Interplay between lncRNAs and the PI3K/AKT signaling pathway in the progression of digestive system neoplasms (Review)

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Abstract. Long non-coding RNA (lncRNA) is a class of non-coding RNA molecules located in the cytoplasm or nucleus, which can regulate chromosome structure and function by interacting with DNA, RNA, proteins and other molecules; binding to mRNA bases in a complementary manner, affecting the splicing, stabilization, translation and degradation of mRNA; acting as competing endogenous RNA competitively binds to microRNAs to regulate gene expression and participate in the regulation of various vital activities of the body. The PI3K/AKT signalling pathway plays a key role in numerous biological and cellular processes, such as cell proliferation, invasion, migration and angiogenesis. It has been found that the lncRNA/PI3K/AKT axis regulates the expression of cancer-related genes and thus tumour progression. The abnormal regulation of lncRNA expression in the lncRNA/PI3K/AKT axis is clearly associated with clinicopathological features and plays an important role in regulating biological functions. In the present review, the expression and biological functions of PI3K/AKT-related lncRNAs both *in vitro* and *in vivo* over recent years, were comprehensively summarized and analyzed. Their correlation with clinicopathological features was also evaluated, with the objective of furnishing a solid theoretical foundation for clinical diagnosis and the monitoring of efficacy in digestive system neoplasms. The present review aimed to provide a comprehensive overview of the expression and biological functions of PI3K/AKT-related lncRNAs in digestive system neoplasms and to assess their correlation with clinicopathological features. This endeavor seeks to establish a solid theoretical foundation for the clinical diagnosis and efficacy monitoring of digestive system tumors.

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Contents

1. Introduction

Cancer is one of the primary lethal factors in the world today. According to the latest data, the number of newly diagnosed cancers worldwide is projected to achieve 28.4 million (1). Furthermore, it has become an important public health concern that severely affects the lives of patients (2,3). Specifically, digestive system neoplasms represent a heterogeneous group of cancers characterized by diverse symptoms and complexities in diagnosis and treatment. Prognosis is often poor and influenced by various factors, highlighting the critical importance of early detection and comprehensive therapy for improving patient survival rate (4). In light of these challenges, there is an urgent need for increased efforts in the prevention and control of digestive system neoplasms (5). Long non-coding RNAs (lncRNAs) are non-coding RNA molecules >200 nucleotides in length, located in the nucleus or cytoplasm. In contrast to protein-coding genes, lncRNAs show a lower transcriptional level and poor sequence conservation, with less evolutionary pressure to bear. Compared with small RNA molecules, lncRNAs have a longer sequence,

more complicated spatial structure, and are involved in more diverse and complex mechanisms. Additionally, lncRNAs modify target genes by binding to epigenetic-related proteins. They also inhibit the translation and degradation of target mRNA by binding to complementary bases. Additionally, lncRNAs participate in various regulatory activities in the body by serving as competing endogenous RNAs (ceRNAs). By competitively binding to mRNA with microRNAs (miRNAs or miRs), they regulate mRNA expression (6-8). Notably, previous findings have revealed that a large number of lncRNAs present aberrant expression during tumorigenesis and development, and some lncRNAs appear to have tumor-specific expression pattern. As a result, lncRNAs possess a multitude of biological functions in cancers, including epigenetic regulation, DNA damage and cell cycle regulation, miRNA regulation, participation in signal transduction pathway and cancer-inducing effect of hormones. This opens a new direction for tumor research (9-11).

The PI3K/AKT signaling pathway, composed of phosphoinositide 3-kinase (PI3K) family members and the downstream serine/threonine (Ser/Thr) protein kinases, is one of the most important intracellular signal transduction pathways. It plays a critical role in regulating cellular processes such as cell proliferation, survival, metabolism and angiogenesis (12,13). Activation of this pathway generally begins with the binding of growth factors to receptor tyrosine kinases (RTKs) on the cell surface, leading to the activation of PI3K, which in turn phosphorylates phosphatidylinositol (4,5)-bisphosphate (PIP2) to generate phosphatidylinositol (3,4,5)-trisphosphate (PIP3). PIP3 then recruits AKT to the plasma membrane, where it is activated by phosphorylation. Once activated, AKT can modulate downstream targets involved in cell cycle progression (such as Cyclin D1), apoptosis inhibition (such as Bcl-2 and MDM2) and protein synthesis (via the mTOR pathway). lncRNAs are emerging as key regulators of the PI3K/AKT pathway. They can modulate this pathway through various mechanisms. Certain lncRNAs, such as MALAT1 and HOTAIR, can recruit chromatin-modifying complexes to specific genomic loci, resulting in the modification of gene expression that impacts the PI3K/AKT pathway. For example, MALAT1 has been reported to influence the expression of AKT1 by altering histone methylation at the AKT1 promoter. Certain lncRNAs can bind directly to proteins or mRNAs involved in the PI3K/AKT pathway. For example, lncRNA TINCR can physically interact with AKT1 and promote its activation, leading to enhanced PI3K/AKT signaling and cancer cell proliferation. Numerous lncRNAs function as molecular sponges by binding to miRNAs, which in turn regulate the expression of the PI3K/AKT pathway components. For instance, lncRNA UCA1 can sequester miR-143, a tumor-suppressive miRNA that inhibits AKT, thereby promoting PI3K/AKT activation and enhancing tumor growth and metastasis. Their ability to act as oncogenes or tumor suppressors through this pathway provides valuable insights into their potential as biomarkers or therapeutic targets in cancer treatment. For example, targeting the interaction between oncogenic lncRNAs and the PI3K/AKT pathway components may offer novel therapeutic strategies for improving outcomes of patients with cancer (14-16).

The novelty of the present review lies in its comprehensive exploration of the interplay between lncRNAs and the PI3K/AKT signaling pathway, specifically in digestive system neoplasms. While previous studies have examined individual aspects of lncRNA functions or the PI3K/AKT pathway (7,10), the current review integrates these elements to provide a more nuanced understanding of how lncRNAs regulate tumor progression through this critical pathway. Additionally, potential clinical implications, such as targeted therapeutic strategies and diagnostic applications, which have not been thoroughly addressed in prior research, were highlighted (14). The present review bridges basic molecular mechanisms with clinical relevance, offering new perspectives on treatment approaches for digestive system cancers.

2. Mechanism of action of lncRNA

As transcriptome sequencing develops, increasing non-coding RNAs, including ~58% lncRNAs, have been discovered (17). It has been previously found that few lncRNAs contain small open reading frames that can be translated into bioactive polypeptides (18). For example, LINC00460 can encode small molecular polypeptides under certain conditions, whereas the molecular mechanism remains unknown (19). In spite of the incapability to encode proteins, most lncRNAs can still play a role in cellular biological processes through regulation of gene expression at the pre-transcriptional, transcriptional and post-transcriptional levels (20).

Pre-transcriptional regulation. During cancer development, lncRNAs can be observed in kinds of processes regulating epigenetic complex, such as the nucleosome positioning or histone modification in chromatin, by which lncRNAs inhibit or activate gene expression at the pre-transcriptional level. For instance, overexpression of MALAT1 promotes the recruitment of chromatin-modifying complexes to the promotor region of TSC2 gene, thereby suppressing the transcription of the TSC2 gene (21). Methylation is a common type of epigenetic modification. MIR20HG binds DNMT1 to promote the methylation of the CACNA2D2 promotor region and then suppress the gene expression of CACNA2D2 (22). DPP10-AS1 and protein-coding gene DPP10, which share 4 methylation sites, are upregulated synergistically in lung cancer, and DPP10-AS1 can regulate the methylation of DPP10 gene (23).

