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Review

A review on the role of GHET1 in different cancers

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ABSTRACT

Gastric cancer High Expressed Transcript 1 (GHET1) is an RNA gene located on chromosome 7q36.1. This non-coding RNA is involved in the pathology of different cancers. It can regulate cell proliferation, apoptosis and cell cycle transition. Moreover, it induces epithelial-mesenchymal transition. Up-regulation of GHET1 has been correlated with poor prognosis of patients with different malignancies. Besides, its up-regulation has been mostly detected in later stages and advanced grades of cancers. This review summarizes recent studies on the expression of GHET1, its in vitro functions, and its impact on the beginning and progression of cancer based on xenograft models of cancer.

1. Introduction

Cancer is a life-threatening disease that is becoming more common around the world [2]. Despite significant advances in cancer diagnosis and treatment, 19.3 million new affected patients and about 10 million mortalities from cancer were reported in 2020 [11,28]. Finding new cancer-related biomarkers can aid in the diagnosis and treatment of this disorder. Long non-coding RNAs (lncRNAs) are a new class of ncRNAs that have a length of more than 200 nucleotides and do not produce proteins [1,5]. These ncRNAs participate in various cellular processes such as cell proliferation, growth, invasion, metastasis, cell cycle regulation, and apoptosis [8,13]. Their inappropriate expression is involved in the occurrence and progression of various malignant tumors [22,25,30]. The molecular mechanisms through which lncRNAs act are complex. They can act as inducing or repressing regulatory molecules for target genes [23,26]. Gastric cancer High Expressed Transcript 1 (GHET1) is an RNA gene located on chromosome 7q36.1. It has a length of 1913 bp [16]. This gene encodes an unspliced lncRNA that has been suggested to promote the proliferation of cancer cells and is abnormally expressed in gastric cancer [36]. According to bioinformatics analyses, GHET1 is related to several microRNAs (miRNAs) and proteins and can influence cell growth and proliferation by interacting with them (Fig. 1). The increased expression of GHET1 in many cancers is associated with clinical data. Comprehensive investigations can help in better understanding the course of cancer and diagnosing cancer in early stages. Up-regulation of GHET1 has been reported in different in vitro studies. Moreover, its up-regulation has been correlated with poor prognosis of patients with different malignancies. This review summarizes recent studies on the expression of GHET1, its in vitro functions, and its impact on the beginning and progression of cancer based on xenograft models of cancer.

2. Cell line studies

The role of GHET1 in the carcinogenesis has been evaluated in a variety of cancer cell lines. Cell experiments in gastric cancer cell lines have shown that GHET1 silencing leads to suppression of cell proliferation, invasion and migration capacities and enhancement of cell apoptosis and the G1 phase. More importantly, GHET1 silencing can increase E-cadherin expression and reduce levels of fibronectin and

