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Roles of long non-coding RNA *HULC* in human digestive system cancers

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Digestive system cancers, including hepatocellular carcinoma (HCC), gastric cancer (GC), pancreatic cancer (PC), and colorectal cancer (CRC), pose a significant global health burden with high morbidity and mortality rates. Their tumorigenesis and progression are driven by complex interactions between genetic alterations and environmental factors. In recent years, long non-coding RNAs (lncRNAs) have emerged as critical regulators in cancer initiation, metastasis, and drug resistance through epigenetic modulation, transcriptional regulation, and post-transcriptional modifications. Among them, HULC, a well-characterized oncogenic lncRNA, was initially identified in HCC due to its remarkable upregulation. Subsequent studies have revealed that HULC is aberrantly overexpressed in multiple gastrointestinal malignancies, including GC, PC, and CRC, and its expression levels strongly correlate with advanced clinical stage, metastatic potential, and poor patient prognosis. Mechanistically, HULC exerts its oncogenic effects by interacting with genes, RNA, and proteins to promoting the Warburg effect, and inducing epithelial-mesenchymal transition (EMT), thereby facilitating tumor progression. This review comprehensively summarizes recent advances in understanding the biological roles, molecular mechanisms, and clinical implications of HULC in digestive system cancers. Furthermore, we discuss its potential as a novel diagnostic biomarker and therapeutic target, providing insights into precision medicine strategies for gastrointestinal malignancies.

KEYWORDS

lncRNA, HULC, digestive system cancers, cancer, ceRNA

1 Introduction

Digestive system tumors, mainly including hepatocellular carcinoma (HCC), pancreatic cancer (PC), gastric cancer (GC), and colorectal cancer (CRC), represent a major cause of cancer-related morbidity and mortality worldwide. According to recent statistics, more than 5 million new cases are diagnosed annually, resulting in approximately 4 million deaths globally. This imposes a substantial economic burden on patients, families, and healthcare systems (1, 2). Despite the availability of diverse treatment modalities, including surgery, chemotherapy, radiotherapy, immunotherapy and targeted therapies,

therapeutic efficacy remains limited, particularly for patients with advanced or metastatic disease (3, 4). Consequently, the identification of novel molecular targets is urgently needed to improve diagnostic precision and develop more effective treatment strategies for digestive system cancers.

Long non-coding RNAs (*lncRNAs*), a class of non-protein-coding transcripts longer than 200 nucleotides, are transcribed by RNA polymerase II and have emerged as key regulators in cancer biology (5). Increasing evidence indicates that *lncRNAs* play critical roles in tumor initiation, proliferation, invasion, and prognosis through various mechanisms, including epigenetic modification, chromatin remodeling, and post-transcriptional regulation (6–9). Among these mechanisms, the competitive endogenous RNA (*ceRNA*) network is particularly noteworthy. In this context, *lncRNAs* act as molecular sponges by binding to microRNAs(*miRNAs*), thereby modulating the expression of downstream target genes. This *ceRNA*-mediated regulatory axis is now recognized as a significant contributor to tumor progression (5, 10, 11).

HULC is located on chromosome 6p24.3 (12). Following transcription and post-transcriptional processing, a mature lncRNA is produced (12). Increasing evidence suggests that *HULC* is aberrantly expressed in various gastrointestinal cancers, including hepatocellular carcinoma, gastric cancer, and colorectal cancer (13–15). Additionnally, *HULC* has also been shown to promote the progression of other systemic cancers, including breast cancer, lung cancer, ovarian cancer, and osteosarcoma (16–19).For instance, *HULC* promotes the metastasis and cisplatin resistance of triple-negative breast cancer cells by targeting the trans-IGF1R-PI3K-AKT axis35981570. Additionally, *HULC* enhances the proliferation of lung squamous cancer cells by regulating the PTPRO/NF-κB signaling pathway (17). However, in comparison to non-gastrointestinal cancers, *HULC* shows a stronger correlation with digestive system cancers (20, 21). Furthermore, *HULC* has been studied most extensively within the context of digestive system cancers.Therefore, we have decided to focus on digestive system tumors to thoroughly investigate the biological functions and clinical significance of *HULC* in this area.

