Long noncoding RNAs in digestive system cancers: Functional roles, molecular mechanisms, and clinical implications (Review)

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Abstract. Long noncoding RNAs (lncRNAs) are emerging as new players in various diseases including cancer. LncRNAs have been shown to play multifaceted roles in the development, progression, and metastasis of cancer. In this review, we highlight the lncRNAs that are critically involved in the pathogenesis of digestive system cancers (DSCs). We summarize the roles of the lncRNAs in DSCs and the underlying mechanisms responsible for their functions. The DSC-associated lncRNAs interact with a wide spectrum of molecules to regulate gene expression at transcriptional, post-transcriptional, and translational levels. We also provide new insights into the clinical significance of these lncRNAs, which are found to be closely associated with the aggressiveness of DSCs and could predict the prognosis of DSC patients. Moreover, lncRNAs have been suggested as promising therapeutic targets in DSCs. Therefore, better understanding of the functional roles of lncRNAs will provide new biomarkers for DSC diagnosis, prognosis, and therapy.

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1. Introduction

Digestive system cancers (DSCs) are common cancers and the leading causes of cancer-related deaths worldwide (1). According to the classification by the World Health Organization in 2010 (2), DSCs consist of alimentary tract cancers of the esophagus, stomach, colorectum, and digestive gland cancers of the liver, gallbladder, bile duct, and pancreas. Although great advances in surgical techniques and chemotherapy have been achieved, the prognosis of DSCs is still poor since they are mostly diagnosed at advanced stage, which may be accompanied by malignant proliferation, extensive invasion, and distant metastasis (3,4). Genetic and epigenetic alterations have been suggested to participate in the development and progression of DSCs (5-7). The elucidation of the molecular regulatory network in DSCs will provide novel biomarkers for early diagnosis and more effective therapy.

Over the past decade, noncoding RNAs are emerging as new players in various diseases. Long noncoding RNAs (lncRNAs) are defined as transcripts of greater than 200 nucleotides that lack protein-coding capability (8). LncRNAs regulate gene expression at various levels, including chromatin modification (9), transcription (10), and post-transcription (11,12). Increasing evidence suggests that lncRNAs play important roles in cancer (13). LncRNAs are critically involved in tumorigenesis, tumor growth, and tumor metastasis (14). In this review, we present an updated view of the roles of lncRNAs in DSCs with an emphasis on the underlying mechanisms. We also provide new insights into the prospective of lncRNAs as potential diagnostic biomarkers and therapeutic targets for DSCs.

2. The functional roles of DSC-related lncRNAs

To identify the lncRNAs most closely related to DSCs, a systematic literature search was conducted to find all the lncRNAs which have been reported in esophageal, stomach, colorectal, liver, gallbladder, bile duct, and pancreatic cancers. LncRNAs that are involved in at least three types of DSCs were included for further review. A total of ten lncRNAs were included, which are H19, Hox transcript antisense intergenic RNA (HOTAIR), metastasis-associated lung

Table I. The expression of lncRNAs in DSCs.

LncRNA	Size	Gene location	Expression change	DSC type	Refs.
H19	2.3 kb	11p15.5	Upregulated	Esophagus, stomach, colorectum, pancreas	(21,23,25,32)
HOTAIR	2.2 kb	12q13.13	Upregulated	Esophagus, stomach, colorectum, liver, gallbladder, pancreas	(36,38-40,137,148)
MALAT1	8.1 kb	11q13.1	Upregulated	Esophagus, stomach, colorectum, liver, gallbladder, pancreas	(52,53,60,149,150)
HULC	~500 nt	6p24.3	Upregulated	Stomach, liver, pancreas	(71,72,75)
MEG3	1.6 kb	14q32.2	Downregulated	Stomach, colorectum, liver, pancreas	(80,82,86,89)
GAS5	630 nt	1q25	Downregulated	Stomach, colorectum, liver, pancreas	(92-94,96)
ANRIL	3.8 kb	9p21.3	Upregulated	Esophagus, stomach, colorectum, liver	(103,104,106,107)
PVT1	>300 kb	8q24	Upregulated	Stomach, colorectum, liver, pancreas	(109-112)
CCAT1	2628 nt	8q24.21	Upregulated	Stomach, colorectum, liver, gallbladder	(12,120,121,151)
LncRNA-ATB	162 kb	14q-	Upregulated	Stomach, colorectum, liver	(122-124)

LncRNAs, long noncoding RNAs; DSCs, digestive system cancers; HOTAIR, Hox transcript antisense intergenic RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; HULC, highly upregulated in liver cancer; MEG3, maternally expressed gene 3; GAS5, growth arrest-specific transcript 5; ANRIL, antisense noncoding RNA in the INK4 locus; PVT1, plasmacytoma variant translocation 1; CCAT1, colon cancer associated transcript 1.

adenocarcinoma transcript 1 (MALAT1), highly upregulated in liver cancer (HULC), maternally expressed gene 3 (MEG3), growth arrest-specific transcript 5 (GAS5), antisense noncoding RNA in the INK4 locus (ANRIL), plasmacytoma variant translocation 1 (PVT1), colon cancer associated transcript 1 (CCAT1), and lncRNA-ATB. The characteristics of these DSCs-related lncRNAs are shown in Table I. The functional roles and clinical correlations of these lncRNAs in DSCs are presented in Table II. The upstream signaling pathways and downstream targets for DSC-related lncRNAs are reviewed in Fig. 1.