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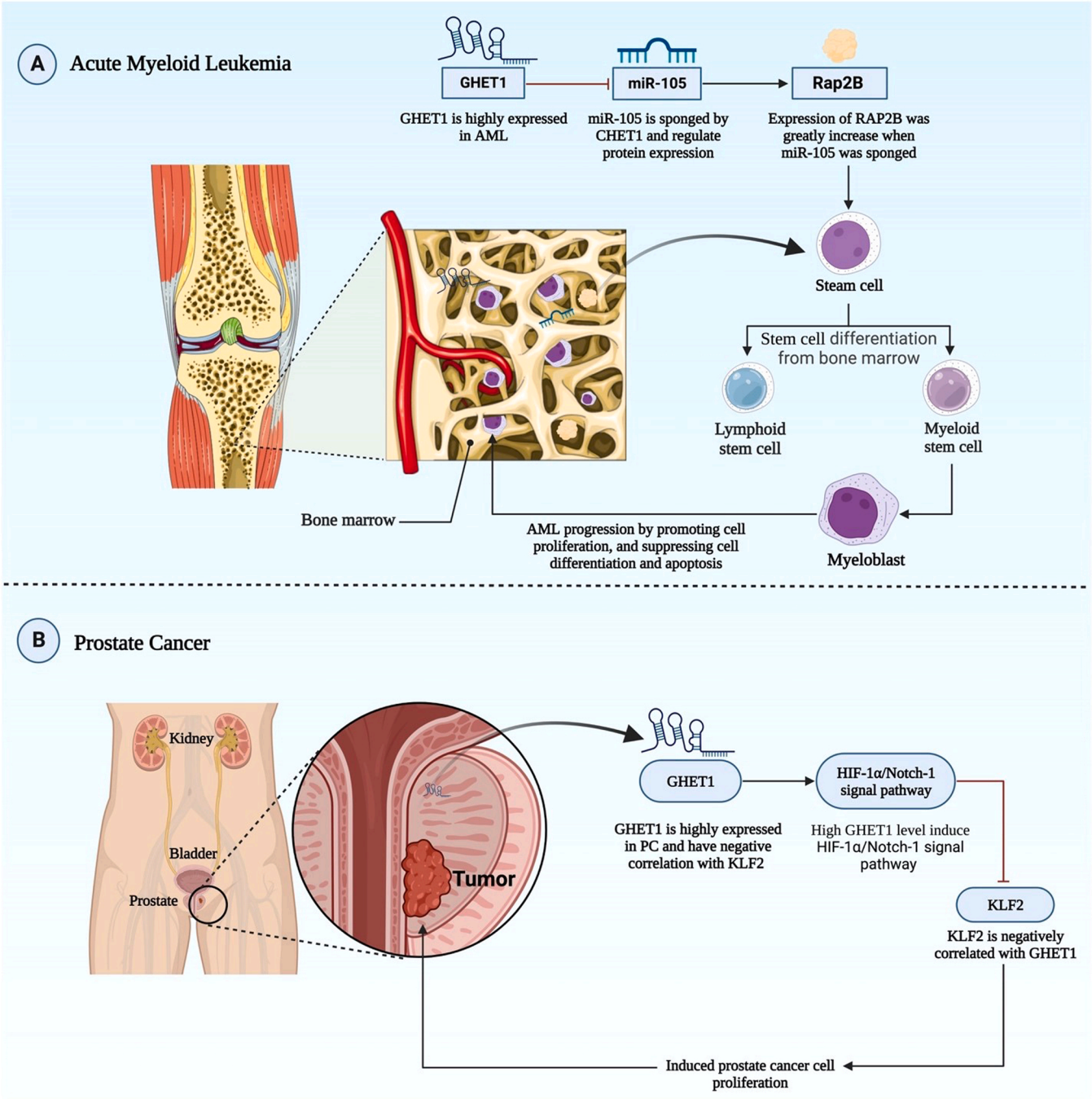

Fig. 1. The functional interplay of GHET1 lncRNA in human acute myeloid leukemia and prostate cancer. (A) High GHET1 expression contributes to the development of AML by enhancing cell proliferation, repressing cell differentiation, and preventing apoptosis. These effects are mediated by miR-105 sponging and RAP2B gene expression regulation. (B) High levels of GHET1 in PC tissues activated the HIF-1/Notch-1 signal pathway by inhibiting KLF2. As a result, GHET1 dramatically increases cell proliferation, suppresses G0/G1 cell cycle arrest, and prevents cell death.

vimentin. Therefore, GHET1 promotes activation of gastric cancer cells activations, and its dysregulation has a possible role in the occurrence and development of this cancer [12]. Similarly, another study has shown that GHET1 knock-down induces G0/G1 arrest in gastric cancer cells and inhibits their proliferation, migration, and invasion. Consistent with these observations, GHET1 silencing has led to the reduction of expression and activity of positive cell-cycle regulators (cyclin D, CDK4, CDK6, cyclin E, CDK2), and the induction of activity of P21, an important negative regulator cell proliferation. Therefore, the underlying mechanism of participation of GHET1 in the regulation of cell cycle progression and cell migration is possibly its role in the regulation of expression of P21, cyclin and CDK [34]. Besides, GHET1 silencing in cisplatin-resistant gastric cancer cells has led to inhibition of multidrug resistance which has been accompanied by an inhibition rate as demonstrated by the MTT assay.