The expression of *HULC* expression is regulated through multiple molecular mechanisms. For instance, *HULC* can interact with IGF2 mRNA-binding protein 1 (IGF2BP1), leading to reduced *HULC* stability and promoting transcript degradation (22). Additionally, *miR-203* has been shown to participate in the post-transcriptional regulation of *HULC* (23). In this review, we summarize the expression patterns, biological functions, and molecular mechanisms of *HULC* in digestive system cancers, and discuss its potential as a novel diagnostic biomarker and therapeutic target. The current body of evidence highlights the pivotal role of *HULC* in the initiation, progression, and metastasis of digestive system tumors, underscoring its promise as a target for future precision medicine strategies.

2 Characterization of *HULC*

HULC is located on chromosome 6, spanning positions 8,435,568 to 9,294,133 on the human genome reference sequence GRCh38.p14. According to Ensembl websites, there are a total of 217 transcripts(splice variants) for *HULC*. Among them, the transcript *lncRNA HULC-202*(Ensembl transcript ID: ENST00000503668.3; NCBI transcript ID: NR_004855.3) is the most well-characterized transcript, with a length of 434 base pairs. Additionally, *lncRNA HULC*-202 has been studied across various types of cancers, including liver, gastric, and colorectal cancer (24–26). Accumulating evidence shows that *HULC* is aberrantly expressed in various gastrointestinal malignancies, including liver, gastric, and colorectal cancers (13–15). Although the physiological functions and molecular mechanisms of *HULC* are not yet fully understood, current findings can be summarized into the following major functional roles:

1. HULC and gene activation and inhibition: HULC regulates the histone modification pattern in the promoter region of the *YAP* gene by increasing the enrichment of H3K4me3 and reducing the enrichment of H3K27me3. Under hyperglycemic conditions, HULC promotes the transcriptional activation of the *YAP* gene, which is linked to the proliferation of pancreatic cancer cells and enhanced drug resistance (27). Furthermore, HULC may also influence the expression of neighboring genes. In radiation-induced liver cancer, HULC was found to downregulate the expression of the nearby gene *CDKN1* through complementary base pairing, thereby affecting tumor progression. Additionally, Li Dan et al. reported that downregulation of HULC expression in hepatoma cell lines such as Hep3B and HepG2 led to reduced expression of the adjacent gene *SLC35B3* (28).
2. The interaction between HULC and RNA(Acting as a ceRNA): HULC functions as a ceRNA by sharing miRNA binding sites with target transcripts. Through this mechanism, *HULC* competitively binds miRNAs, thereby mitigating their inhibitory effects on downstream target gene expression. This is currently the most extensively studied mechanism. For example, in liver cancer, *HULC* directly binds to *miR-372*, leading to *miR-372* decreased expression and activity. In turn, *miR-372* normally reduces the phosphorylation of cAMP response element-binding protein (CREB), thus diminishing CREB's binding to the *HULC* promoter and lowering *HULC* transcription. Consequently, a positive feedback loop is established, further enhancing *HULC* expression (29). Moreover, *HULC* promotes autophagy through the *miR-675*/PKM2 axis, leading to upregulation of Cyclin D1 and accelerated proliferation of liver cancer stem cells (30). Similarly, via the *miR-9*/PPARA signaling pathway, *HULC* activates ACSL1 and induces abnormal lipid metabolism in liver cancer cells, contributing to disease progression (31). In gastric cancer, *HULC* promotes cell proliferation, migration, invasion and resistance to apoptosis through the *miR-9-5p*/MYH9 axis (25).
3. The interaction between *HULC* and proteins: Lactate dehydrogenase A (LDHA) and pyruvate kinase M2 (PKM2) are two key enzymes involved in glycolytic reprogramming, a hallmark of cancer that promotes rapid

cell growth and survival. Studies have demonstrated that *HULC* can directly bind to and increase the phosphorylation of both LDHA and PKM2, thereby enhancing glycolysis in HCC cell lines and facilitating tumor progression (32). Furthermore, *lncRNA MEG3* promotes the binding of the p53 protein to *HULC*, influencing the interaction between the telomere length maintenance complex and telomeric DNA, which leads to reduced telomere stability (33).

4. Overall, *HULC* interacts with genes, RNA, and proteins to promote tumor cell metabolism reprogramming(Warburg effect), and an anti-apoptotic phenotype. Ultimately, it contributes to epithelial-mesenchymal transition (EMT), invasion and metastasis, and immune escape in cancers.

