and the results showed that upregulated GHET1 was closely related to lymph node metastasis ($P = .020$) and TNM stage ($P = .026$). Furthermore, NSCLC patients with elevated GHET1 expression had a poor overall survival time ($P < .05$). Biologically, knocking down GHET1 suppressed cellular proliferation ($P < .05$), invasion ($P < .05$) and the EMT phenomenon ($P < .05$) [31]. Subsequently, additional study also confirmed that GHET1 was markedly overexpressed in 105 NSCLC tissues ($P < .05$). Enhanced GHET1 expression was

**Table 2**
Clinical significance of GHET1 in diverse cancers.

| Cancer types | Overexpression of GHET1 and clinical features | Refs |
|---|---|---|
| Gastric cancer | Tumor size, tumor invasion, and poor survival | 23 |
| Hepatocellular carcinoma | Vascular invasion, cirrhosis, tumor size, edmindson grade, and poor survival | 29 |
| Non-small cell lung cancer | Tumor size, lymph node metastasis, advanced TNM stage, and poor overall survival | 31,32 |
| Breast cancer | Tumor size, advanced clinical stage, lymph node metastasis, and poor overall survival | 33 |
| Colorectal cancer | – | 34 |
| Bladder cancer | Tumor size, advanced tumor grade, and poor overall survival | 35 |
| Esophageal squamous cell carcinoma | Poor differentiation, advanced TNM stage, and lymph node metastasis | 36 |
| Pancreatic cancer | Advanced TNM stage | 24 |
| Head and neck cancer | Lymph node metastasis, advanced TNM stage, and poor survival | 37 |
| Glioma | – | 38 |

GHET1, gastric carcinoma high expressed transcript 1.

significantly correlated with disease stage ($P < .05$), lymph node metastasis ($P < .05$) and tumor size ($P < .05$). In addition, multivariate analysis indicated that enforced GHET1 expression was an independent poor prognostic factor of NSCLC ($P < .05$) [32]. GHET1, a well-characterized oncogenic lncRNA in cancers, may be a feasible diagnostic and therapeutic option for NSCLC patients.

### 2.4. GHET1 in breast cancer

GHET1 expression was significantly increased in 60 BCE tissues compared with normal adjacent tissues ($P < .001$), and upregulated GHET1 was also identified in 4 BCE cell lines ($P < .001$). The correlation analysis showed that increased GHET1 was positively associated with larger tumor size ($P = .0379$), advanced clinical stage ($P = .0191$) and lymph node metastasis ($P = .037$). Furthermore, BC patients with elevated GHET1 expression had a poorer overall survival ($P < .01$). Functionally, knockdown of GHET1 inhibited the proliferation ($P < .01$), invasion and migration ($P < .01$) of BC cells but boosted apoptosis ($P < .01$) and cell cycle arrest ($P < .01$). Elevated GHET1 also promoted EMT by means of increasing the protein expression of N-cadherin and Vimentin but decreasing E-cadherin expression [33]. GHET1 plays a vital role in BC progression and exhibits wonderful characteristics as a tumor indicator and therapeutic target.

### 2.5. GHET1 in colorectal cancer

Zhou et al. [34] demonstrated that GHET1 expression was significantly increased in 20 CRC samples in comparison with the matched adjacent normal tissues using qRT-PCR ($P < .001$); similar results were observed in 3 CRC cell lines ($P < .001$). Functionally, knocking down GHET1 inhibited the proliferation ($P < .001$), migration and invasion ($P < .01$) of CRC cells but induced cell cycle arrest ($P < .01$) *in vitro*. In addition, upregulated GHET1 dramatically increased the expression of Fibronectin and Vimentin but reduced E-cadherin expression, thereby inducing the EMT process. Taken together, GHET1 is expected to become a promising tumor marker and therapeutic target for the detection and therapy of CRC.