Compared to healthy bone marrow mononuclear cells, AML cell lines have significantly higher GHET1 expression levels. Xiao et al. showed that reducing GHET1 levels in AML cell caused them to stop dividing and instead undergo differentiation and apoptosis. In addition, they proved that GHET1 linked to miR-105 in a direct manner, which suppressed the expression of miR-105 [35] (Fig. 1a).

Moreover, the Annexin V/PI test has shown that GHET1 silencing

Table 1
Role of GHET1 in cancer cell lines (EMT: epithelial-to-mesenchymal transition, MDR: multidrug resistance, PCNA: proliferating cell nuclear antigen, VHL: von Hippel-Lindau, KLF2: Kruppel-like factor 2, Δ: knock-down or deletion).

Tumor type	Related Pathways	Related genes/proteins/ Drugs	Cell lines		Function	References
			Cancer cell lines	Normal cell lines		
Gastric cancer	_	E-cadherin, fibronectin, vimentin, numb	BGC-823, SGC-7901 and AGS	GES-1	ΔGHET1: ↓cell proliferation, invasion and migration activities and ↑cell apoptosis and G1 phase, ↑E-cadherin, ↓fibronectin and vimentin GHET1 has a negative correlation with Numb (tumor suppressor gene).	[12]
Gastric cancer	_	PCNA, cyclin D, cyclin E, CDK4, CDK6, CDK2, P21	AGS, BGC-823, HGC-27, SGC-7901 and MGC-803	GES-1	ΔGHET1 induces G0/G1phase arrest and inhibits cell proliferation, migration, and invasion, decreases DNA synthesis and the expression of PCNA. Furthermore, GHET1 knockdown reduces positive cell cycle regulators while increasing negative ones.	[34]
Gastric cancer	_	Bax, Bcl-2, MDR1, MRP1, cisplatin	BGC823/DPP and SGC7901/DDP	_	ΔGHET1 inhibits MDR. ↑↑GHET1: ↓Bax and ↑Bcl-2, MDR1 and MRP1 expression, ↓sensitivity of BGC823 and SGC7901 cells to cisplatin.	[39]
Gastric cancer	_	IGF2BP1, c-Myc	MKN45 and AGS	_	GHET1 increases c-Myc mRNA stability.	[36]
Breast cancer	PI3K/AKT signaling pathway	EGFR, c-Myc, Cyclin D1, MMP2/9	MCF-7	_	ΔGHET1: ↓cell proliferation, induces cell apoptosis and cell cycle arrest and ↓expression PI3K, AKT, cyclin D1, MMP-2 and − 9.	[10]
Breast cancer	_	N-cadherin, vimentin, and E-cadherin	SKBR3, ZR-75–1, BT-20 and MCF-7	MCF-10A	ΔGHET1: ↓proliferation, invasion and migration, and ↑apoptosis and G0/G1 cell cycle arrest, ↓N-cadherin and vimentin, but ↑E-cadherin. ↑↑GHET1 promotes EMT.	[27]
Triple-Negative Breast Cancer (TNBC)	miR-377–3p/ GRSF1 Signaling Axis	MMP-9 and MMP-2	MDA-MB-468 and HCC1937	MCF10A	↑↑GHET1: ↑ MMP-9 and MMP-2 protein expression levels and ↑proliferation and migration ability, ↓apoptosis.	[31]
Cervical cancer	_	_	SiHa, C-33A, HeLa and CaSki	Ect1/E6E7	ΔGHET1: ↓proliferation, migration, and invasion.	[38]
Cervical cancer	PTEN/PI3K/AKT signaling pathway	P53, matrix metalloproteinase (MMP)− 2 and MMP-9	HeLa and SiHa	_	ΔGHET1: ↑G1 phase, apoptosis and ↓cell proliferation, invasion, migration.	[18]
Ovarian cancer	_	E3 ubiquitin ligase (VHL), HIF1a	OVCAR3, SKOV3, 3AO and A2780	HOSEpiC	↑↑GHET1: promotes the proliferation and colony formation GHET1: ↑expression of HIF1α via interacting with the E3 ubiquitin ligase VHL, ↑glucose consumption and lactate production of both A2780 and SKOV3 cells which indicates that GHET1 up-regulation promotes the glycolysis.	[19]
Bladder cancer	_	ABCC1, Gemcitabine resistance	J82, T24 and SV-HUC-1	_	GHET1 contributes to Gemcitabine chemoresistance by upregulating ABCC1 Expression.	[24]
Bladder cancer	_	_	RT4, RT112, 253 J and T24	CRL-9520	ΔGHET1: ↓proliferation and invasion and inhibition of GHET1 reverses the EMT in bladder cancer cell lines.	[17]
Hepatocellular carcinoma	_	KLF2, PRC2/ EZH2	HepG2, Hep3B, Bel-7402 and SMMC-7721	L02	ΔGHET1: ↓cell proliferation, induces apoptosis and cell cycle arrest. GHET1 represses KLF2 via interacting with EZH2/ PRC2.	[14]
Hepatocellular carcinoma	_	ATF1, H3K27	SMMC-7721, Huh7 and HepG2	LO2	ΔGHET1: ↓ proliferation, migration, invasion, EMT and ATF1 expression. ↑↑ATF1 reverses the above process H3K27 acetylation activates GHET1.	[6]
Osteosarcoma	_	_	U2OS, MG-63 and KHOS	NHOst	ΔGHET1: ↓cell proliferation, invasion, migration, EMT and ↑cell apoptosis.	[37]
Osteosarcoma	Wnt/β-catenin signaling pathway	_	U2OS, MG-63 and SaOs-2	hFOB	ΔGHET1: ↓proliferation, migration, invasion and EMT, and ↑apoptosis.	[4]
Esophageal Squamous Cell Carcinoma (ESCC)	_	Vimentin, N-cadherin, E-cadherin	EC109, EC9706, KYSE30, and KYSE450	Het-1A	ΔGHET1: ↓ESCC cells proliferation, migration, invasion, EMT and ↑cells apoptosis.	[21]
Prostate cancer	HIF-1α/Notch-1	KLF2	LNCap and C4–2	_	GHET1 has a negative correlation with KLF2 expression. ΔGHET1 induces KLF2 upregulation and HIF-1α/ Notch-1 pathway suppression, also ↓proliferation, ↑cell cycle arrest at G0/G1 phase and promotes cell apoptosis.	[42]
Glioma	GHET1-miR-216a axis, JAK2/STAT3 and p53/survivin	_	U251	_	↑↑ GHET1: ↑viability, migration and invasion of U251 cells and ↑pro-cell cycle genes (Cyclin D1, CDK4 and CDK6), and pro-metastasis genes (MMP-	[3]