H19. The H19 gene, located at chromosome 11p15.5, belongs to a highly conserved cluster of imprinted genes which involve the insulin-like growth factor 2 gene (15). H19 is expressed exclusively from the maternal allele and encodes a 2.3 kb lncRNA (16). During the past decade, extensive research has been carried out on H19 in various cancers. Initially, H19 was found to be tumor-suppressive because of its abilities to repress tumorigenicity (17). However, increasing evidence suggests that H19 is upregulated in most cancers and has oncogenic properties (18-20). In particular, the upregulated levels of H19 have been confirmed in most DSCs, except the less studied gallbladder cancer (21-25). The role of H19 in liver cancer is still controversial, with some studies showing beneficial (26,27) and the others showing detrimental (28,29) effects to cancer progression.

Yang *et al* demonstrated that H19 expression is markedly increased in gastric cancer cell lines and tumor tissues. The ectopic expression of H19 increases cell proliferation, whereas H19 knockdown induces cell apoptosis in gastric cancer cells. They also suggest that the oncogenic role of H19 is associated with the inactivation of p53 tumor suppressor (30). Zhang *et al* demonstrated that c-Myc can regulate H19 expression and H19 level is positively correlated with that of c-Myc in gastric

cancer tissues (31). H19 is also highly expressed in colorectal cancer cell lines and tumor tissues, promoting tumor growth and metastasis both *in vitro* and *in vivo* (23). Notably, miR-675 is co-expressed with H19 and acts as a pivotal mediator of H19 function in DSCs (28,32-34). In gastric cancer, the tumor suppressor runt-related transcription factor 1 (RUNX1) is validated as a direct target of miR-675 (32). In addition, H19 directly upregulates ISM1 and indirectly suppresses CALN1 via miR-675 in gastric cancer (34). In colorectal cancer, the tumor suppressor retinoblastoma (RB) is directly targeted by miR-675. H19-derived miR-675 promotes colorectal cancer cell growth through suppressing the expression of its target RB (33). In hepatocellular carcinoma, Lv *et al* showed that the downregulation of H19 and miR-675 promotes the migration and invasion of hepatocellular carcinoma cells (28). Moreover, miR-675 acts as a positive regulator of H19 (26). In addition to miR-675, other miRNAs have also been confirmed to interact with H19 in DSCs. Zhou *et al* demonstrated that H19 expression is inversely correlated to miR-141 expression in gastric cancer cells and tissues. miR-141 interacts with H19 in a sequence specific manner and suppresses H19 expression and function (22). In colorectal cancer, H19 acts as a competing endogenous RNA for miR-138 and miR-200a, thereby eliminating the repression of core marker genes for epithelial-to-mesenchymal transition (EMT) including vimentin, ZEB1, and ZEB2 (23). Zhang *et al* demonstrated that the miR-200 family mediates H19-mediated inhibition of metastasis in hepatocellular carcinoma. H19 activates miR-200 family by promoting histone acetylation, thus resulting in tumor suppression (29).

HOTAIR. The HOTAIR is expressed from the developmental HOXC locus located on chromosome 12q13.13. It was first revealed in breast cancer that lncRNA HOTAIR could promote cancer metastasis through inducing polycomb

Table II. The functional roles of lncRNAs in DSCs.