Transcriptional regulation. Gene transcription is a process involving multiple factors including transcription factors, polymerases and enhancers. LncRNAs can bind with these factors and then regulate their activity, thereby affecting gene transcriptional control (24). For example, FOXC2-AS1 binding to transcription factor FOXC2 forms an RNA-RNA duplex, increasing FOXC2 expression and further enhancing ABCB1 gene expression (25). It was also reported that lncRNA could inhibit the transcription of specific mRNA by directly contacting RNA polymerase II during heat shock (26).

Post-transcriptional regulation. LncRNAs can specifically bind with some other RNA or DNA in a base-pairing manner at any time point, and therefore, they play a role in mRNA transcription, processing, editing, translation or

degradation (27). WT1-AS exhibits downregulated expression in non-small cell lung cancer (NSCLC), whereas lncRNA UCA1 shows upregulated expression in NSCLC, suggesting negative correlation between WT1-AS and UCA1. In addition, overexpression of WT1-AS inhibits the expression of UCA1 and promotes p53 to suppress the proliferation, migration and invasion of NSCLC cells, while by contrast, UCA1 expression potentiates the cellular biological behaviors (28). LncRNAs can also serve as ceRNAs to bind the 5'-end of miRNA and then affect the expression of downstream mRNA. For instance, lncRNA 5GAS5 regulates the expression of ATG3 through binding miR-23a (29). Additionally, miR-365 can target the 3'-non-coding region of ATG3 mRNA to suppress its expression, while the lncRNA PVT1 as a ceRNA for miR-365 can reduce the effect of miR-365 on ATG3 mRNA and thereby upregulate ATG3 mRNA expression (30).

3. The PI3K/AKT signaling pathway in tumorigenesis

PI3K itself has the activity of Ser/Thr kinase and phosphatidylinositol kinase. It can be classified into three categories with varying structures and functions. Class I PI3Ks are the most extensively studied, and they are known as heterodimers containing one regulatory subunit and one catalytic subunit. The regulatory subunit, which is commonly known as p85 based on the first isotype, contains SH2 and SH3 domains that can bind with corresponding binding sites on target proteins. The catalytic subunit includes four isotypes: p110α, β, δ and γ, with the former two widely distributed in various cell types while the latter two only found in leukocytes. PI3K is composed of one regulatory subunit p85 and one catalytic subunit p110 (31). There are two pathways by which PI3K can be activated: One is the binding with the tyrosine kinase receptors at the cell surface through multiple extracellular factors (32); another one is the binding between Ras protein and p110 subunit (33).

AKT, also known as protein kinase B (PKB), is a 57-kDa Ser/Thr kinase and also a core protein of the PI3K/AKT/mTOR signaling. There are three isotypes: AKT1, AKT2 and AKT3 (34,35), with three common highly conserved domains: A pleckstrin homology (PH) domain in the N-terminus that mainly functions to promote AKT translocation to the plasma membrane, an ATP-binding kinase domain (KD) and a hydrophobic motif in the C-terminus that contain a binding site to activate kinase 3-phosphoinositide-dependent protein kinase 1 (PDK1) and enable allosteric modulation of PDK1 catalytic activity. There is also a linker region between the PH domain and the KD (36). Activated PI3K can phosphorylate PIP2 to form PIP3, which binds with the PH domain of AKT to induce AKT translocation to the cell membrane. The membrane localization of AKT makes AKT easy to be activated at Ser124 and Thr450 via phosphorylation induced by PDK, while the subsequent nuclear translocation enables AKT to regulate multiple downstream proteins (for example mTOR, Bad, caspase-9, NF-κB and forkhead box class O subfamily) and then play a regulatory role in cell survival, proliferation, apoptosis and angiogenesis (37-41).

The PI3K/AKT signaling pathway is regulated by multiple genes including tumor suppressor genes such as phosphatase and tensin (PTEN), Src Homology 2-containing Inositol phosphatase (SHIP) and carboxyl-terminal modulator protein (CTMP). PTEN can suppress the dephosphorylation of PIP3 back to PIP2, reducing the level of intracellular PIP3 and then inhibiting the activation of AKT and downstream molecules (42). CTMP can bind AKT to suppress its phosphorylation and then block downstream signal transduction. SHIP also can suppress the activation of AKT and downstream molecules via modulating the dephosphorylation of PIP3 (43). In addition, AKT can regulate its own activity through direct binding with some proteins, such as calcium-regulatory protein (Fig. 1).

Studies found that the PI3K/AKT signal transduction pathway is aberrantly activated in types of human malignancies, such as nervous system tumor (44,45), gynecological tumor (46-48) and gastrointestinal tumor (49-51). Additionally, it is closely correlated with tumorigenesis and development and plays an important role in proliferation (52), aerobic glycolysis (53), apoptosis (54), angiogenesis (55), invasion and metastasis (56), and chemoradiation resistance (57) of tumor cells.

4. The lncRNA/PI3K/AKT axis in cancer

LncRNAs play an essential role in the occurrence and development of human cancer (58). However, study on lncRNAs alone is not sufficient to promote the diagnosis and treatment of cancer (10,59). Besides, use of conventional signaling pathways or molecules alone may also be useless. A substantial number of research has revealed the key roles of lncRNAs and the PI3K/AKT signaling pathway in various biological and cellular functions during cancer development, such as cell proliferation, invasion, migration and angiogenesis. Notably, the crosstalk between lncRNAs and the PI3K/AKT signaling pathway has sparked great interest in recent years. It has been reported that lncRNAs regulate cellular functions via interaction with the PI3K/AKT signaling pathway, thereby playing a role in control of cancer occurrence and development. With further in-depth studies on lncRNA structure and function, the role of the lncRNA/PI3K/AKT axis in cancer is expected to be further specified.

5. Cell biological functions related to the lncRNA/PI3K/AKT axis in digestive system neoplasms

The lncRNA/PI3K/AKT axis plays an important role in the occurrence and development of digestive system neoplasms by regulating the expression of cancer-related genes (Fig. 2). Current research may lay the foundation for further study on digestive system neoplasms progression and shed new light on lncRNA-based clinical applications (Table I). In this part, the expression and function of the PI3K/AKT-related lncRNAs in digestive system neoplasms are summarized.

Gastric cancer (GC). GC is a malignancy originating from gastric mucosal epithelial cells. It has a high rate of incidence and case fatality but a low rate of early diagnosis, and patients usually experience poor outcomes (60-62). Studies have found that the PI3K/AKT-related lncRNAs, including HNF1A-AS1 (63), UCA1 (64), LINC01559 (65), FOXD1-AS1 (66), LINC01279 (67), LINC02465 (68), HOTAIR (69), LINC00511 (70), AK023391 (71),