(*continued on next page*)

Table 1 (*continued*)

Tumor type	Related Pathways	Related genes/proteins/ Drugs	Cell lines		Function	References
			Cancer cell lines	Normal cell lines		
	signaling pathways				9 and Vimentin). Also, ↑↑ GHET1 activates the JAK2/STAT3 and p53/survivin.	
Non-small cell lung cancer	LATS1/YAP pathway	_	A549, H1299 and SK-MES-1	BEAS-2B	ΔGHET1: ↓cell proliferation, invasion, EMT and LATS1/YAP pathway by ↓YAP1 expression.	[9]
Renal cell carcinoma	_	_	786-O and A498	293 cells	ΔGHET1: ↓cell proliferation, migration and EMT.	[15]
Pancreatic cancer	_	_	SWl99, CFPAC-1, Panc-1, BxPC-3 and L3.6P1	HPDE6c7	ΔGHET1: ↓proliferation, and ↑apoptosis.	[40]
Colorectal cancer (CRC)	_	E-cadherin, fibronectin and vimentin	Lovo, HCT-116, and Caco-2	HCoEpiC	ΔGHET1: ↓proliferation, migration, and invasion and inhibition of GHET1 reverses the EMT in CRC cell lines.	[41]
Head and neck cancer	_	_	FaDu, OECM1, SCC25, SAS and Cal-27	HOK	ΔGHET1: ↓cell proliferation, migration, invasion and ↑cell apoptosis and causes cell cycle arrest.	[20]
Thyroid cancer (TC)	_	_	TPC-1 and BCPAP	Nthy-ori3–1	ΔGHET1: ↓ proliferation, invasion and migration, and ↑cell apoptosis and cell cycle arrest. (BCPAP cell line) ↑↑GHET1: ↑ invasion, migration, proliferation, and cell cycle transition and ↓cell apoptosis. (TPC-1 cell line)	[32]
Acute Myeloid Leukemia (AML)	GHET1/miR-105/RAP2B axis	_	NB4, HL-60 and HEK293T	_	ΔGHET1: ↓proliferation and ↑differentiation and apoptosis in AML cell lines. GHET1 binds to miR-105 and downregulates miR-105 expression. ↓miR-105: ↑RAP2B and vice versa.	[35]