LncRNA	DSC type	Functional roles	Downstream targets	Refs.
H19	Esophagus	Promotes cell proliferation and invasion	E-cadherin, vimentin, fibronectin	(21)
	Stomach	Promotes cell proliferation, migration, and invasion	ZEB1, miR-675, RUNX1, CALN1	(32,34,130)
	Colorectum	Promotes cell proliferation and invasion	miR-138/vimentin, miR-200a/ZEB1/2, miR-675/Rb	(23,33)
	Pancreas	Promotes cell migration and invasion	Let7/HMGA-2	(25)
HOTAIR	Esophagus	Promotes cell proliferation, migration, and invasion	WIF-1	(41,44)
	Stomach	Promotes cell survival, proliferation, migration, and invasion	miR-331-3p/HER2, miR-152/HLA-G, PRC2/miR-34a/HGF/c-Met/Snail	(45-47)
	Colorectum	Promotes cell proliferation, migration, invasion, and radiotherapy resistance	PRC2 (SUZ12, EZH2, H3K27me3)	(9,43,137)
	Liver	Promotes cell survival, proliferation, migration, and invasion	SUZ12, ZNF198, RBM38, E-cadherin, SETD2	(38,48-50)
	Gallbladder	Promotes cell proliferation and invasion	miR-130a	(39)
	Pancreas	Promotes cell proliferation and invasion	PRC2	(40)
MALAT1	Esophagus	Promotes cell proliferation, migration, and invasion	p21, p27	(52,64,152)
	Stomach	Promotes cell proliferation	SF2/ASF	(53,153)
	Colorectum	Promotes cell proliferation, migration, and invasion	AKAP-9, Snail, SFPQ/PTBP2	(58-60)
	Liver	Promotes cell survival, proliferation, migration, and invasion	-	(65,66,149)
	Gallbladder	Promotes cell proliferation, migration, and invasion	ERK/MAPK	(56)
	Pancreas	Promotes cell stemness, proliferation, migration, and invasion; angiogenesis; chemoresistance	Sox2, Bmi-1, c-Myc	(57,63)
HULC	Stomach	Promotes cell proliferation, migration, and invasion	-	(71)
	Liver	Promotes cell proliferation, migration, and invasion; angiogenesis	p18, CLOCK, miR-107/E2F1/SPHK1, miR-9/PPARA/ACSL1/cholesterol	(10,70,74,75)
	Pancreas	Promotes cell proliferation	-	(72)
MEG3	Stomach	Inhibits cell proliferation, migration, and invasion	miR-181/Bcl-2	(79)
	Colorectum	Inhibits cell proliferation	p53, cylcin D1	(80)
	Liver	Inhibits cell proliferation	p53	(90)
	Pancreas	Inhibits cell proliferation	c-Met	(82)
GAS5	Stomach	Inhibits cell proliferation	YBX1, E2F1, p21, CDK6	(93,97,98)
	Colorectum	Inhibits cell proliferation	-	(92)
	Liver	Inhibits cell proliferation, migration, and invasion	miR-21/PDCD4, PTEN, vimentin	(94,95,140)
	Pancreas	Inhibits cell proliferation	CDK6	(96)
ANRIL	Esophagus	Promotes cell proliferation	p15	(103)
	Stomach	Promotes cell proliferation	miR-99a, miR-449a	(104)
	Colorectum	Promotes cell proliferation	-	(106)
	Liver	Promotes cell proliferation, migration, and invasion	PRC2/KLF2	(105,107)
PVT1	Stomach	Promotes cell proliferation	MDR1, MRP, mTOR, HIF-1α, p15 p16	(109,113,141)
	Colorectum	Promotes cell proliferation, and invasion	SMAD4	(110)
	Liver	Promotes cell stemness and proliferation	NOP2	(111,114)

Table II. Continued.

LncRNA	DSC type	Functional roles	Downstream targets	Refs.
	Pancreas	Promotes chemoresistance	-	(112,154)
CCAT1	Stomach	Promotes cell proliferation and migration	-	(117,151)
	Colorectum	Promotes cell proliferation and invasion	-	(115,120)
	Liver	Promotes cell proliferation, migration, and invasion	let-7/HMGA2	(118,119,121)
	Gallbladder	Promotes cell proliferation and invasion	miR-218-5p/Bmi-1	(12)
LncRNA-ATB	Stomach	Promotes cell invasion	miR-200s/ZEB	(123)
	Colorectum	Promotes cell proliferation, migration, and invasion	E-cadherin	(124,125)
	Liver	Promotes cell invasion	miR-200s, IL-11	(122,127)