### 2.6. GHET1 in bladder cancer

GHET1 was markedly upregulated in 80 bladder cancer tissues compared with that in the paired adjacent normal tissues ($P < .0001$). GHET1 overexpression was closely correlated with tumor size ($P = .005$) and advanced tumor grade ($P = .003$). Kaplan-Meier analysis confirmed that enforced GHET1 expression in bladder cancer tissues was observably related to worse overall survival ($P = .0083$). Moreover, silencing GHET1 suppressed the proliferation ($P < .01$) and invasion ($P < .01$) of bladder cancer cells *in vitro*. In the meantime, knocking down GHET1 reversed the EMT process in bladder cancer cells [35]. Consequently, the research of GHET1 likely offers a feasible direction for the diagnosis and treatment of bladder cancer.

### 2.7. GHET1 in esophageal squamous cell carcinoma

GHET1 expression was significantly increased in 55 ESCC tissues ($P < .05$) and 4 cell lines ($P < .05$) compared with expression in nontumor controls. Upregulated GHET1 expression was evidently associated with poor differentiation ($P = .032$), advanced TNM stage ($P = .022$) and lymph node metastasis ($P = .001$). Knocking down GHET1 suppressed cellular proliferation ($P < .05$), migration and invasion ($P < .05$) but facilitated the apoptosis ($P < .05$) of ESCC cells. In addition, silencing GHET1 significantly increased E-cadherin expression ($P < .05$) and decreased the expression of Vimentin ($P < .05$) and N-cadherin ($P < .05$), implying that upregulated GHET1 could induce EMT [36]. These results indicate that GHET1, an oncogene in ESCC, may be an outstanding therapeutic target to overcome this severe disease.

### 2.8. GHET1 in pancreatic cancer

The expression of GHET1 in 64 pancreatic cancer tissues ($P < .01$) and 5 cell lines ($P < .01$) was observably increased compared with its expression in nontumor controls. Upregulated GHET1 was noticeably correlated with advanced TNM stage ($P = .011$). In addition, functional experiments confirmed that knocking down GHET1 could inhibit the proliferation ($P < .01$) of pancreatic cancer cells and promote cellular apoptosis ($P < .05$) [24]. According to this finding, ongoing and in-depth investigations of GHET1 are likely to lead to a significant breakthrough in the diagnosis and treatment of pancreatic cancer.

### 2.9. GHET1 in head and neck cancer

Liu et al. [37] observed elevated GHET1 expression in 86 HNC tissues ($P < .01$) and 5 cell lines ($P < .01$) in comparison with paired adjacent nontumor tissues and a normal cell line, respectively. Furthermore, upregulated GHET1 expression was significantly related to lymph node metastasis ($P = .0019$), advanced TNM stages ($P = .0171$) and poor prognosis ($P = .0061$). Pertinent to biological function, silencing GHET1 inhibited cellular proliferation ($P < .01$), migration and invasion ($P < .01$) but induced cell cycle arrest ($P < .01$) and apoptosis ($P < .01$) of HNC cells *in vitro*. These findings indicate the great clinical value of GHET1 as a sensitive tumor predictor or a specific therapeutic target.

### 2.10. GHET1 in glioma

GHET1 expression was also significantly increased in 30 glioma tissues compared with normal controls ($P < .001$). Upregulated GHET1 promoted the proliferation ($P < .001$), migration and invasion ($P < .05$) of glioma cells but restrained cellular apoptosis ($P < .001$). In addition, silencing GHET1 suppressed the volume ($P < .05$) and weight ($P < .05$) of tumors *in vivo*. Thus, GHET1 may serve as a potential biomarker and therapeutic target for glioma; however, further

experiments are needed to support this finding [38].

## 3. Regulatory mechanisms of GHET1

IGF2BP1, a type of single-stranded RNA-binding protein, exhibits critical roles in embryogenesis and carcinogenesis by impacting the stability, translatability or localization of target genes [39]. c-Myc is traditionally considered to be an oncogenic molecule in various human carcinomas. IGF2BP1 physically interacts with c-Myc mRNA and prevents its degradation. Interestingly, GHET1 can bind IGF2BP1 ($P < .01$) to reinforce the physical correlation between IGF2BP1 protein and c-Myc mRNA, thereby increasing the stability of c-Myc mRNA ($r = 0.5512$, $P = .0002$) and elevating its expression [23]. This finding implies that the GHET1/IGF2BP1/c-Myc pathway may exert pivotal effects on the occurrence and progression of gastric cancer. Nevertheless, the detailed regulatory mechanism between GHET1 and the c-Myc-IGF2BP1 complex remains to be further investigated.