reduces half maximal inhibitory concentration (IC50) of cisplatin in cisplatin-resistant gastric cancer cells. On the other hand, over-expression of GHET1 could reduce sensitivity to cisplatin, decrease inhibition rate and apoptotic cell rate and enhance IC50 in BGC823 and SGC7901 cells. Expression assays have confirmed that GHET1 up-regulation results in the downregulation of Bax expression and upregulation of Bcl-2, MDR1 and MRP1 expressions in BGC823 and SGC7901 cell lines [39]. Gain-of-function and loss-of-function assays have also verified the role of GHET1 in the enhancement of gastric cancer cells proliferation in another study [36]. The physical association between GHET1 and IGF2BP1 has been affirmed through RNA pull-down and immunoprecipitation studies. This lncRNA can also enhance the interaction between c-Myc mRNA and IGF2BP1, leading to enhancement of stability of c-Myc transcript and elevation of its expression. Suppression of c-Myc eliminates the impacts of GHET1 on cell proliferation in gastric cancer [36].

In the context of breast cancer, GHET1 suppression has also been shown to decrease growth and metastatic ability of MCF-7 through modulation of EGFR expression. GHET1 knockdown has led to suppression of proliferation, migratory aptitude, and invasive characteristics of MCF-7 cells and enhancement of cell apoptosis through keeping these cells in the G1 phase. Moreover, GHET1 silencing has resulted in reduction of expression of EGFR and related proteins leading to inhibition of PI3K/AKT/Cyclin D1/MMP2/9 pathway [10]. The impact of GHET1 silencing on suppression of cell proliferation, invasiveness and migration, and induction of apoptosis and G0/G1 arrest has also been confirmed in MCF cells in another study [27]. GHET1 silencing has also decreased expression of N-cadherin, vimentin, and reduced E-cadherin levels in MCF-7 cells. Instead, up-regulation of GHET1 has led to induction of proliferation, invasion and migration, and inhibition of cell apoptosis in BT-20 cell line. The latter has been accompanied by induction of epithelial mesenchymal transition (EMT) in these cells [27]. GHET1 has also been found to be over-expressed in triple negative breast cancer cell lines where it increases proliferation rate and migration ability, but decreases apoptosis. Besides, up-regulation of GHET1 in these cells leads to upregulation of MMP-9 and MMP-2 proteins. Expression of miR-377–3p is positively related with GRSF1 levels, but negatively related with levels of GHET1. The effect of GHET1 on migration and proliferation of triple negative breast cancer cells has been attenuated by miR-377–3p mimics [31].

Table 2
Animal studies on the role of GHET1.

Tumor type	Results	References
Triple-Negative Breast Cancer	Tumor volume and weight are significantly reduced after lncRNA GHET1 knockdown, whereas the opposite changes occurred after GHET1 overexpression.	[32]
Breast cancer	ΔGHET1: ↓tumor volume and weight	[10]
Osteosarcoma	ΔGHET1: ↓tumor growth and metastasis and ↑apoptosis.	[37]
Osteosarcoma	ΔGHET1: ↓tumor volume and weight	[4]
Breast cancer	ΔGHET1: ↓tumor growth, N-cadherin and vimentin, and ↑ E-cadherin	[27]
Gastric carcinoma	↑↑GHET1: ↑tumor growth	[36]

Small interfering RNA-mediated knock-down of GHET1 in cervical cancer cells has led to induction of cell apoptosis and maintenance of cells in the G1 phase. Moreover, it has suppressed invasion and migration of these cells in parallel with influencing expressions of PTEN, PI3K, AKT, P53, MMP-2 and MMP-9 [18]. Additionally, inhibiting the HIF-1/Notch-1 signaling pathway via KLF2 after GHET1 lncRNA knockdown reduces prostate cancer cell growth [42] (Fig. 1b).