LncRNAs, long noncoding RNAs; DSCs, digestive system cancers; HOTAIR, Hox transcript antisense intergenic RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; HULC, highly upregulated in liver cancer; MEG3, maternally expressed gene 3; GAS5, growth arrest-specific transcript 5; ANRIL, antisense noncoding RNA in the INK4 locus; PVT1, plasmacytoma variant translocation 1; CCAT1, colon cancer associated transcript 1; RUNX1, runt-related transcription factor 1.
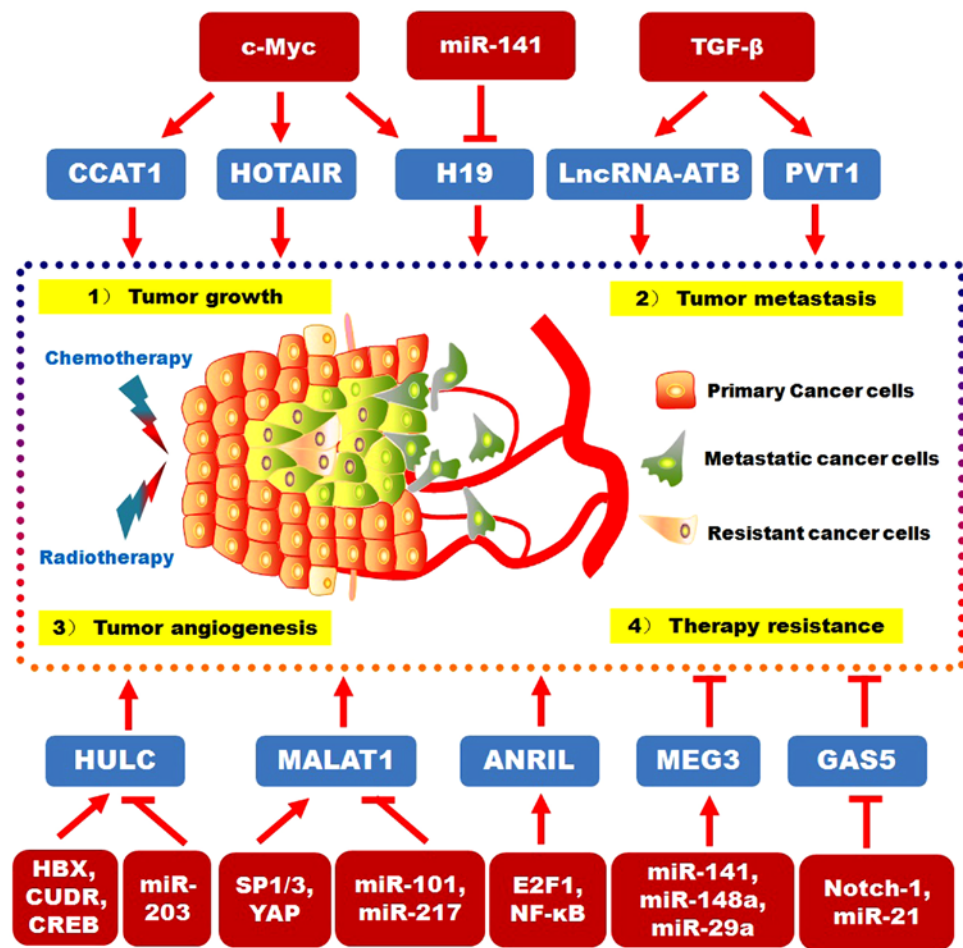

Figure 1. The modulation of long noncoding RNAs (lncRNAs) in digestive system cancers (DSCs). The DSCs-related lncRNAs play either oncogenic or tumor-suppressive roles in tumor growth, metastasis, angiogenesis, and therapy resistance. The deregulated expression of lncRNAs in DSCs is controlled by various factors, including oncoproteins (c-Myc, SP1/3, YAP and Notch1), transcription factors (NF-κB, E2F1 and CREB), microRNAs (miR-141, miR-21 and miR-203), and lncRNA (CUDR).

repressive complex 2 (PRC2)-mediated trimethylation of histone H3 lysine-27 (H3K27me3) (35). The enhanced expression of HOTAIR is reported in the cell lines and tumor tissues of most DSCs (9,36-41). In gastric cancer, the increased

expression of HOTAIR is associated with TNM stage, lymph node metastasis, venous invasion, and poor survival (37,42). HOTAIR knockdown leads to a promotion of radio-sensitivity in colorectal cancer cells (43). In esophageal squamous cell carcinoma, HOTAIR promotes cell migration and invasion by directly downregulating WIF-1 expression and activating the Wnt/β-catenin pathway (44). Song et al suggested that the enhanced expression of HOTAIR in gastric cancer is associated with tumor escape by inhibiting miR-152 and upregulating HLA-G (45). HOTAIR could act as a ceRNA in gastric cancer cells by efficiently binding to miR-331-3p and thereby reactivating HER2 to promote cancer cell growth, migration, and invasion (46). HOTAIR induces the silence of miR-34a via PRC2, promoting EMT in human gastric cancer cells (47). Kogo et al demonstrated that HOTAIR is involved in a genome-wide reprogramming of PRC2 in colorectal cancer. The upregulation of HOTAIR is critical to the metastatic progression (9). Recently, Zhang et al suggested that HOTAIR can promote the proteasomal degradation of SUZ12 and ZNF198 during liver carcinogenesis induced by hepatitis B virus (48). Ye et al demonstrated that HOTAIR induces malignant transformation of liver normal stem cells by downregulating E-cadherin and inducing EMT (49). In liver cancer stem cells, HOTAIR has been shown to promote malignant growth through downregulating SETD2 (50). HOTAIR negatively regulates RNA binding motif protein 38 (RBM38) in hepatocellular carcinoma cells to promote cell motility (38). Ma et al demonstrated that c-Myc induces HOTAIR expression through direct interaction with the promoter region of HOTAIR in gallbladder cancer. In addition, they also suggested that the oncogenic role of HOTAIR functions in part through negatively regulating miRNA-130a (39).