3 *HULC* in digestive tumors

Recent studies have highlighted the pivotal role of lncRNAs in the pathogenesis of digestive system cancers. Aberrant expression of lncRNAs has been implicated in key oncogenic processes such as cell proliferation, invasion, metastasis, epithelial-mesenchymal transition, and resistance to apoptosis. As research has progressed, *HULC* has been found to be abnormally expressed in a range of digestive system malignancies, where it contributes to the regulation of tumor cell behavior (Figure 1).

3.1 *HULC* in hepatocellular carcinoma

3.1.1 Aberrant up-regulation of *HULC*

In 2007, Panzitt et al. first identified the abnormal expression of *HULC* in HCC using genome-wide microarray analysis (12). This study included 46 HCC tissues, 4 liver focal nodular hyperplasia samples, 7 liver cirrhosis samples, and 2 normal liver samples. The results demonstrated a gradual upregulation of *HULC* expression across liver cirrhosis, focal nodular hyperplasia, and ultimately HCC. These findings have been consistently validated in subsequent studies (22, 34, 35). Furthermore, radioactive *in situ* hybridization confirmed the elevated expression of *HULC* in liver cancer tissues (12). In addition, quantitative real-time polymerase chain reaction (qRT-PCR) has shown significantly increased *HULC* levels in HCC cell lines (29, 36). A clinical study conducted in Egypt further supported these findings, revealing that *HULC* expression in the blood of HCC patients was significantly higher than in patients with chronic hepatitis C virus (HCV) infection (35). These collective data suggest that *HULC* may serve as a novel biomarker for the early diagnosis of HCC. A meta-analysis involving 6,426 HCC patients indicated that *HULC* exhibits superior sensitivity and specificity for HCC diagnosis compared with traditional biomarkers or other non-coding RNAs (37). Moreover, elevated serum *HULC* levels are associated with poor prognosis and have clinical utility in predicting metastasis and outcomes after radical resection of HCC (38, 39).

Notably, Yao et al. recently developed a probe-based rolling circle amplification-induced fluorescence biosensor for detecting *lncRNA HULC*. This biosensor demonstrated high selectivity and sensitivity in both HCC cell lines and whole blood samples from HCC patients (40). These advancements highlight a promising new approach for the clinical application of *HULC* in the diagnosis, prognosis, and potentially treatment monitoring of HCC.

3.1.2 Mechanism of *HULC* in hepatocellular carcinoma

Studies have demonstrated that *HULC* plays a critical role in promoting the progression of liver cancer by interacting with genes, RNA, and proteins. This section summarizes the key regulatory mechanisms in HCC driven by *HULC*.

3.1.2.1 *HULC/miRNA-9*/PPARA

Aberrant lipid metabolism has been recognized as a key contributor to malignant tumor progression. Long-chain acyl-CoA synthetase 1 (ACSL1), a critical enzyme involved in cholesterol biosynthesis and fatty acid oxidation, plays a pivotal role in these metabolic alterations. Clinical studies in patients with HCC have shown that *HULC* expression is positively correlated with ACSL1 expression, as well as with serum triglyceride and cholesterol levels. Supporting these findings, *in vitro* experiments demonstrated that *HULC* activates ACSL1 expression in HepG2 hepatoma cells via the *miRNA-9*/PPARA signaling pathway, thereby inducing lipid metabolic reprogramming that facilitates HCC progression. Moreover, elevated intracellular cholesterol levels may further amplify *HULC* expression through activation of retinoid receptors in hepatoma cells, establishing a positive feedback loop that exacerbates tumor development (22).

3.1.2.2 *HULC/miR-377-5p*/HIF-1α

In the HCC cell lines, including HB611, H22 and HepG2, qRT-PCR showed significant increases in both *HULC* expression, while *miR-377-5p* expression was decreased. Inhibition of *HULC* expression in HepG2 cells suppressed both cell proliferation and invasion. Conversely, *miR-377-5p* inhibition promoted hepatoma cell proliferation and invasion. Further experiments suggested that *HULC* may promote HCC progression by directly targeting the *miR-377-5p*/HIF-1α pathway (36).