Mounting evidence confirms that lncRNAs can act as molecular scaffolds to recruit miRNAs or proteins to target genes, thereby epigenetically modulating their expression. KLF2, a member of the zinc finger transcription factor family, has been identified as a tumor suppressor in diverse cancers [40]. EZH2 (a histone modification enzyme) was found to directly bind to the promoter region of KLF2 and induce H3K27me3 modification [41]. Further study uncovered that GHET1 could facilitate HCC cell proliferation partially through recruiting EZH2 to the KLF2 promoter and epigenetically repressing KLF2 expression ($P < .01$) [29]. Hence, epigenetic regulation is one of the vital methods by which GHET1 boosts tumor development.

In addition to the above regulatory mechanisms, GHET1 can also activate signaling pathways. Both LATS1 and YAP1 are core kinases of the Hippo pathway. LATS1 is located upstream of YAP1 [42]. LATS1/YAP1 signaling is a susceptible pathway and accelerates cellular proliferation in various tumors. Silencing GHET1 increased LATS1 expression ($P < .05$) but decreased the expression of YAP1 in NSCLC cells ($P < .05$), suggesting that GHET1 facilitated the occurrence and progression of NSCLC partially through activating LATS1/YAP1 signaling [31]. Further studies are warranted to clarify the exact mechanism involved in GHET1 and LATS1/YAP1 signaling.

In addition, upregulated GHET1 restrained the apoptosis of GC cells by decreasing Bax expression ($P < .01$) and increasing Bcl-2 expression ($P < .01$). Notably, elevated GHET1 also increased the expression of MDR1 ($P < .01$) and MRP1 ($P < .01$) to induce drug resistance in GC [28]. Another investigation revealed that GHET1 could bind to ATF1 and promote its expression both at the mRNA and protein levels in HCC cells ($P < .01$). Thus, GHET1 is involved in the development of HCC in part by regulating ATF1 [30]. The EMT is a crucial mechanism in tumor metastasis. Multiple studies have reported that GHET1 could induce EMT to promote the migration, invasion and metastasis of cancer cells [30,31,33–36] (Fig. 1).

## 4. Conclusions and future perspectives

The dysregulation of lncRNAs has been gradually identified as a hallmark feature in carcinoma progression, as these RNAs play important roles in the transcription and translation of genes. Understanding these molecules will be a potential field for the diagnosis and treatment of cancers. LncRNAs are likely to be identified as tumor biomarkers or therapeutic targets. Up to now, the aberrant expression of several outstanding lncRNAs has been confirmed in body fluids, such as urinary PCA3 and plasma H19. These RNAs have been used as feasible tumor biomarkers in prostate cancer and GC, respectively [43,44].

GHET1 is a well-characterized cancer-related lncRNA and is upregulated in GC, bladder cancer, CRC, HCC, ESCC, pancreatic cancer, NSCLC, HNC, BC, and glioma. Increased GHET1 expression is significantly related to poorer clinicopathological characteristics, such as metastasis and reduced survival. Moreover, GHET1 contributes to the proliferation, migration and invasion of cancer cells *via* extraordinarily complicated regulatory mechanisms. GHET1 can modulate the c-Myc-IGF2BP1 complex, recruit EZH2 to the KLF2 promoter, activate LATS1/YAP1 signaling, regulate apoptosis-related genes and drug resistance-related genes, facilitate ATF1 expression, and induce EMT (Fig. 2). The above studies indicate that GHET1 exerts significant regulatory functions in tumor development. Therefore, GHET1 may act as a promising diagnostic and prognostic biomarker. In addition, GHET1 has strong tumor specificity and reduced systemic toxicity compared with