MALAT1. MALAT1, a metastasis-associated lncRNA, was originally discovered to be a marker for metastasis development in early stage lung adenocarcinoma (51). Recently, the upregulated expression of MALAT1 was observed in both cell lines and clinical tissue samples in all types of human DSCs (52-57). Among them, colorectal cancer is most studied for MALAT1 dysregulation (54,58-62). Overexpression of MALAT1 promotes colorectal cancer cell proliferation, migration, and invasion *in vitro*, and stimulates tumor growth and metastasis *in vivo*. Reciprocally, the knockdown of MALAT1 inhibits tumor growth and metastasis (60). The higher level of MALAT1 significantly correlates with peritoneal metastasis in gastric cancer patients (53). The knockdown of MALAT1 significantly inhibits the proliferation and metastasis of gall-bladder carcinoma cell lines both *in vitro* and *in vivo* (56). The inhibition of MALAT-1 could suppress pancreatic cancer cell proliferation, migration, and invasion *in vitro* (63). A recent study suggests that MALAT-1 overexpression could increase the proportion of cancer stem cells in pancreatic cancer (57).

In esophageal cancer cells, miR-101 and miR-217 conduct an Ago2-dependent post-transcriptional regulation of MALAT1, leading to reduced cell proliferation, migration, and invasion. MALAT1 knockdown significantly represses the proliferation of esophageal squamous cell carcinoma cells, which may be associated with the upregulation of p21 and p27 expression (52). It was suggested that MALAT1 may regulate

esophageal squamous cell carcinoma cell proliferation by inactivating the ATM-CHK2 pathway (64). In liver cancer, MALAT1 is upregulated by the oncoprotein Yes-associated protein (YAP) through the interaction with TCF/β-catenin on the MALAT1 promoter, which can be inhibited by serine/arginine-rich splicing factor 1 (SRSF1) (65). The knockdown of Sp1 and Sp3 in hepatocellular carcinoma jointly downregulates MALAT1 expression (66). In gallbladder cancer cells, MALAT1 knockdown significantly inhibits the proliferation and metastasis of gallbladder cancer cells *in vitro* and *in vivo* through the inactivation of ERK/MAPK signaling pathway (56).

HULC. The lncRNA HULC is regarded as the first lncRNA with highly specific upregulation in hepatocellular carcinoma (67). Compared with normal controls, HULC expression is significantly higher in tumor cells, tumor tissues and plasma of hepatocellular carcinoma patients (68-70). The overexpression of HULC is also reported in gastric cancer and pancreatic cancer and is correlated with advanced lymph node metastasis (71,72). Hepatitis B virus X protein (HBx) contributes to the development of hepatocellular carcinoma. Intriguingly, HULC is involved in HBx-mediated hepatocarcinogenesis. HBx could activate the HULC expression to promote hepatocellular carcinoma cell proliferation through the downregulation of p18 (70). HULC is both a target and a regulator of CREB through its interaction with microRNA-372 in liver cancer cells, providing a fine-tuned auto-regulatory loop (73). HULC is responsible for the perturbations in circadian rhythm through upregulating circadian oscillator CLOCK in hepatoma cells, resulting in the promotion of hepatocarcinogenesis (74). HULC contributes to abnormal lipid metabolism to support the growth of hepatoma cells through the regulation of miR-9-mediated RXRA signaling (10). Recently, Lu et al demonstrated that HULC promotes angiogenesis in liver cancer by upregulating sphingosine kinase 1 (SPHK1). HULC sequesters miR-107 from binding to E2F1 transcription factor and therefore activates E2F1-dependent transcription of SPHK1 (75). Wan et al suggested that HULC could be downregulated by miR-203, leading to the suppression of hepatocellular carcinoma (76). Moreover, HULC could be upregulated by another lncRNA, cancer upregulated drug-resistant gene (CUDR), contributing to the malignant differentiation of liver cancer stem cells (77).

MEG3. MEG3 represents an imprinted gene belonging to the imprinted DLK1-MEG3 locus located at human chromosome 14q32.2 (78). Accumulating evidence suggests that the expression of MEG3 is decreased in DSCs (79-82). MEG3 is decreased in gastric cancer cell lines and tissues, and its expression is associated with the metastasis of gastric cancer. The overexpression of MEG3 in gastric cancer cells inhibits cell proliferation, migration, invasion, and promotes cell apoptosis (79). MEG3 overexpression could inhibit colorectal cancer cell proliferation both *in vitro* and *in vivo* (80). The enforced expression of MEG3 in hepatocellular carcinoma cells significantly decreases both anchorage-dependent and -independent cell growth, and induces apoptosis (81).