Table 1 shows the role of GHET1 in different cancers based on cell line studies.

3. Studies in animal models

The effect of GHET1 over-expression on enhancement of gastric cancer proliferation has been verified through conduction of gain-of-function and loss-of-function assays in vivo [36]. Administration of a GHET1 inhibitor has also led to prevention of breast tumor growth in vivo [10]. Besides, GHET1 silencing has suppressed in vivo growth of MCF-7 cells, reduced N-cadherin and vimentin levels, and enhanced E-cadherin expression in the tumor tissues of animal [27]. Other studies in animal models have also affirmed the oncogenic role of GHET1 (Table 2).

Table 3
Expression studies in clinical samples on the role of GHET1 (OS: overall survival, DFS: disease free survival, PTN: parried tumor and non-tumoral samples).

Tumor type	Samples	Expression (tumor vs. normal)	Kaplan–Meier analysis (impact of GHET1 dysregulation)	Cox regression analyses	Association of dysregulation of GHET1 with clinical features	References
Thyroid cancer	43 PTN	Up	_	_	Tumor invasion, gender and lymph node metastasis	[32]
Triple-Negative Breast Cancer	_	Up	_	_	_	[32]
Cervical cancer	40 patients	Up	_	_	_	[33]
Breast cancer	30 PTN	Up	_	_	Tumor invasion	[10]
Acute Myeloid Leukemia	_	Up	_	_	_	[35]
Cervical cancer	94 cancer tissue specimens and 47 normal tissue specimens	Up	worse OS	High expression of GHET1 is an independent prognostic factor.	Advanced clinical stage, lymph node metastasis, distant metastasis and poor histological grade	[38]
Cervical carcinoma	36 PTN	Up	_	_	PTEN low expression	[18]
Bladder cancer	74 patients	Up	_	_	High grade, muscle invasion and low Gemcitabine sensitivity	[24]
Hepatocellular carcinoma	68 PTN	Up	shorter OS	high expression of GHET1 is an independent prognostic factor.	Vascular invasion, cirrhosis, tumor size, edmindson grade, and poor prognosis.	[14]
Hepatocellular carcinoma	20 PTN	Up	_	_	_	[6]
Esophageal Squamous Cell Carcinoma	55 PTN	Up	_	_	Poor differentiation, advanced tumor nodes metastasis stage, and lymph node metastasis	[21]
Triple-Negative Breast Cancer	20 PTN	Up	_	_	_	[31]
Prostate cancer	30 patients	Up	_	_	Gleason score and Tumor stage	[42]
Non-small cell lung cancer	105 patients	Up	shorter OS and PFS	GHET1 expression, lymph node metastasis and disease stage are independent prognostic factors of NSCLC.	disease stage, lymph node metastasis and tumor size	[29]
Gastric Cancer	20 patients	Up	_	_	Tumor invasion	[12]
Osteosarcoma	60 patients	Up	shorter OS	TNM stage, distant metastasis and lymph node metastasis	TNM stage, distant metastasis and lymph node metastasis	[37]
Non-small cell lung cancer (NSCLC)	52 PTN	Up	Poor OS	GHET1 expression is a prognostic biomarker for NSCLC patients.	Lymph node metastasis and TNM stage	[9]
Renal cell carcinoma	40 PTN	Up	shorter OS	_	Histological grade, clinical stage and metastasis	[15]
Pancreatic cancer	64 patients	Up	_	_	TNM stage	[40]
Breast cancer	60 PTN	Up	poorer OS	_	Larger tumor size, advanced clinical stage and lymph node metastasis	[27]
Bladder cancer	80 PTN	Up	worse OS	_	Tumor size, advanced tumor and lymph node status	[17]
Colorectal cancer	20 PTN	Up	_	_	_	[41]
Gastric carcinoma	42 PTN	Up	worse OS	_	Tumor size and tumor invasion	[36]
Gastric cancer	42 PTN	Up	_	_	Tumor invasion depth	[34]
Gastric cancer	30 PTN	Down	_	_	Lymph node status	[7]
Head and neck cancer	86 PTN	Up	shorter OS	_	Advanced TNM stage and lymph node metastasis	[20]
Ovarian cancer	50 patients	Up	_	_	Tumor size and metastasis	[19]