3.1.2.3 *HULC* in HBV-associated HCC

chronic hepatitis B virus (HBV) infection is a major cause of cirrhosis and HCC. Hepatitis B virus X protein (HBx) is the key pathogenic factor in HBV infection. Luciferase reporter gene and chromatin immunoprecipitation assays have demonstrated that HBx activates the *HULC* promoter via cAMP response element-binding protein (CREB), thereby promoting *HULC* expression (41). Further studies revealed that HBx enhances hepatoma cell proliferation by upregulating the *HULC*/p18 pathway (41). In HBV-related HCC, metformin has been shown to inhibit tumor cell proliferation by negatively regulating the *HULC*/p18/miR-200a/ZEB1 signaling pathway. This regulation improves survival rates

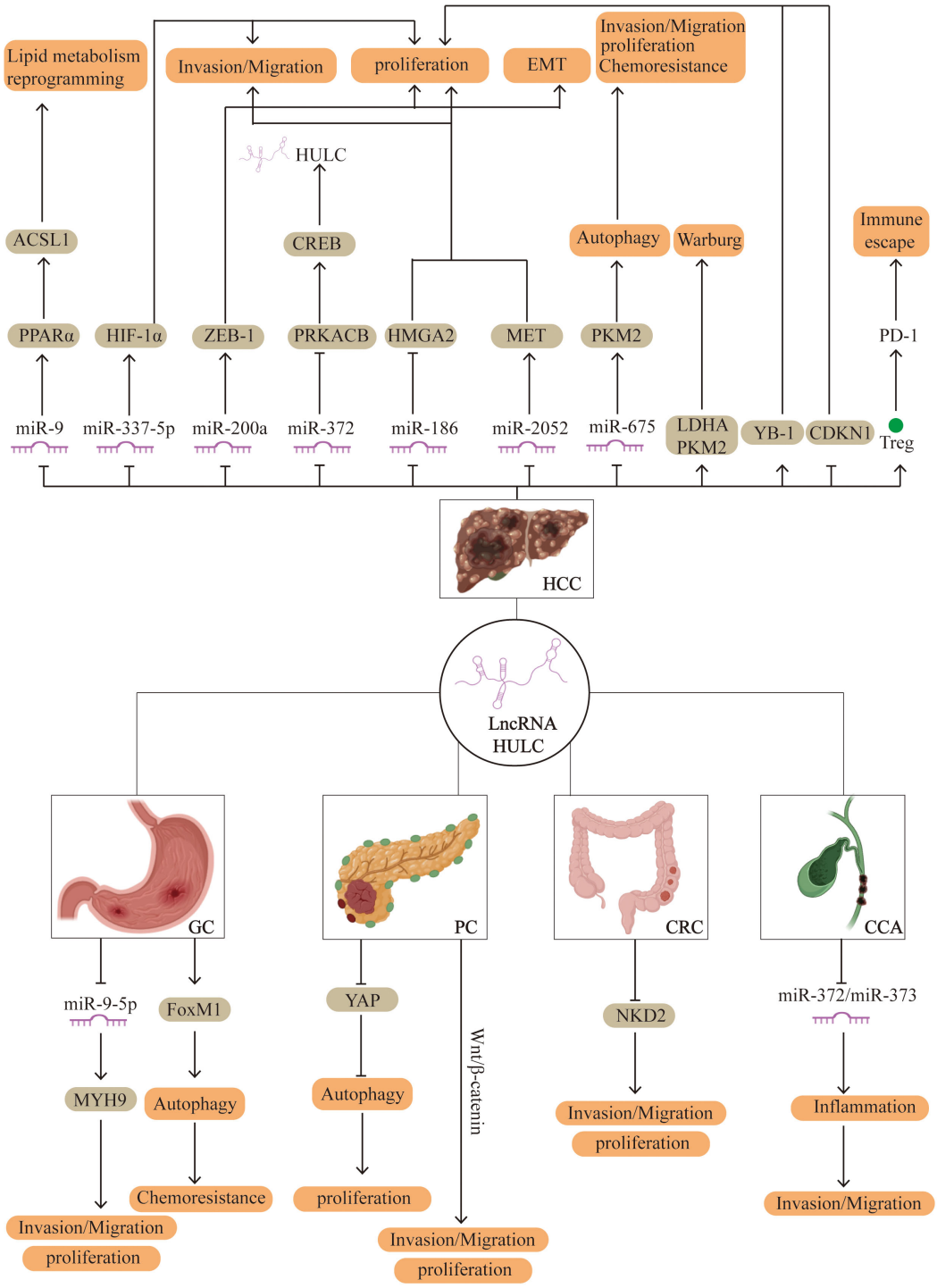

FIGURE 1
Potential regulatory mechanisms of *HULC* in human digestive system cancer. HCC, hepatocellular carcinoma; PC, pancreatic cancer; GC, gastric cancer; CRC, colorectal cancer; CCA, Cholangiocarcinoma.

and reduces recurrence in HCC patients (42). Moreover, upregulation of *HULC* promotes the HBx/STAT3/*miR-539*/APOBEC3B pathway, which further supports HBV replication and accelerates hepatoma cell growth (43).