The mechanism responsible for the downregulation of MEG3 in cancer remains unclear. The interactions between MEG3 and other molecules in DSCs have been widely studied. Peng et al suggested that lncRNA MEG3 competitively binds

to the miR-181 family and functions as a ceRNA, upregulating downstream target B-cell lymphoma-2 (Bcl-2), and then suppressing gastric cancer progression (79). Zhou *et al* recently demonstrated that there is a positive correlation between MEG3 and miR-141 in gastric cancer tissues. They further suggested that miR-141 activates MEG3 by targeting E2F3, which inhibits the proliferation of gastric cancer cells (83). Yan *et al* demonstrated that the ectopic expression of miR-148a activates MEG3 via modulation of DNMT-1 (84). It has been shown that methylation-dependent regulation of MEG3 by miR-29a is involved in hepatocellular carcinoma (81,85,86). Similarly, dendrosomal curcumin upregulates miR-29a and miR-185 and induces DNA hypomethylation, thus promoting the expression of MEG3 in hepatocellular carcinoma (87). The re-expression of MEG3 could lead to the accumulation of p53 protein and its target gene expression, inducing inhibition of cancer cell growth (88). Sun *et al* also suggested that MEG3 overexpression upregulates the protein level of p53 in gastric cancer cells harboring wild-type p53, indicating that MEG3 may function as a tumor suppressor partially through the activation of p53 in gastric cancer (89). In colorectal and liver cancers, the tumor suppressive role of MEG3 through the activation of p53 is also revealed (80,90). In addition, Modali *et al* identified MEG3 as a tumor suppressor lncRNA by targeting c-MET to elicit Menin tumor-suppressor activity in pancreatic cancer (82).

GAS5. GAS5, encoded at chromosome 1q25, with about 630 nucleotides in length, was initially discovered during screening for potential tumor suppressor genes (91). Previous studies have shown that GAS5 is downregulated in DSCs, including gastric, colorectal, liver, and pancreatic cancers (92-96). The lower expression of GAS5 is positively correlated with aggressive tumor behavior (92,93). The underlying mechanism for the roles of GAS5 in DSCs is not yet well characterized. In gastric cancer cells, GAS5 binds to the YBX1 protein and regulates its turnover. The downregulation of GAS5 decreases the YBX1 protein level, subsequently inhibiting YBX1-transactivated p21 expression and G1 phase arrest (97). Sun *et al* also suggested that GAS5 regulates the expression of p21, E2F1, and cyclin D1 in gastric cancer cells through post-transcriptional mechanism (93). In gastric cancer cells and pancreatic cancer cells, GAS5 functions as a tumor suppressor by suppressing the expression of cyclin-dependent kinase (CDK) 6 (96, 98). Chang *et al* revealed that GAS inhibits hepatoma cell proliferation by the regulation of vimentin (95). GAS5 could also act as ceRNA by binding to miR-21, inhibiting the migration and invasion of hepatocellular carcinoma cells (94).

ANRIL. ANRIL is transcribed as a 3.8 kb lncRNA from the INK4b-ARF-INK4a gene cluster in the opposite direction (99,100). ANRIL has been identified as a genetic susceptibility locus associated with various diseases including cancer (101,102). Previous studies have shown that ANRIL is upregulated in esophageal squamous cell carcinoma, gastric cancer, colorectal cancer, and hepatocellular carcinoma (103-105). ANRIL is verified as a growth stimulator in esophageal, gastric, and colorectal cancer cells (103,104,106). The knockdown of ANRIL could not only inhibit hepatocellular carcinoma cell proliferation, but

also induced cell apoptosis both *in vitro* and *in vivo* (107). In esophageal squamous cell carcinoma, the inhibition of ANRIL upregulates the expressions of p15 and TGFβ1, suggesting a significant role of ANRIL in the development of esophageal squamous cell carcinoma (103). In gastric cancer, ANRIL could indirectly regulate mTOR and CDK6/E2F1 pathway through binding to PRC2 and epigenetically silencing miR-99a/miR-449a, partially accounting for ANRIL-mediated cell growth regulation. In addition, the upregulated E2F1 promotes ANRIL expression and forms a positive feedback loop to promote gastric cancer cell proliferation (104). In hepatocellular carcinoma, ANRIL could epigenetically silence the transcription of Krüppel-like factor 2 (KLF2) by interacting with PRC2 and recruiting it to the promoter region of KLF2, leading to increased cell proliferation and decreased cell apoptosis (107).

PVT1. PVT1 is documented as an oncogenic lncRNA mapping to chromosome 8q24 (108). PVT1 locates at a recognized cancer risk locus sharing with the well-known MYC oncogene, which is among the top target loci of copy number alterations in cancer (108). In DSCs, PVT1 expression is upregulated in the tumor tissues of gastric, colorectal, liver, and pancreatic cancers (109-112). The higher level of PVT1 is associated with invasion and advanced TNM stage (113). Univariate and multivariate analyses have revealed that the higher PVT1 expression is associated with poor overall survival and poor recurrence-free survival, which could be an independent prognostic indicator (110,111). Kong *et al* have recently shown that PVT1 inhibition increases the expression of p15 and p16 and induces G1 phase arrest in gastric cancer cells (113). NOP2 is identified as an RNA-binding protein that binds to PVT1. It is further shown that PVT1 promotes the proliferation and stem cell-like property of hepatocellular carcinoma cells by enhancing the stability of NOP2 (114).