4. Studies in clinical samples

Over-expression of GHET1 has been reported in clinical samples from diverse types of tumors. In gastric samples, its expression has been found to be higher in cancerous tissues compared with adjacent non-tumor tissues. Moreover, expression of GHET1 has been correlated with the pathological features of gastric tumors, particularly invasion depth of tumors [34]. Another study in gastric cancer has revealed that GHET1 over-expression correlates with tumor dimension, tumor invasion and poor survival [36]. Moreover, a strong correlation has been found between expressions of GHET1 and c-Myc in gastric cancer tissues [36]. GHET1 has also been demonstrated to be over-expressed in breast cancer tissues, and its up-regulation has been positively correlated with greater tumor size, advanced clinical stages, lymph node metastases and shorter overall survival [27].

Elevation of GHET1 expression has also been detected in cervical cancer tissues compared with adjacent normal cervical tissues. Notably, elevated levels of GHET1 have been found to useful markers for discrimination of cervical cancer tissues from non-tumorous tissues. Additionally, GHET over-expression has been associated with advanced clinical stages, lymph node metastases, distant metastases and poor differentiation in cervical cancer, indicating unfavorable prognosis in this type of cancer [38]. Another study in cervical tissues has shown significant difference in the levels of GHET1 and PTEN protein between cancerous and adjacent normal tissues. Expression of both has also been correlated with clinical data [18].

Cumulatively, GHET1 is recognized as an oncogenic lncRNA in different types of cancers (Table 3). The only exception is a study in Iranian patients with gastric cancer which reported down-regulation of GHET1 [7].

5. Discussion

GHET1 is an example of oncogenic lncRNAs that contributes to the development of numerous types of cancers [3,15]. This lncRNA has been firstly identified in gastric cancer [36] and the bulk of in vitro studies