3.1.2.4 HULC/miR-372

Luciferase assays indicated that *miR-372* reduced the promoter activity of *HULC* in Hep3B hepatoma cells. Overexpression of *miR-372* inhibited the translation of its target gene PRKACB, leading to a

decrease in CREB phosphorylation. This reduction impaired the binding of CREB to the proximal *HULC* promoter, thereby lowering *HULC* expression. Conversely, *HULC* inhibits *miR-372* activity, leading to upregulation of *HULC* expression in liver cancer (29).

3.1.2.5 HULC/miR-186

High-mobility group protein A2 (HMGA2), a transcription factor, is involved in various cancers, including liver, colorectal, and gastric cancers. In HCC tissues, qRT-PCR analysis revealed a positive correlation between *HULC* and HMGA2 expression. *In vitro* studies demonstrated that *HULC* upregulates HMGA2 expression in HCC cells. Further investigation showed that *HULC* promotes the expression of HMGA2 by inhibiting *miR-186*, thereby facilitating liver cancer progression (44).

3.1.2.6 HULC/miR-2052

Bioinformatics analyses suggest that *HULC* acts as a sponge for *miR-2052*. In 42 pairs of HCC and matched non-cancer tissues, the expression of *miR-2052* was negatively correlated with *HULC* levels. Both *in vitro* and *in vivo* experiments confirmed that *HULC* promotes HCC cell proliferation, migration, invasion, and progression through the *miR-2052*/MET axis (45).

3.1.2.7 *HULC* and autophagy

Autophagy plays a critical role in the initiation and progression of HCC, and *HULC* has emerged as a key modulator of this process. In liver cancer stem cells, *HULC* was shown to induce autophagy via the *miR-675*/PKM2 pathway, leading to upregulation of Cyclin D1 and promoting the proliferation of liver cancer stem cells (30). Additionally, *HULC* activates autophagy by enhancing the expression of LC3-I and LC3-II (canonical markers of autophagy) through the deacetylase Sirt1 (24). Further studies by Liu et al. demonstrated that *HULC* also promotes phosphorylation of p65 and IκBκB, thereby increasing LC3-II levels in an NF-κB-dependent manner (46). Mechanistically, *HULC* inhibits PTEN via autophagy-mediated degradation through the ubiquitin-proteasome system, which in turn activates the PI3K/AKT/mTOR pathway to promote hepatocarcinogenesis (24). Moreover, autophagy contributes to chemoresistance in HCC. Anti-tumor agents such as oxaliplatin, 5-fluorouracil, and pirarubicin have been observed to increase both *HULC* expression and autophagic activity in human HCC tissues. *In vivo* data indicate that *HULC* overexpression reduces HCC cell sensitivity to oxaliplatin, whereas silencing *HULC* enhances drug sensitivity. Further *in vitro* experiments revealed that the USP22/Sirt1/autophagy axis underlies this effect, suggesting that targeting this pathway could provide a novel therapeutic approach to overcoming chemoresistance in HCC (47, 48).

3.1.2.8 *HULC* and Warburg effect

Warburg effect is a hallmark of cancer metabolism wherein cancer cells preferentially undergo glycolysis over oxidative phosphorylation, even under normoxic conditions. This metabolic shift supports rapid tumor growth and survival. *HULC* has been found to bind directly to and increase the phosphorylation of key glycolytic enzymes LDHA and PKM2, thereby promoting glycolysis and enhancing tumor progression (32).

3.1.2.9 *HULC* and EMT

EMT is essential for tumor invasion and metastasis. Clinical data reveal that *HULC* expression is positively correlated with EMT phenotypes in HCC. *In vitro* studies further demonstrated that *HULC* upregulates EMT markers such as N-cadherin and vimentin. Mechanistically, *HULC* induces EMT via the *miR-200a-3p*/ZEB1 signaling pathway, thereby facilitating tumor progression and metastasis (49).