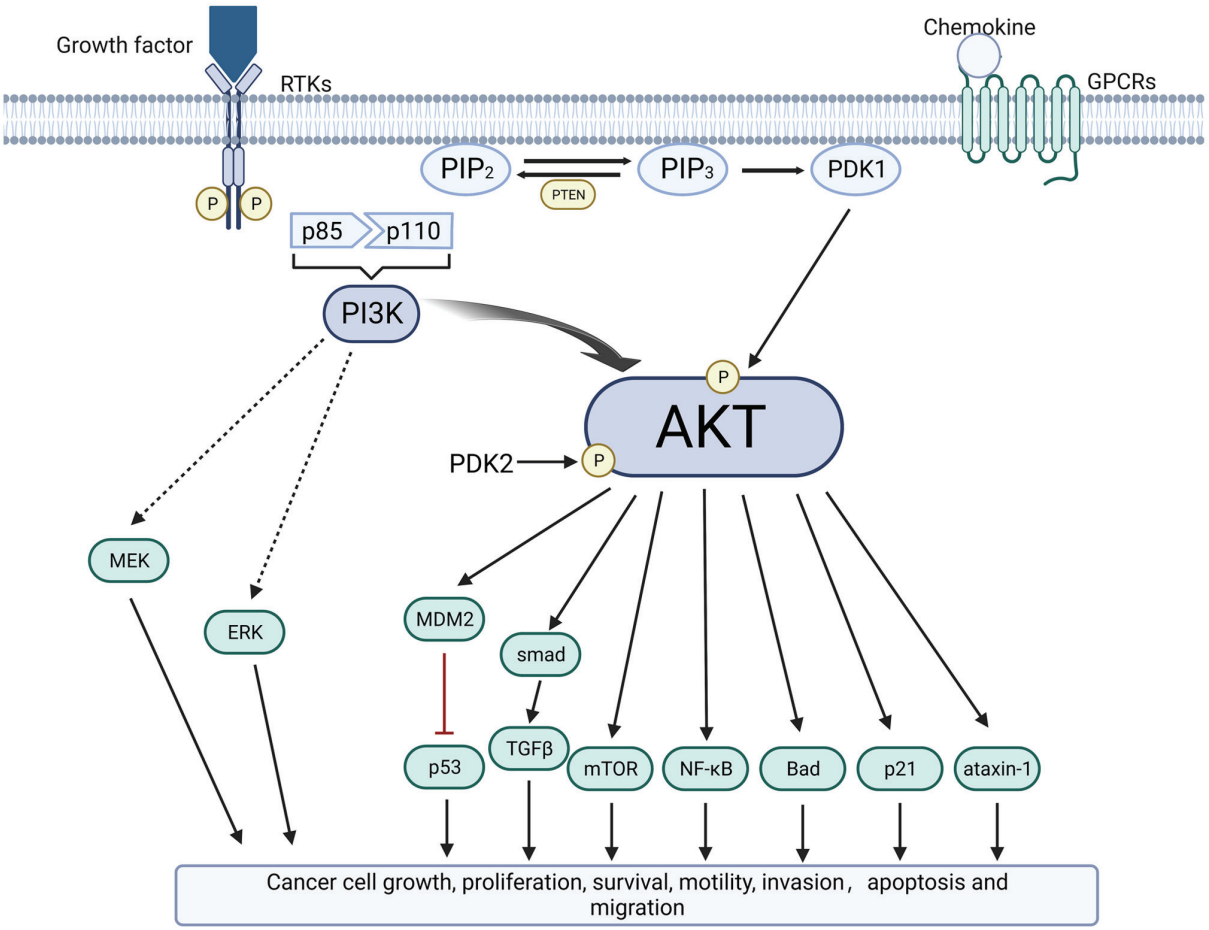

Figure 1. A schematic representation of the PI3K/Akt pathway. The figure was created using Adobe Illustrator 2024 (v28.0; Adobe Inc.). RTK, receptor tyrosine kinase; GPCR, G protein-coupled receptor; PIP_2, phosphatidylinositol 4,5-biphosphate; PIP_3, phosphatidylinositol (3,4,5)-triphosphate; PDK1, phosphoinositide-dependent kinase-1.

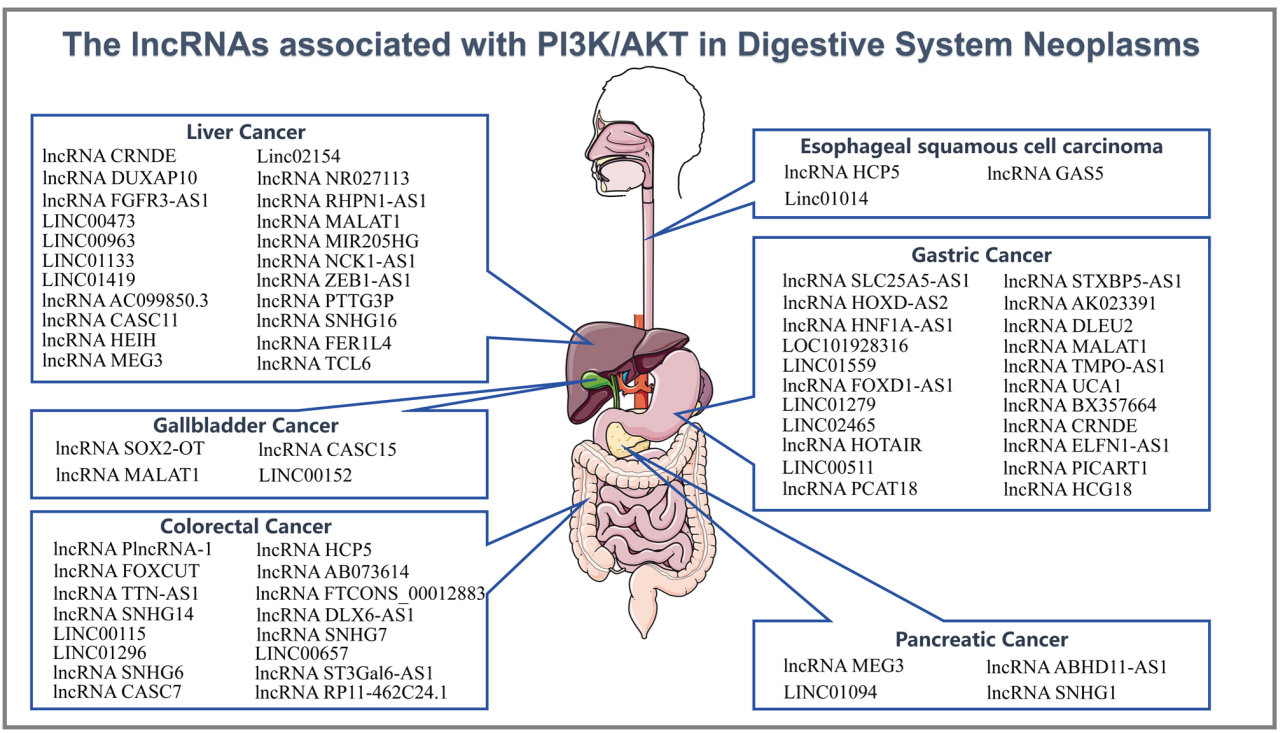

Figure 2. lncRNAs associated with PI3K/AKT in digestive system neoplasms. The figure was created using Adobe Illustrator 2024 (v28.0; Adobe Inc.). LINC, long intergenic non-coding; lncRNA, long non-coding RNA.

Table I. Role and biological functions of lncRNA/PI3K/AKT axis in progression of digestive system neoplasms.