CCAT1. CCAT1, a 2628 nucleotide-lncRNA located on chromosome 8q24.21, was first discovered in colon cancer by Nissan *et al* in 2012 (115). CCAT1 is strongly expressed in colon cancer tissues but not in normal tissues (115). The upregulation of CCAT1 is evident in pre-malignant conditions and through all disease stages, including advanced metastatic colon cancer (116). Emerging evidence suggests that CCAT1 is also upregulated in other DSCs including gastric cancer, hepatocellular cancer, and gallbladder cancer (12,117,118). The upregulation of CCAT1 is correlated with the growth of primary tumor, lymph node metastasis, and metastatic disease (117), while patients with low expression of CCAT1 demonstrate better overall and relapse-free survival (119,120). He and colleagues suggest that in colon cancer cells, c-Myc could accelerate CCAT1 transcription by direct binding to its promoter region, and the enhanced expression of CCAT1 promotes cell proliferation and invasion (120). The regulation of CCAT1 by c-Myc is also revealed in gastric cancer and hepatocellular carcinoma (117,119). Moreover, CCAT1 competitively binds to let-7 to antagonize its function and de-represses its targets HMGA2 and c-Myc, thus promoting cell proliferation and migration in hepatocellular carcinoma cells (121). Similarly, CCAT1 promotes the proliferation and invasiveness of gallbladder cancer cells partially through

'spongeing' miRNA-218-5p and inducing the expression of oncogenic gene Bmi1 (12).

LncRNA-ATB. LncRNA-AL589182.3 (ENST00000493038) is identified in hepatocellular carcinoma cells as lncRNA-activated by TGF-β (lncRNA-ATB) (122). Yuan *et al* suggested that lncRNA-ATB is a key regulator of TGF-β signaling pathway. LncRNA-ATB can be activated by TGF-β, and subsequently competitively binds to the miR-200 family, leading to the upregulation of ZEB1 and ZEB2 and the induction of EMT. In addition, lncRNA-ATB facilitates hepatocellular carcinoma cell colonization by increasing autocrine induction of IL-11 and activating STAT3 signaling (122). Recent studies have demonstrated the pathological roles of lncRNA-ATB in other DSCs including gastric cancer, colorectal cancer, and pancreatic cancer. LncRNA-ATB is also upregulated in gastric cancer and colorectal cancer and this overexpression is correlated with clinical features and prognosis (123,124). Yue *et al* demonstrated that lncRNA-ATB suppresses E-cadherin expression and promotes EMT (125). However, lncRNA-ATB expression is decreased in pancreatic cancer tissues and cell lines. Downregulated expression level of lncRNA-ATB is significantly correlated with lymph node metastases, neural invasion, and clinical stage in pancreatic cancer (126). The roles of lncRNA-ATB in interacting with other miRNAs and mRNA still need to be investigated (127).

3. The clinical significance of DSC-related lncRNAs

Diagnostic biomarker. The early diagnosis is critical for the improvement of patient survival. However, traditional tumor biomarkers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9, present low sensitivity and specificity. Recently, circulating RNA have emerged as non-invasive diagnostic markers. Although the earlier studies concentrated on microRNAs (128,129), the investigations on the diagnostic role of lncRNAs are increasing. In DSCs, there are growing numbers of lncRNAs which have the potential to serve as diagnostic biomarkers. Zhou *et al* systematically characterized the potential of circulating lncRNAs in plasma as diagnostic markers for gastric cancer. They detected the expression of eight lncRNAs in plasma from gastric cancer patients and healthy subjects. Three lncRNAs (H19, HOTAIR, and MALAT1) were identified with significantly elevated levels in plasma from gastric cancer patients compared to normal controls. Moreover, H19 shows a good stability in the blood and can distinguish early stage gastric cancer, presenting higher sensitivity and specificity than traditional biomarkers (130). Circulating lncRNAs are thought to be unstable due to the high RNase level in plasma, especially in cancer patients carrying more RNase in plasma (131). However, Zhou *et al* showed that circulating lncRNAs are very stable even when digested directly with RNase A (130), in accordance with another study (132). One possible explanation is that lncRNAs are protected by packaging into microparticles such as exosomes (133,134). Li *et al* suggested that there is no significant difference in LINC00152 levels between plasma and exosomes, indicating that LINC00152 may be released into the blood by exosomes (135). LINC00152 and HULC are screened out from eight lncRNAs for evaluating the diagnostic value of plasma lncRNAs in hepatocellular carcinoma. Circulating HULC and LINC00152 are significantly upregulated in the plasma of hepatocellular carcinoma patients (69). The combination of HULC, LINC00152, and AFP shows a high prediction value of hepatocellular carcinoma (69). Therefore, the combined analysis of individual lncRNA with traditional biomarkers may improve the sensitivity and specificity of diagnosis and enhance the diagnostic value of lncRNAs.