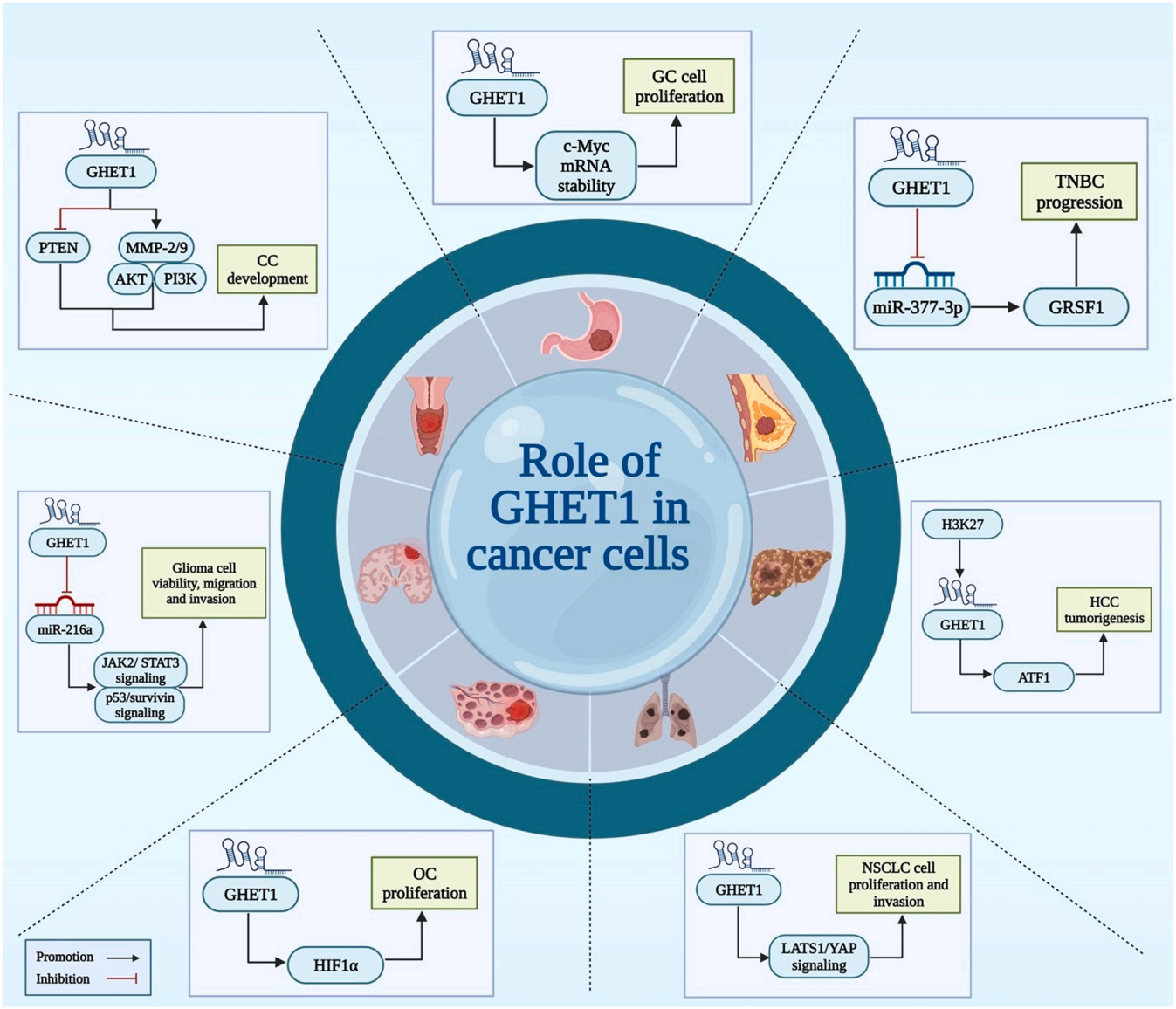

Fig. 2. Examples and mechanisms of GHET1 lncRNA in different types of cancer. GHET1 can progress different cancers through miRNA sponging, inhibiting or promoting specific genes, and direct targeting signaling cascades.

have been focused on its role in this type of cancer. Experiments in animal models of cancers have also affirmed the oncogenic role of GHET1 [4].

This lncRNA can act as a molecular sponge for miRNAs [31], but this aspect of GHET1 function has not been studied comprehensively. The sponging effect of GHET1 on miR-377–3p and subsequent regulation of GRSF1 expression is an example of such mechanism which is involved in the pathogenesis of triple negative breast cancer [31]. Moreover, the regulatory role of GHET1 on miR-105/RAP2B axis contributes to the pathogenesis of leukemia [35]. Other examples of competing endogenous RNA effects should be studied in future studies.

GHET1 has been shown to affect activity of PTEN/PI3K/AKT, Wnt/β catenin, HIF-1α/Notch-1, JAK2/STAT3, p53/surviving and LATS1/YAP signaling pathways (Fig. 2).

Association between GHET1 expression and clinicopathological data has been well studied in different cancers. These studies have indicated that over-expression of GHET1 is more commonly seen in advanced stages, poorly differentiated cancers, and cancers with higher propensity for distant metastases. Thus, GHET1 expression level is a predictive marker for poor clinical outcome of cancers.

Although function of GHET1 has been investigated in several cancer cell lines and its expression has been found to be elevated in different types of cancers, several issues have not been assessed about this lncRNA. First, role of single nucleotide polymorphisms in the function and expression of this lncRNA and their association with risk of malignancies have not been investigated. Moreover, the significance of GHET1 levels in determination of response of cancer patients to anticancer treatments has not been assessed. Besides, the possibility of application of GHET1 inhibitors in the treatment of cancer should be studied.

Taken together, GHET1 is an oncogenic lncRNA that might be used as a therapeutic target for cancers.

Ethics approval and consent to participant

Not applicable.

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CRediT authorship contribution statement

SGF wrote the draft and revised it. MT designed and supervised the study. SAT, BMH and HZ collected the data and designed the figures and tables. All the authors read the submitted version and approved it.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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Consent of publication

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