Category, digestive system neoplasms					
A, Gastric cancer					
First author, year	lncRNA	Role	Function	Related targets	(Refs.)
Yao *et al*, 2020	HOXD-AS2	Tumor suppressor	Invasion, migration, proliferation, and apoptosis	HOXD8, PI3K, AKT	(78)
Li *et al*, 2019	SLC25A5-AS1	Tumor suppressor	Tumour size, TNM stage and lymph node metastasis, cell proliferation, apoptosis	miR-19a-3p, PTEN, PI3K, AKT	(79)
Liu *et al*, 2020	HNF1A-AS1	Oncogene	Invasion, metastasis, angiogenesis and lymphangiogenesis	miR-30b-3p, PI3K, AKT	(63)
Li *et al*, 2019	LOC101928316	Tumor suppressor	Migration, invasion and proliferation	PI3K, AKT, mTOR	(80)
Wang *et al*, 2020	LINC01559	Oncogene	Proliferation, migration	miR-1343-3p, PGK1, PTEN, PI3K, AKT	(65)
Wu *et al*, 2021	FOXD1-AS1	Oncogene	Proliferation, metastasis	PIK3CA, PI3K, AKT, mTOR	(66)
Zhao *et al*, 2022	LINC01279	Oncogene	Tumor size, TNM stage, and metastasis, invasion, proliferation, cell cycle	PI3K, AKT, mTOR	(67)
Han *et al*, 2019	LINC02465	Oncogene	Proliferation, migration, invasion and EMT	PI3K, AKT	(68)
Cheng *et al*, 2018	HOTAIR	Oncogene	Cisplatin-resistance	miR-34a, PI3K, AKT	(69)
Wang *et al*, 2021	LINC00511	Oncogene	Proliferation, migration, stemness, apoptosis and EMT process	SOX4, PTEN, PI3K, AKT	(70)
Huang *et al*, 2017	AK023391	Oncogene	Invasion, apoptosis and cell cycle	PI3K, AKT	(71)
Hu *et al*, 2022	DLEU2	Tumor suppressor	Cell apoptosis, migration, invasion and EMT process	PI3K, AKT	(85)
Zhu *et al*, 2019	MALAT1	Oncogene	Proliferation, migration and invasion	PI3K, AKT	(72)
Dai *et al*, 2020	MALAT1	Oncogene	Proliferation, migration, invasion	PI3K, AKT, STAT3	(73)
Wu *et al*, 2021	TMPO-AS1	Oncogene	Proliferation, migration and angiogenesis.	miR-126-5p, BRCC3, PI3K, AKT, mTOR	(66)
Dai *et al*, 2020	UCA1	Oncogene	Proliferation, Cisplatin-resistance	EZH2, PI3K, AKT	(64)
Liang *et al*, 2021	BX357664	Tumor suppressor	Proliferation, migration, apoptosis and invasion	miR-183-3p, PTEN, PI3K, AKT	(81)
Du *et al*, 2017	CRNDE	Oncogene	Proliferation, migration and invasion	PI3K, AKT	(75)
Zhuang *et al*, 2022	ELFN1-AS1	Oncogene	Proliferation, invasion, migration and apoptosis	ZBTB16, PI3K, AKT	(76)
Li *et al*, 2019	PICART1	Tumor suppressor	Proliferation, apoptosis	PI3K, AKT, ERK, MAPK	(82)
Cen *et al*, 2019	STXBP5-AS1	Tumor suppressor	Proliferation, migration, and invasion	PI3K, AKT	(83)
Ma *et al*, 2020	HCG18	Oncogene	Proliferation, migration, invasion, and apoptosis	PI3K, AKT	(77)
Chen *et al*, 2019	PCAT18	Tumor suppressor	Proliferation	miR-107, PTEN, PI3K, AKT	(84)

Table I. Continued.

Category, digestive system neoplasms					
B, Colorectal cancer					
First author, year	lncRNA	Role	Function	Related targets	(Refs.)
Song *et al*, 2018	PlncRNA-1	Oncogene	Proliferation, migration, invasion and apoptosis	PI3K, AKT	(88)
Yun *et al*, 2019	HCP5	Oncogene	Proliferation, migration and cell cycle	AP1G1, PI3K, AKT	(89)
Zhang *et al*, 2020	FOXCUT	Oncogene	Proliferation and invasion	FOXC1, PI3K, AKT	(90)
Wang *et al*, 2017	AB073614	Oncogene	Proliferation, migration, invasion, apoptosis and cell cycle	PI3K, AKT	(91)
Yang *et al*, 2020	TCONS_ 00012883	Oncogene	Proliferation and metastasis	DDX3, YY1, MMP1, PI3K, AKT	(92)
Cui *et al*, 2019	TTN-AS1	Oncogene	Proliferation, migration, invasion and EMT	mir-497, PI3K, AKT	(93)
Pei *et al*, 2019	SNHG14	Oncogene	Proliferation, migration, invasion and apoptosis	miR-944/KRAS, PI3K, AKT	(94)
Duan *et al*, 2020	KCNQ1OT1	Oncogene	Proliferation, migration and invasion	PI3K, AKT	(95)
Zhang *et al*, 2019	DLX6-AS1	Oncogene	Proliferation, invasion and migration	PI3K, AKT, mTOR	(96)
Fang *et al*, 2022	LBX2-AS1	Oncogene	Proliferation, metastasis and apoptosis	miR-627-5p, RAC1, PI3K, AKT	(97)
Feng *et al*, 2020	LINC00115	Oncogene	Proliferation, apoptosis, migration and invasion	miR-489-3p, PI3K, AKT	(98)
Li *et al*, 2018	SNHG7	Oncogene	Proliferation, metastasis, cell cycle, and apoptosis	miR-34a, GALNT7, PI3K, AKT, mTOR	(99)
Liu *et al*, 2018	linc01296	Oncogene	Tumorigenesis, liver metastasis and chemoresistance	MUC1, PI3K, AKT	(100)
Lei *et al*, 2021	LINC00657	Tumor suppressor	Proliferation, invasion, and apoptosis	CAPN7, PI3K, AKT	(101)
Meng *et al*, 2019	SNHG6	Tumor suppressor	Proliferation, invasion and migration	ETS1, PI3K, AKT, mTOR	(102)
Hu *et al*, 2019	ST3Gal6-AS1	Tumor suppressor	Proliferation, metastasis, and apoptosis	PI3K, AKT	(103)
Hao *et al*, 2021	CASC7	Tumor suppressor	Proliferation, invasion and migration	PI3K, AKT	(104)
Zhang *et al*, 2021	RP11-462C24.1	Tumor suppressor	Proliferation, cell cycle, apoptosis and invasion	HSP70, PI3K, AKT	(105)
C, Liver cancer					
Tang *et al*, 2018	CRNDE	Oncogene	Proliferation	PI3K, AKT, GSK3β-Wnt, β-catenin	(117)
Han *et al*, 2019	DUXAP10	Oncogene	Migration, EMT, apoptosis, proliferation and invasion	PI3K, AKT	(108)
Zhuang *et al*, 2018	FGFR3-AS1	Oncogene	Proliferation, cell apoptosis, G0 stage, migration and invasion	PI3K, AKT	(109)

Table I. Continued.

Category, digestive system neoplasms					
C, Liver cancer					
First author, year	lncRNA	Role	Function	Related targets	(Refs.)
Song *et al*, 2020	LINC00473	Oncogene	Proliferation, migration, invasion and metastasis	miR-29-3p, Robo1, PI3K, AKT, mTOR	(118)
Wu *et al*, 2018	LINC00963	Oncogene	Proliferation, G0/G1 phase	PI3K, AKT	(119)
Chen *et al*, 2018	LINC01133	Oncogene	Proliferation, cell apoptosis, G1 phase, migration and invasion	PI3K, AKT	(113)
Hou *et al*, 2021	LINC01419	Oncogene	Proliferation and apoptosis	ZIC1, PI3K, AKT	(120)
Zhong *et al*, 2022	AC099850.3	Oncogene	Proliferation, metastatic and apoptosis	PRR11, PI3K, AKT	(121)
Han *et al*, 2019	CASC11	Oncogene	Migration, invasion and EMT	PI3K, AKT	(111)
Shen *et al*, 2020	HEIH	Oncogene	Invasion, apoptosis and migration	miR-98-5p, PI3K, AKT	(122)
Peng *et al*, 2020	Linc02154	Oncogene	Proliferation, migration and invasion	SPC24, PI3K, AKT	(123)
Chen *et al*, 2018	NR027113	Oncogene	Proliferation, invasion, EMT and metastasis	PTEN, PI3K, AKT	(113)
Song *et al*, 2020	RHPN1-AS1	Oncogene	Proliferation, migration and invasion	miR-7-5p, PI3K, AKT, mTOR	(114)
Peng *et al*, 2020	MALAT1	Oncogene	Proliferation, apoptosis and autophagy	miR-146a, PI3K, AKT	(123)
Zhang *et al*, 2022	MIR205HG	Oncogene	Proliferative, migratory and invasion	PI3K, AKT	(115)
Zhou *et al*, 2022	NCK1-AS1	Oncogene	Invasion, apoptosis and migration	miR-22-3p, YARS, PI3K, AKT	(124)
Ma *et al*, 2020	ZEB1-AS1	Oncogene	Migration, invasion, metastasis	PI3K, AKT	(125)
Huang *et al*, 2018	PTTG3P	Oncogene	Proliferation, migration, EMT, invasion, metastasis, cell cycle and apoptosis	PTTG1, PI3K, AKT	(116)
Li *et al*, 2021	SNHG16	Oncogene	Proliferation, migration and angiogenesis	miR-4500, GALNT1, PI3K, AKT, mTOR	(126)
Wang *et al*, 2019	FER1L4	Tumor suppressor	Proliferation, migration, cell apoptosis and invasion	PI3K, AKT	(127)
Sun *et al*, 2019	MEG3	Tumor suppressor	Proliferation, invasion and cell cycle	AP1G1, PI3K, AKT	(128)
Luo *et al*, 2020	TCL6	Tumor suppressor	Proliferation, migration and invasion	miR-106a-5p, PI3K, AKT	(129)
D, Pancreatic cancer					
Gu *et al*, 2017	MEG3	Oncogene	Proliferation, invasion and apoptosis	PI3K, AKT, Bcl-2, Bax, Cyclin D1, P53, MMP-2, MMP-9	(135)

Table I. Continued.