3.1.2.10 *HULC*/YB-1

HULC interacts with Y-box-binding protein 1 (YB-1), a multifunctional protein involved in mRNA splicing, translation regulation and DNA repair. Mass spectrometry, localization, and co-immunoprecipitation studies revealed that *HULC* binds YB-1 and promotes its phosphorylation via extracellular signal-regulated kinase signaling. This phosphorylation leads to the release of YB-1 from silenced oncogenic mRNAs, including cyclin D1, cyclin E1, and matrix metalloproteinase 3, thereby enhancing their translation and accelerating tumor growth (50).

3.1.2.11 *HULC*/CDKN1

In radiation-induced liver carcinogenesis, *HULC* also plays a significant role. Downregulation of *HULC* impairs hepatocyte proliferation following radiation exposure. CDKN1, a gene located adjacent to *HULC*, has been implicated in radiation-induced cell cycle regulation. *In vitro* studies indicate that *HULC* suppresses CDKN1 expression via complementary base pairing, thereby promoting cell cycle progression and contributing to radiation-related liver cancer (51).

3.1.2.12 *HULC*/Treg/PD-1

Immune escape represents a major challenge in malignant tumor therapy. In a liver cancer xenograft model, overexpression of *HULC* increased regulatory T cell (Treg) proliferation and upregulated PD-1 expression in the tumor microenvironment. Additional studies revealed that the *HULC*–Treg–PD-1 axis suppresses IL-10 and TGF-β1 expression, facilitating immunosuppression and promoting immune escape. Targeting this axis may represent a promising strategy to overcome immune resistance in HCC (52).

Collectively, these findings underscore the multifaceted role of *HULC* in hepatocellular carcinoma. *HULC* expression is significantly elevated in HCC, especially in cases with focal nodular hyperplasia and liver cirrhosis, highlighting its potential as a diagnostic biomarker. It promotes HCC initiation, progression, metastasis, and therapy resistance by modulating key mechanisms such as interactions with multiple miRNAs/transcription factors, autophagy, the Warburg effect, EMT, and immune escape. Inhibition of *HULC* and its downstream pathways may offer new therapeutic opportunities for HCC treatment and prognosis improvement.

3.2 *HULC* in gastric cancer

Multiple clinical studies have demonstrated that *HULC* is significantly overexpressed in both plasma and tissue samples from patients with GC compared to healthy controls. Survival analyses have shown that elevated *HULC* expression is significantly associated with poorer overall survival (53, 54). In addition, circulating *HULC* levels correlate with tumor size, lymph node involvement, distant metastasis, and Helicobacter pylori infection in GC patients (13, 55). Notably, the combination of *HULC* expression and H. pylori status improves the predictive accuracy for GC risk (56). These findings suggest that *HULC* is a promising biomarker for GC diagnosis and prognosis.

In vivo, silencing *HULC* significantly inhibited tumor growth in a mouse xenograft model of gastric cancer (25). *In vitro*, overexpression of *HULC* promotes the proliferation and invasion of human gastric cancer cells, while inhibiting cell apoptosis. Conversely, knockdown of *HULC* reverses these effects (57). Mechanistically, dual-luciferase reporter assays and RNA pull-down experiments revealed that *HULC* directly targets *miR-9-5p* to exert its biological functions. Further studies have demonstrated that *HULC* enhances proliferation, EMT, migration, and invasion of gastric cancer cells through the *miR-9-5p*/MYH9 axis (25, 57). Additionally, *HULC* promotes gastric cancer growth and metastasis by epigenetically suppressing the expression of p53. Specifically, RIP- and ChIP-qPCR assays have shown that *HULC* recruits EZH2 to the p53 promoter region, mediating its transcriptional repression in gastric cancer cells (58). Moreover, *HULC* plays a critical role in regulating chemoresistance. Inhibition of *HULC* enhances cisplatin-induced apoptosis in gastric cancer cells (47), and the *HULC*/FoxM1 signaling pathway has been shown to promote cisplatin resistance by inducing autophagy (52).

Taken together, these findings highlight *HULC* as an important regulator of tumor growth, metastasis, and drug resistance in gastric cancer. *HULC* represents a promising biomarker for early detection and prognosis and may serve as a novel therapeutic target in the prevention and treatment of GC.