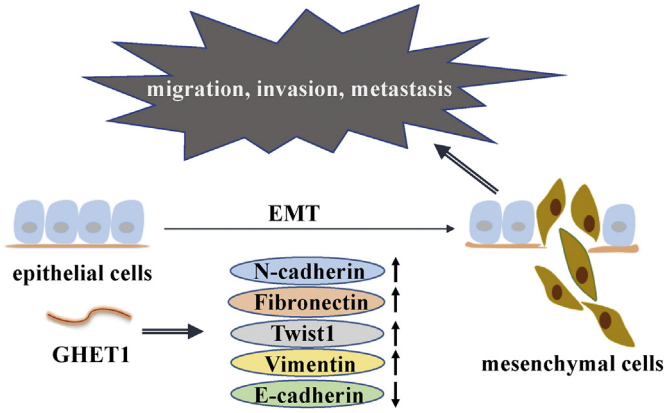


**Fig. 1.** Schematic of the linkage between GHET1 and the EMT in tumors. N-cadherin, Vimentin, Twist1 and Fibronectin are mesenchymal markers, and E-cadherin is an epithelial marker in EMT-related proteins. GHET1 induces the EMT through increasing the expression of N-cadherin, Vimentin, Twist1 and Fibronectin and decreasing E-cadherin expression, thereby facilitating the migration, invasion and metastasis of cancer cells. GHET1, gastric carcinoma high expressed transcript 1. EMT, epithelial-mesenchymal transition.

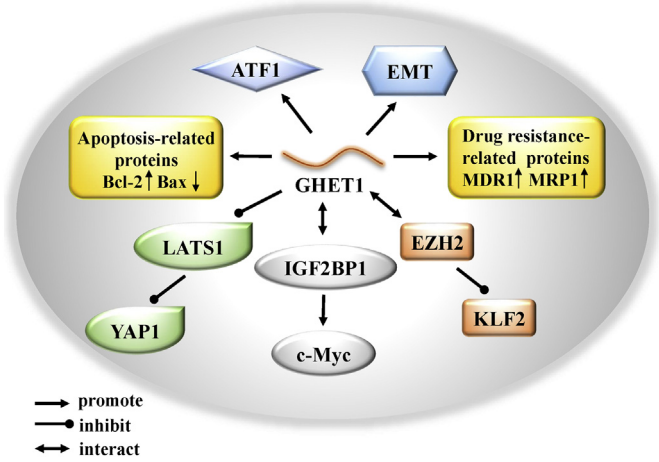


**Fig. 2.** Overview of the regulatory mechanisms of GHET1 during tumor development. GHET1 interacts with IGF2BP1 to enhance the physical association between IGF2BP1 protein and c-Myc mRNA, thereby increasing the stability of c-Myc mRNA and elevating its expression. GHET1 also recruits EZH2 to the promoter region of KLF2 and epigenetically inhibits KLF2 expression. Pertinent to signaling pathways, GHET1 activates LATS1/YAP1 signaling to promote cellular proliferation. Moreover, GHET1 binds to ATF1 and boosts ATF1 expression. GHET1 can also induce the EMT to accelerate cellular migration, invasion and metastasis. In addition, GHET1 increases the expression of Bcl-2, MDR1 and MRP1 and decreases Bax expression to contribute to cancer progression. GHET1, gastric carcinoma high expressed transcript 1. IGF2BP1, insulin-like growth factor-2 mRNA-binding protein 1. EZH2, enhancer of zeste homolog 2. KLF2, kruppel-like factor 2. LATS1, large tumor suppressor 1. YAP1, yes-associated protein 1. ATF1, activating transcription factor 1. EMT, epithelial-mesenchymal transition. Bcl-2, B-cell lymphoma 2. MDR1, multidrug resistance protein 1. MRP1, multidrug resistance-related protein 1. Bax, Bcl-2-associated X protein.

traditional cytotoxic chemotherapy. Hence, GHET1 has great potential to serve as a viable therapeutic target. Nevertheless, the research on GHET1 is still in the preliminary stages, and some critical problems still remain to be systematically investigated. For example, the detailed molecular mechanisms upstream and downstream of GHET1 are not thoroughly understood. Furthermore, the chemical stability and expression of GHET1 in other biological samples (*e.g.*, serum) remain quite obscure. Undoubtedly, larger sample studies and more precise mechanisms will be the research trend and emphasis in the future. It is hopeful that GHET1 will ultimately achieve clinical application.

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## Conflicts of interests

None.

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