Category, digestive system neoplasms					
D, Pancreatic cancer					
First author, year	lncRNA	Role	Function	Related targets	(Refs.)
Luo *et al*, 2021	LINC01094	Oncogene	Proliferation and metastasis	miR-577, LIN28B, PI3K, AKT	(132)
Qiao *et al*, 2018	ABHD11-AS1	Oncogene	Proliferation, migration, invasion, and EMT	PI3K, AKT	(133)
Zhang *et al*, 2018	SNHG1	Tumor suppressor	Proliferation, apoptosis and cell cycle	PI3K, AKT	(134)
E, Esophageal squamous cell carcinoma					
Fu *et al*, 2020	Linc01014	Oncogene	Proliferation, apoptosis and gefitinib resistance	EGFR, PI3K, AKT, mTOR	(141)
Xu *et al*, 2021	HCP5	Oncogene	Proliferation, apoptosis, migration and invasion	PI3K, AKT, mTOR	(139)
Wang *et al*, 2018	GAS5	Tumor suppressor	Proliferation and migration	PI3K, AKT, mTOR	(140)
F, Gallbladder cancer					
Wei *et al*, 2018	SOX2-OT	Oncogene	Proliferation and metastasis	PI3K, AKT	(145)
Wang *et al*, 2017	MALAT1	Oncogene	Proliferation, EMT and metastasis	PI3K, AKT	(146)
Zhang *et al*, 2021	CASC15	Tumor suppressor	Proliferation, migration, invasion, cell apoptosis and G1/S stage	PRDX2, PI3K, AKT	(147)
Cai *et al*, 2016	LINC00152	Oncogene	Proliferation, metastasis and cell apoptosis	SP1, PI3K, AKT	(148)

LINC, long intergenic non-coding; EMT, epithelial-mesenchymal transition; lncRNA, long non-coding RNA; miR, microRNA.

MALAT1 (72,73), TMPO-AS1 (74), CRNDE (75), ELFN1-AS1 (76) and HCG18 (77) exhibit significantly increased expression after GC occurs. The high expression of UCA1 (64), FOXD1-AS1 (66), HOTAIR (69) and MALAT1 (71) can promote cisplatin resistance in GC. LINC01559 (65) and LINC00511 (70) can regulate PTEN to trigger the PI3K/AKT pathway, thereby accelerating the progression of GC. Concerning the biological function, overexpression of LINC01279 (67), LINC02465 (68), MALAT1 (72,73), AK023391 (71) and CRNDE (75) can promote the proliferation, migration and invasion of GC via activating the PI3K/AKT signaling pathway. In addition, TMPO-AS1 (66) also plays a positive role in angiogenesis of GC cells. Animal experiments revealed that reductions in the expression of ELFN1-AS1 (76) and HCG18 (77) decreased the growth rate of xenograft GC tumor in mice.

In addition to the lncRNAs with increased expression in GC, lncRNAs including HOXD-AS2 (78), SLC25A5-AS1 (79), LOC101928316 (80), BX357664 (81), PICART1 (82), STXBP5-AS1 (83) and PCAT18 (84) show significantly decreased expression after GC occurs. The expression of HOXD-AS2 (78), SLC25A5-AS1 (79), LOC101928316 (80), BX357664 (81) and DLEU2 (85) in GC tissue is significantly lower than that in adjacent normal tissue, and notably, it has significant associations with tumor size, TNM stage and differentiation. Overexpression of LOC101928316 (80), PICART1 (82) and STXBP5-AS1 (83) can remarkably suppress the migration, invasion and proliferation of GC cells. Moreover, the result of xenograft experiment demonstrated significant suppression of tumor formation after PICART1 overexpression (82). PCAT18 was found to be highly correlated with tumor size and exhibit suppressive effect on GC tumor growth upon overexpression both *in vivo* and *in vitro* (84). While GC has been extensively studied for its interaction with lncRNAs in the context of the PI3K/AKT pathway, colorectal cancer (CRC) represents another major malignancy of the digestive system with significant findings in this area.

CRC. CRC is one of the most common malignancies of the digestive system that leads to ~0.715 million deaths annually (1,86,87). The lncRNAs, including PlncRNA-1 (88), HCP5(89),FOXCUT(90),AB073614(91),TCONS_00012883(92), TTN-AS1 (93), SNHG14 (94), KCNQ1OT1 (95), DLX6-AS1 (96), LBX2-AS1 (97) and LINC00115 (98), have significantly upregulated expression in CRC and promote the proliferation, invasion and migration of CRC cells by targeting the PI3K/AKT signaling pathway. TTN-AS1 is also correlated with the epithelial-mesenchymal transition (EMT) of CRC cells (93). An *in vivo* xenograft experiment revealed that suppression of PlncRNA-1 expression significantly inhibited the growth of tumor (88). Cellular experiment results demonstrated that HCP5 (89) and KCNQ1OT1 (95) induced cell cycle arrest in G0/G1 phase, while AB073614 (91) led to cell cycle arrest in G1 phase. SNHG7 (99) promotes the proliferation and metastasis of CRC, and it plays an oncogenic role by serving as a ceRNA for miR-34a to regulate GALNT7 expression and the PI3K/AKT/mTOR signaling pathway. LINC01296 (100) can facilitate the tumorigenesis, liver metastasis and chemoresistance of CRC cells *in vivo*.

Other lncRNAs, including LINC00657 (101), SNHG6 (102), ST3Gal6-AS1 (103), CASC7 (104) and RP11-462C24.1 (105), reversely exhibit significantly downregulated expression in CRC, and functionally, they repress the proliferation and metastasis but promote the apoptosis of CRC cells. LINC00657 suppresses the expression of CAPN7 through activating the PI3K/AKT pathway, and additionally, it exhibits significantly reduced expression upon distant metastasis (101). Overexpression of SNHG6 can decrease the activity and proliferation of colonocytes by targeting ETS1 and via the PI3K/AKT/mTOR axis (102). RP11-462C24.1 was reported to suppress the growth of xenograft CRC tumor in mice (105). Liver cancer, another prevalent and highly malignant tumor of the digestive system, also exhibits a strong association between lncRNAs and the PI3K/AKT pathway.