3.3 *HULC* in pancreatic cancer

Pancreatic cancer ranks as the fourth leading cause of cancer-related deaths in the United States and the sixth in China (14, 27). Bioinformatics analyses have identified *HULC* as one of the most significantly dysregulated lncRNAs in pancreatic ductal adenocarcinoma cells (27). A clinical study involving tumor and matched normal tissues from 304 PC patients revealed that *HULC* is highly expressed in both the tissues and serum of PC patients. Notably, elevated *HULC* levels were significantly associated with larger tumor size, lymph node metastasis, and vascular invasion.

In vivo, using PC xenografts in nude mice demonstrated that *HULC* knockdown significantly suppressed tumor growth compared to controls (59). Complementary *in vitro* studies further showed that silencing *HULC* reduced pancreatic ductal adenocarcinoma cell proliferation, viability, invasion, and migration. *HULC* knockdown also led to decreased expression of EMT markers(N-cadherin, vimentin, and Snail), while increasing the expression of E-cadherin (59). Mechanistically, *HULC* appears to promote pancreatic ductal adenocarcinoma progression via multiple pathways. It inhibits YAP activation, thereby promoting autophagy and enhancing tumor cell proliferation (27). Additionally, *HULC* may facilitate pancreatic ductal adenocarcinoma cell proliferation and invasion through the Wnt/β-catenin signaling pathway (14). *HULC* also plays a role in intercellular communication through extracellular vesicles, where it promotes invasion and migration by inducing EMT in recipient cells. This effect can be counteracted by miR-622, which targets *HULC* to suppress EMT-related signaling, providing new insights into pancreatic ductal adenocarcinoma pathogenesis and potential therapeutic targets (60).

3.4 *HULC* in colorectal carcinoma

Colorectal cancer is one of the main causes of cancer deaths worldwide. By bioinformatics analysis, lncRNA *HULC* is regarded as a potential biomarker for colorectal cancer (2, 61). Additionally, previous research has demonstrated that serum *HULC* levels are significantly elevated in patients with CRC compared to healthy individuals. This elevation suggests that *HULC* may serve as a promising biomarker for the diagnosis of CRC (15). *HULC* expression was significantly upregulated in human primary colorectal cancer and colorectal cancer cell lines. Kaplan-Meier survival analysis showed that the upregulation of *HULC* was significantly associated with poor prognosis in patients with colorectal cancer. Knockdown of *HULC* significantly inhibited the proliferation, migration and invasion of CRC cells and promoted cell apoptosis *in vitro*. In BALB/c nude mice tumorigenic experiments show that knockdown of *HULC* can inhibit the proliferation of CRC cells. Mechanically speaking, RNA immunoprecipitation (RIP) and RNA pull-down experiments indicated that in colorectal cancer cells, *HULC* promoted CRC by directly binding to EZH2 to inhibit the expression of NKD2 (62).

3.5 Others

Cholangiocarcinoma (CCA) is a highly fatal malignancy with a poor overall survival rate. Bioinformatics analysis of 36 CCA tumor tissues and 9 normal control tissues from WMU cohort revealed that *HULC* was significantly upregulated and strongly associated with shorter overall survival in CCA patients (63). Functional assays, including cell migration, and invasion experiments, demonstrated that *HULC* overexpression enhances the migratory and invasive capacities of CCA cells. Further mechanistic studies showed that *HULC* acts by targeting *miR-372/miR-373*, leading to upregulation of inflammation-related genes such as *IL-6* and *CXCR4*. This, in turn, induces aberrant inflammatory responses and promotes cancer cell migration and invasion (64).

HULC is also implicated in the pathogenesis of oral squamous cell carcinoma (OSCC), one of the most prevalent malignancies in

the oral and maxillofacial region worldwide (65). In a murine xenograft model, depletion of *HULC* reduced tumor growth and suppressed EMT. *In vitro*, *HULC* knockdown inhibited proliferation, migration, and invasion of OSCC cells, while increasing apoptosis (66). These findings suggest that *HULC* plays a key role in OSCC tumorigenesis and progression.

In nasopharyngeal carcinoma (NPC), clinical studies have shown that *HULC* is highly expressed in tumor tissues and is associated with poor patient prognosis. *HULC* overexpression promotes the growth of NPC cells, whereas its downregulation activates the tumor suppressor p53, increases p21 expression, and induces cell cycle arrest and apoptosis (67). These data support a role for *HULC* as a carcinogenic lncRNA and highlight its potential as a therapeutic target in NPC.