Liver cancer. Liver cancer is one of the common malignancies with a poor prognosis. The 5-year survival rate in cases with advanced liver cancer was estimated ≤5%, posing a serious threat to the health and life of individuals (106,107). Some studies found that a large number of lncRNAs play a role in liver cancer via the PI3K/AKT signaling pathway. lncRNAs, including DUXAP10 (108), FGFR3-AS1 (109), LINC01133 (110), CASC11 (111), LINC02154 (112), NR027113 (113), RHPN1-AS1 (114), MIR205HG (115) and PTTG3P (116), promote the proliferation and invasion of liver cancer cells. Additionally, DUXAP10 (108), CASC11 (111), NR027113 (113) and PTTG3P (116) suppress the EMT of liver cancer cells. Downregulation of FGFR3-AS1 can significantly induce apoptosis in liver cancer cells and alleviate tumor growth *in vivo*. In addition, FGFR3-AS1 knock-out can lead to more significant cell cycle arrest in G0 phase in hepatocellular carcinoma (HCC) cells (109). CRNDE promotes the proliferation of HCC cells both *in vivo* and *in vitro* (117). LINC00473 may serve as a sponge for miR-29a-3p to upregulate Robo1 expression, activating the PI3K/AKT/mTOR signaling pathway and then promoting the proliferation, migration, invasion, progression and metastasis of liver cancer cells (118). LINC00963 activates the PI3K/AKT pathway to promote proliferation of HCC cells and prolong the G0/G1 phase (119). LINC01133 could induce cell cycle arrest in G1 phase, while suppression of LINC01133 was found to significantly suppress the xenograft tumor growth *in vivo* (113). LINC01419 can enhance the methylation of ZIC1 promotor to inhibit ZIC1 expression and activate the PI3K/AKT signaling pathway, thereby enhancing the malignant phenotypes of liver cancer cells *in vitro* while promoting the formation and metastasis of tumor *in vivo* (120). AC099850.3 demonstrates significant positive correlations with key immune checkpoint molecules: PD-1, PD-L1, PD-L2 and CTLA4, and therefore, it has the potential to be an immunotherapy target for HCC (121). HEIH acts as a sponge for miR-98-5p, and it activates the PI3K/AKT pathway via modulating the expression of miR-98-5p, thereby enhancing Sorafenib resistance in liver cancer (122). LINC02154 may promote the proliferation of HCC cells by enhancing the SPC24 promotor activity and activating the PI3K/AKT signaling pathway (112). MALAT1 may play a regulatory role in proliferation, apoptosis and autophagy of liver cancer cells via regulating the expression of miR-146a (123). MIR205HG promotes the progression of hepatoblastoma by acting as a

sponge for miR-205-5p and activating the PI3K/AKT signaling pathway. NCK1-AS1 activates the PI3K/AKT signaling pathway through the miR-22-3p/YARS axis, in turn promoting HCC progression (124). ZEB1-AS1 significantly reduces the migration, invasion and metastasis of liver cancer cells both *in vivo* and *in vitro*. ZEB1-AS1 promotes HCC bone metastasis by targeting miR-302b and activating the PI3K/AKT signaling pathway (125). SNHG16 could exhibit increased expression in exosome from plasma of patients with HCC, while the exosome SNHG16 could promote angiogenesis via the miR-4500-GALNT1 axis (126).

The expression of FER1L4 (127), MEG3 (128) and TCL6 (129) in liver cancer tissue and cell lines is reduced, especially the expression of MEG3 in patients with advanced liver cancer. Overexpression of FER1L4 can significantly attenuate the proliferation, migration and invasion, and potentiate the apoptosis of liver cancer cells (127). Low expression of MEG3 can suppress AP1G1 expression and activate the PI3K/AKT signaling pathway, promoting the proliferation and invasion and accelerating cell cycle progress of liver cancer cells (128). TCL6 is a cancer-inhibiting molecule that can directly bind miR-106a-5p to regulate the PI3K/AKT signaling pathway, suppressing the proliferation, migration and invasion of HCC cells (129). Similar to liver cancer, pancreatic cancer (PC) involves similar molecular mechanisms, where lncRNAs regulate cancer progression via the PI3K/AKT signaling pathway.

PC. PC is a digestive system tumor characterized by an occult onset and extremely high degree of malignancy (130,131). LINC01094 (132) and ABHD11-AS1 (133) show significantly increased expression in PC tissue, and SNHG1 (134) is highly expressed in pancreatic ductal adenocarcinoma tissue and predicts a poor prognosis. Downregulation of LINC01094, SNHG1 and ABHD11-AS1 can reduce the proliferation and metastasis of PC cells. In addition, decrease in ABHD11-AS1 can also inhibit the EMT of PC cells, and the reduction in SNHG1 can further promote cell apoptosis and alter cell cycle process. Moreover, the reductions in LINC01094 and SNHG1 could also suppress the formation and metastasis of xenograft PC tumor in mice. MEG3 acts as a cancer-inhibiting molecule in PC, and overexpression of MEG3 effectively decreases the proliferation, invasion and migration of PC cells (135). In addition to PC, esophageal squamous cell carcinoma (ESCC) is another aggressive malignancy where lncRNAs play critical roles, particularly through the PI3K/AKT signaling pathway.

ESCC. ESCC is the most common among all histological types of esophageal cancer. It is more common in men than women, and the prognosis is often poor (136-138). The expression of lncRNA HCP5 is increased in ESCC. HCP5 stimulates the PI3K/AKT/mTOR signaling pathway through the miR-139-5p/PDE4A axis, which promotes the proliferation, migration, invasion but inhibits the apoptosis of ESCC cells, increasing the activity of ESCC cells (139). Another lncRNA, GAS5, also shows downregulated expression in ESCC, and overexpression of GAS5 suppresses the proliferation and migration of esophageal cancer cells by inhibiting the PI3K/AKT/mTOR signaling (140). Silence of LINC01014 can significantly increase the sensitivity of ESCC cells to Gefitinib and promote apoptosis in cells via the PI3K/AKT/mTOR signaling pathway (141). Lastly, gallbladder cancer (GBC), though less common than other gastrointestinal tumors, also involves dysregulated lncRNAs and PI3K/AKT signaling.

GBC. GBC is the most common malignancy of the biliary system, and its incidence ranks sixth among all gastrointestinal tumors (142-144). SOX2-OT (145) and MALAT1 (146) exhibit significantly increased expression in cholangiocarcinoma (CCA) tissue, and they can promote the proliferation and metastasis of CCA cells. In addition, MALAT1 also facilitates the occurrence of EMT in CCA cells. CASC15 (147) displays high expression in intrahepatic CCA (ICC) and predicts a high TNM stage. Downregulation of CASC15 can reduce the proliferation, migration and invasion, increase the apoptosis, block the G1/S phase of ICC cells, and inhibit the development of xenograft tumor. LINC00152 shows significantly increased expression in GBC tissue and cells, and it can remarkably promote the proliferation and metastasis whereas suppress the apoptosis of GBC cells (148). Additionally, overexpression of LINC00152 can also potentiate the growth of tumor *in vivo* (Fig. 3).

6. lncRNAs related to the PI3K/AKT pathway as biomarkers

Tumor markers are bioactive substances produced by the tumor tissue or through interactions between the host and the tumor. They can indicate the presence of a tumor and changes in its growth (149). They have significant implications for the tumor prevention, early diagnosis and differential diagnosis, classification, monitoring, treatment guiding, and prognosis which can compensate for the deficiency of other techniques in tumor diagnosis, treatment and prognosis (150). In recent years, an increasing number of studies have found that lncRNAs and the PI3K/AKT signaling pathway are potential biomarkers for the diagnosis, treatment and prognosis of types of digestive system neoplasms. In this section, the important roles of lncRNA and the PI3K/AKT signaling pathway in clinical practice are discussed (Table II).

Diagnostic biomarkers. The role of lncRNAs as diagnostic biomarkers has garnered significant attention, especially in their potential to provide non-invasive diagnostic approaches (10,151,152). Early screening is of great significance in cancer diagnosis and treatment (153,154). It was reported that abnormally expressed lncRNA is key for the cancer diagnosis, and it can be used as a non-invasive tumor biomarker to play an irreplaceable role in early tumor diagnosis. Multiple lncRNAs involved in the PI3K/AKT signaling pathway have been found with aberrant expression during the development of types of cancers. For instance, DLX6-AS1 (96), LINC00115 (98), LINC01296 (100) and CASC7 (104) exhibit significantly higher expression in the CRC tissue relative to that in normal tissue. lncRNAs, including LINC00963 (119), LINC02154 (112) and RHPN1-AS1 (114), also have remarkably increased expression in the liver cancer tissue. While in the PC, the expression of MEG3 (135), LINC01094 (132) and ABHD11-AS1 (133) also exhibit a significant increasing trend. Additionally, emerging evidence suggests that several of these

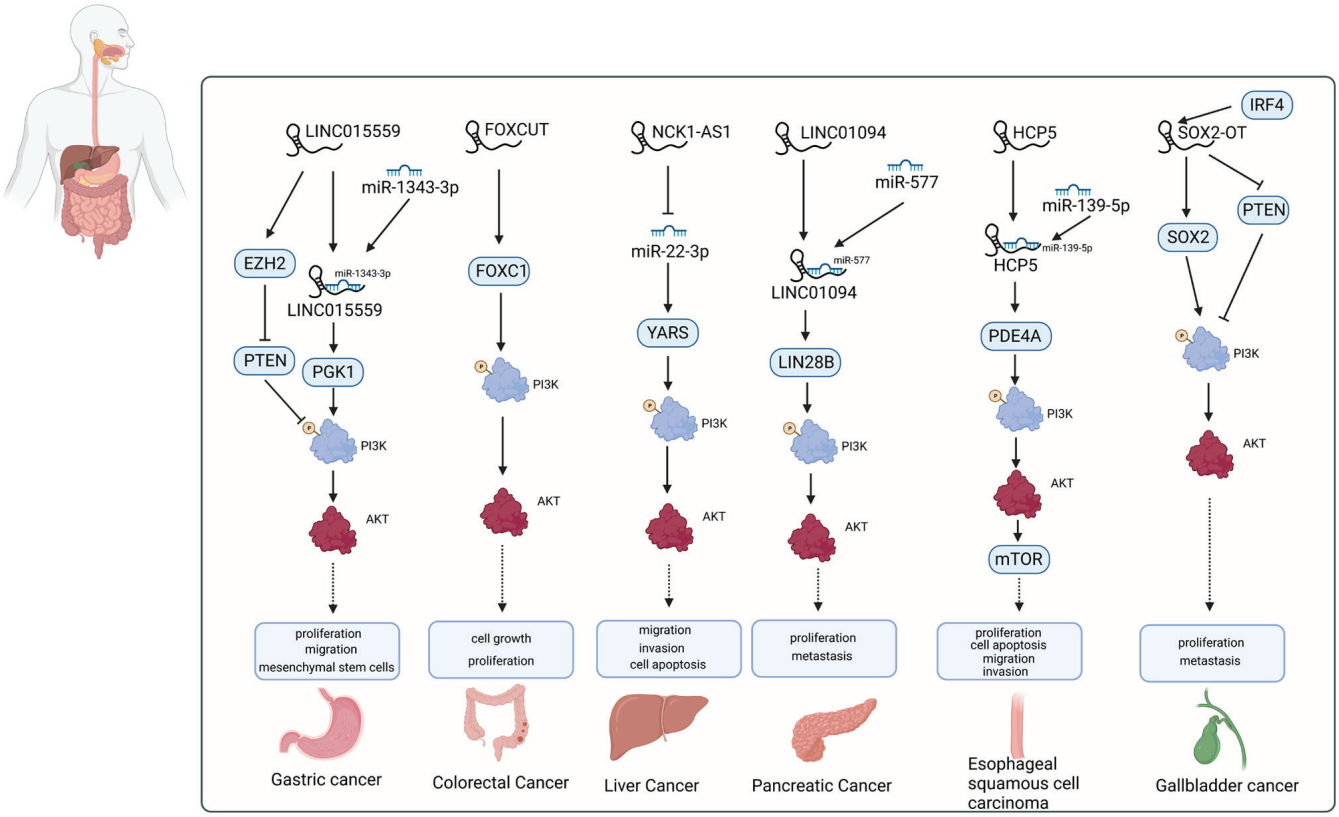

Figure 3. Specific mechanisms of digestive system tumor progression between long non-coding RNAs and the PI3K/AKT pathway. The figure was created using Adobe Illustrator 2024 (v28.0; Adobe Inc.). miR, microRNA; LINC, long intergenic non-coding.

lncRNAs may also play significant roles as biomarkers in other tumor types, such as breast and lung cancers, highlighting the potential for broader applications in cancer diagnostics and therapy.

Prognosis prediction. In addition to aiding in diagnosis, lncRNAs also show considerable promise in predicting patient prognosis, providing insights into survival outcomes and treatment strategies. lncRNA has the potential to predict the prognosis of patients with cancer, providing an important guide for the cancer treatment. For example, TTN-AS1 (93), LINC02154 (112), LASTR (155), LINC00982 (156), DBH-AS1 (157) and LINC00265 (158) are significantly associated with the survival outcomes, such as overall survival (OS) and disease-free survival of patients with cancer. High expression of SNHG20 (159), MSC-AS1 (160), XLOC013218 (161) and LPP-AS2 (162) suggests a low OS in patients with glioblastoma. Additionally, lncRNA also has significant associations with other clinical features of cancer. In the GC, the expression of HNF1A-AS1 is closely related to the lymph node metastasis of the GC (63). While in the CRC, PlncRNA-1 and CASC7 show positive associations with lymph node metastasis and TNM stage in patients with CRC, while the expression of PlncRNA-1 is also related to the depth of tumor infiltration (88,104). Another lncRNA, LBX2-AS1, exhibits a clear correlation with the tumor size and early distant metastasis in patients with CRC (97). In liver cancer, the expression of LINC00963 is significantly correlated with the tumor size and TNM stage (119). In addition, the expression of RHPN1-AS1 in HCC shows a close relationship between vascular invasion, TNM stage and Barcelona Clinic Liver Cancer stage (114). The PTTG3P expression is also positively associated with the tumor size, TNM stage and poor survival in patients with HCC (116). In PC, high expression of ABHD11-AS1 and SNHG1 is associated with distant metastasis, TNM stage and tumor differentiation in a positive manner (126,133), whereas the expression of MEG3 is negatively associated with the tumor size, metastasis and vascular invasion (135). In GBC, high LINC00152 expression has a positive association with tumor progression, lymph node infiltration and TNM stage (148).

Targeted therapies. Beyond diagnostic and prognostic capabilities, lncRNAs also provide new avenues for targeted therapies, which are revolutionizing cancer treatment by focusing on molecular pathways. Targeted therapy, which has been in clinical use since the late 1990s, has significantly enhanced the efficiency and specificity of cancer treatment. The approval of the first targeted drug, trastuzumab (Herceptin), for HER2-positive breast cancer in 1998 marked a pivotal moment in this therapeutic approach (163,164). lncRNA has significant implications for cancer progression via various signaling pathways. For instance, HNF1A-AS1 acts as a ceRNA to bind miR-30b-3p in the GC, activating the PI3K/AKT signaling pathway and then affecting the cancer progression (63). In the CRC, FOXCUT regulates cancer cell proliferation through increasing FOXC1 expression and activating the PI3K/AKT signaling pathway (90). While in liver cancer, MIR205HG as a molecular sponge for miR-205-5p activates the PI3K/AKT signaling pathway, thereby promoting the proliferation, migration and invasion of cancer cells (115). In addition, the GAS5

Table II. Relationship between lncRNA/PI3K/AKT axis and clinical features in digestive system neoplasms.