Although *HULC* has been strongly implicated in the development and progression of several digestive system cancers, its role in esophageal cancer remains unclear. From 2014 to 2018, comparative analyses of tumor tissues from 95 patients with esophageal cancer and 121 healthy control samples showed no significant association between *HULC* expression and cancer prognosis across any clinical subgroup (68, 69). This suggests that the contribution of *HULC* to esophageal cancer may be limited or context-dependent, warranting further investigation.

4 Conclusion

HULC has emerged as a critical molecule in the progression of various digestive system malignancies, including hepatocellular carcinoma, pancreatic cancer, gastric cancer, and colorectal cancer liver metastasis. Multiple studies have shown that *HULC* is significantly upregulated in various digestive system cancers. Its abnormal upregulation is thought to result from a complex interplay between environmental factors (such as HBV infection) and intrinsic cellular dysregulation involving transcription factors and miRNAs.Importantly, the overexpression of *HULC* is associated with poor prognosis, highlighting its potential as a prognostic biomarker and therapeutic target. Mechanistically, *HULC* induces malignant phenotypes such as Warburg effect and EMT in tumor cells through interactions with genes, RNA, and proteins. These mechanisms do not exist in isolation but have extensive interactions. Therefore, as a promising therapeutic target, *HULC* has the following advantages: 1) High tissue specificity: *HULC* is significantly upregulated in digestive system tumors and is expressed at a lower level in most normal tissues, minimizing potential off-target effects. 2) Multimechanism carcinogenicity: It mediates the Warburg effect, EMT, and resistance to cell apoptosis through multiple mechanisms, making it a core node in combined therapy. 3) Non-coding features: As an LncRNA, *HULC* is less prone to mutation than protein-coding genes, reducing the risk of developing treatment resistance through genetic variations. 4) Detectability in liquid biopsy: *HULC* is elevated and stable in the blood of digestive system cancers, facilitating non-invasive monitoring and early intervention. Currently, the related mechanism studies of *HULC* in liver cancer are the most in-depth. In pancreatic cancer, gastric cancer, and colorectal cancer and other digestive system cancers, the research on *HULC* is relatively less. This suggests two possible interpretations: either *HULC* may warrant further investigation in other digestive system cancers, or it may possess higher specificity and clinical utility in liver cancer. Notably, clinical evidence indicates that *HULC* is associated with nearly all digestive system cancers, with the exception of esophageal cancer. Therefore, further research on *HULC* is crucial for comprehensively elucidating its biological function and clinical application.

5 Limitation

5.1 Heterogeneity among patients and tissues

Digestive system cancers exhibit tumor heterogeneity, both across different cancer types and among individual patients. This heterogeneity complicates the interpretation of findings and may affect the generalizability of results. Specifically, the expression levels and functional roles of *HULC* can differ significantly among patients. To elucidate the broader patterns and clinical relevance of *HULC*, larger, well-powered studies are necessary. In future research, machine learning algorithms may be employed to construct predictive models capable of identifying *HULC* expression signatures from diverse patient-derived samples.

5.2 Complexity of mechanisms

HULC exerts its effects through multiple molecular interactions, involving genes, RNA, and proteins. These interactions include diverse epigenetic mechanisms such as DNA methylation, histone modifications, and regulation by non-coding RNAs. The diversity of these epigenetic processes present a substantial challenge for studying the potential mechanisms of *HULC* in tumorigenesis. To address this, future studies should incorporate high-throughput sequencing, single-cell analysis, multi-omics integration, and large-scale sample validation, along with investigations into newly discovered epigenetic modifications.

5.3 Methodological challenges in studying *HULC*

Accurate detection and quantification of *HULC* require highly sensitive and specific techniques, which depend on sophisticated laboratory infrastructure and skilled personnel to ensure data quality and reproducibility. Furthermore, high-throughput technologies generate vast amounts of data, the analysis of which demands advanced bioinformatics tools and expertise. Extracting biologically meaningful insights from these datasets remains a critical challenge. Future investigations should leverage cutting-edge sequencing platforms and innovative functional assays to elucidate the oncogenic role and clinical significance of *HULC* in digestive system cancers.

Author contributions

LH: Supervision, Writing – original draft, Software, Resources, Writing – review & editing, Investigation, Project administration, Data curation, Methodology, Formal Analysis, Validation, Conceptualization, Visualization.

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