First author, year	Cancer type	LncRNA	Expression	Related feature	(Refs.)
Ma *et al*, 2020	Gastric cancer	HCG18	Upregulated	Stage of tumor node metastasis and invasion depth	(77)
Du *et al*, 2017		CRNDE	Upregulated	Invasion depth, TNM stage and lymph node metastasis	(75)
Hu *et al*, 2021		TMPO-AS1	Upregulated	Clinical prognosis	(74)
Han *et al*, 2019		LINC02465	Upregulated	Tumour size, tumour stage, lymph node metastasis and differentiation	(68)
Zhao *et al*, 2022		LINC01279	Upregulated	Tumor size, TNM stage, and metastasis of lymph nodes	(67)
Yao *et al*, 2020		HOXD-AS2	Downregulated	Lymph node metastasis	(78)
Hu *et al*, 2022		DLEU2	Downregulated	Tumor differentiation, cancer antigen 19-9 (CA19-9) and Lauren histologic classification	(85)
Chen *et al*, 2019		PCAT18	Downregulated	Tumor size	(84)
Li *et al*, 2019		SLC25A5-AS1	Downregulated	Tumour size, TNM stage and lymph node metastasis	(79)
Dai *et al*, 2020		UCA1	Downregulated	TNM stage	(64)
Li *et al*, 2019		LOC101928316	Downregulated	TNM stage and degree of differentiation	(80)
Song *et al*, 2018	Colorectal cancer	PlncRNA-1	Upregulated	Depth of invasion, lymph node metastasis, TNM stage and overall survival	(88)
Yun *et al*, 2019		HCP5	Upregulated	Survival period	(89)
Wang *et al*, 2017		AB073614	Upregulated	Tumor grade, tumor size, cell differentiation status, and the presence of distant metastases	(91)
Cui *et al*, 2019		TTN-AS1	Upregulated	Overall survival	(93)
Zhang *et al*, 2019		DLX6-AS1	Upregulated	Advanced T stage and distant metastasis	(96)
Fang *et al*, 2022		LBX2-AS1	Upregulated	Tumor volume and early distant metastasis	(97)
Feng *et al*, 2020		LINC00115	Upregulated	TNM stage	(98)
Liu *et al*, 2018		LINC01296	Upregulated	Clinical prognosis	(100)
Lei *et al*, 2021		LINC00657	Downregulated	Clinical prognosis, tumor size and TNM stage	(101)
Hao *et al*, 2021		CASC7	Downregulated	Survival rate, lymph node metastasis, and TNM stage.	(104)
Wu *et al*, 2018	Liver cancer	LINC00963	Upregulated	Tumor size and TNM stage	(119)
Zhong *et al*, 2022		AC099850.3	Upregulated	Clinical prognosis	(121)
Yue *et al*, 2022		LINC02154	Upregulated	Overall survival	(112)
Chen *et al*, 2018		NR027113	Upregulated	Overall survival	(113)
Zhou *et al*, 2022		NCK1-AS1	Upregulated	TNM stage, BCLC stage and survival status	(124)
Huang *et al*, 2018		PTTG3P	Upregulated	Tumor size, TNM stage and overall survival	(116)
Gu *et al*, 2017	Pancreatic cancer	MEG3	Upregulated	Tumor size, Metastasis and Vascular invasion	(135)

Table II. Continued.

First author, year	Cancer type	LncRNA	Expression	Related feature	(Refs.)
Luo *et al*, 2021		LINC01094	Upregulated	Clinical prognosis	(132)
Qiao *et al*, 2018		ABHD11-AS1	Upregulated	Distant metastasis, TNM stage and tumor differentiation	(133)
Zhang *et al*, 2018		SNHG1	Downregulated	Tumor size and TNM stage	(134)
Wang *et al*, 2018	Esophageal squamous cell carcinoma	GAS5	Downregulated	TNM stage	(140)
Zhang *et al*, 2021	Gallbladder cancer	CASC15	Downregulated	TNM stage	(147)
Cai *et al*, 2016		LINC00152	Upregulated	Tumor status progression, lymph node invasion and TNM stage	(148)

lncRNA, long non-coding RNA; LINC, long intergenic non-coding.

in OS serves as a ceRNA for miR-23a-3p to regulate the PI3K/AKT signaling pathway and increase PTEN expression, in turn suppressing the proliferation and invasion of tumor cells (165). ST3Gal6-AS1 is a target of the transcription factor FOXO1 and under the control of FOXO1. The positive feedback loop composed of ST3Gal6-AS1, ST3Gal6, PI3K/AKT and FOXO1 may play a key role in CRC progression (103).

7. Conclusion

Digestive system tumors remain a significant health challenge globally, with increasing incidence rates and a pressing need for improved diagnostic and therapeutic strategies to enhance patient outcomes (166,167). lncRNAs are emerging biomarkers for cancer diagnosis and treatment, with complex lncRNA-centric regulatory networks playing a crucial role in cancer occurrence, development and treatment. Research has shown that lncRNAs can influence cancer through interactions with molecules involved in key signaling pathways, notably the PI3K/AKT signaling pathway, which significantly impacts tumorigenesis, progression, invasion and metastasis. However, agents targeting the PI3K/AKT signaling pathway currently used in clinical tumor suppression have limited efficacy, rendering combination regimens the preferred option for anticancer treatment. A substantial body of research indicates that lncRNAs both positively and negatively regulate biological functions during the occurrence and development of digestive system neoplasms via their interactions with the PI3K/AKT signaling pathway. However, differences in the expression patterns and functional roles of lncRNAs have been observed across various types of digestive system cancers. For instance, in GC, lncRNAs such as HOTAIR (69) and LINC00511 (70) are overexpressed, which enhances the PI3K/AKT signaling, contributing to tumor progression and poor prognosis. In GC, on the other hand, certain lncRNAs such as LINC01559 (65) have been implicated in PI3K/AKT pathway activation, driving proliferation and metastasis. In PC, it has been demonstrated that lncRNAs such as MEG3 (128) can modulate the PI3K/AKT pathway, influencing chemoresistance and cancer cell survival. These variations highlight the need for a more nuanced approach to targeting lncRNAs in different digestive system neoplasms. Furthermore, the expression of lncRNAs has been significantly associated with patient survival in these neoplasms, providing valuable prognostic information. However, the expression patterns and stability of lncRNAs in circulating body fluids (including urine and blood) require further exploration. Notably, lncRNAs have demonstrated potential in targeted therapies for other cancers, such as MALAT1 and HOTAIR, which are currently under investigation in breast (168,169), lung (170,171) and prostate cancers (172,173) for their roles in tumor progression and therapeutic responses. These findings suggest that lncRNA-targeted treatments could be expanded to gastrointestinal cancers, potentially opening new avenues for therapeutic intervention. To this end, a more thorough understanding of the functions and mechanisms of lncRNAs related to the PI3K/AKT signaling pathway in both physiological and pathophysiological conditions is essential. Moreover, the translational potential of these insights is currently limited by the lack of comprehensive clinical trial data. Structural and functional understanding

of lncRNAs associated with the PI3K/AKT pathway remains sparse, obscuring the mechanisms of their interactions. Therefore, the development of targeted treatment strategies based on the PI3K/AKT pathway faces significant challenges due to the incomplete understanding of lncRNA structure and function. In conclusion, bridging the gap between basic research and clinical applications is imperative to unlock the therapeutic potential of targeting the lncRNA/PI3K/AKT axis in digestive system neoplasms. Future studies should focus on exploring clinical implications of these findings, investigating new diagnostic or therapeutic approaches, and considering strategies for targeting lncRNAs or modulating the PI3K/AKT pathway to improve patient outcomes. Additionally, comparative studies on lncRNA functions across different types of digestive system cancers could provide valuable insights into their diverse roles, further aiding in the development of more specific and effective therapeutic strategies. However, since lncRNAs are still in their emerging stages, there are currently no targeted drugs specifically for tumor treatment available in clinical settings. In the future, the authors shall focus on clinical applications and conduct in-depth research on the role of lncRNAs in tumors, aiming to aid clinicians.

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Availability of data and materials

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Authors' contributions

XZ wrote the manuscript and created the images. LS and CL collected and organized the literature. MX and FM proofread the manuscript. YunM and YuxM are fully responsible for the study designing, research fields, drafting and finalizing the review. All authors contributed to the article. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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