Prognostic biomarker. The prognostic biomarkers can predict therapeutic effects after certain treatments, thus providing valuable guidance for therapy. There are a number of lncRNAs that have been well characterized as prognostic biomarkers in DSCs (136). The performance of H19 as prognostic marker is still elusive. It is evident that high H19 expression is an independent predictor of the poor overall survival in gastric cancer patients (31). However, in hepatocellular carcinoma patients, low ratio of H19 expression in intratumoral hepatocellular carcinoma tissues to that in peritumoral tissues predicts poor prognosis (29). High ANRIL expression has been suggested to serve as an independent predictor of poor prognosis in both gastric cancer and hepatocellular carcinoma patients (104,105). HOTAIR may serve as an outstanding biomarker for its prognostic value in DSCs including esophageal, gastric, colorectal, liver, and pancreatic cancers (40,41,47,137,138). In particular, the upregulated HOTAIR expression in blood of colorectal cancer patients is associated with unfavorable prognosis, representing an alternative prognostic marker for colorectal cancer (137). For esophageal squamous cell carcinoma, HOTAIR is most commonly identified as negative prognosis marker among these DSC-related lncRNAs (36,41,44,139). Since identified in 2014 (121), lncRNA-ATB has been well characterized for its prognostic value in DSCs. The high level of lncRNA-ATB is correlated with poor prognosis in liver cancer (121), gastric cancer, and colorectal cancer (122,123). However, the patients with low lncRNA-ATB expression exhibit markedly poor overall survival (125), suggesting a tumor type-dependent role of lncRNA-ATB. The decreased expression of GAS5, a tumor-suppressive lncRNA, could independently predict poor overall survival of gastric, colorectal, and liver cancer patients (92,93,95,140). Frequent recurrence is a major obstacle for long-term survival. Several DSC-related lncRNAs could predict recurrence of hepatocellular carcinoma patients, demonstrating their potential as prognostic biomarkers for recurrence (55,86,111,119,122,138).

Therapeutic target. LncRNAs are considered as potential therapeutic targets in cancer. The specific targeting of lncRNAs could greatly affect the malignant phenotypes such as tumor growth and metastasis. LncRNA-oriented therapies involving small interfering RNAs (siRNAs) target specific oncogenic lncRNAs and show promising anticancer effects. For example, Liu *et al* showed that HOTAIR knockdown inhibits the metastasis of gastric cancer cells both *in vitro* and *in vivo*. They also suggested that therapies targeting HOTAIR lead to improvement for gastric cancer treatment (47). The ectopic overexpression of tumor-suppressive lncRNAs may

also have anticancer effects. For instance, GAS5 transfected hepatocellular carcinoma cells exhibit decreased migration and invasion, indicating the potential of GAS5 as a target for hepatocellular carcinoma therapy (94). Another strategy is to interfere with the functional molecules that interact with DSC-related lncRNAs. PRKA A-kinase anchor protein 9 (AKAP-9) is a target of MALAT1 and highly expressed in human primary colorectal cancer tissues with lymph node metastasis. The knockdown of AKAP-9 inhibits MALAT1-mediated *in vivo* cell proliferation, migration and invasion, which may become a potential therapy for colorectal cancer (60). The development of multidrug resistance (MDR) is a major reason for therapy failure in cancer, leading to recurrence and metastasis. Recent studies revealed that lncRNAs play an important role in MDR for DSCs. For example, the cisplatin-resistant gastric cancer cells transfected with PVT-1 siRNA and treated with cisplatin exhibit significant higher apoptosis and lower survival rate, suggesting that PVT1 may be an effective target for reversing MDR in gastric cancer therapy (141). Similarly, the lncRNAs MRUL and HOTTIP also represent potential targets to reverse the MDR phenotype in DSC (142,143). In addition, the intra-arterially administered DTA-H19 plasmid (also known as BC-819), carrying the diphtheria toxin A-chain gene under the regulation of the H19 promoter sequence, significantly repress the tumor growth of the rat liver metastases from colon cancer (144). The combined treatment of BC-819 and gemcitabine show desirable antitumor activity in animal models with pancreatic carcinoma (145), suggesting a promising therapeutic value to be further evaluated in clinical trial (146). Despite the emerging studies, the research is still in its infancy for the therapeutic role of lncRNAs. Further studies and large clinical trials need to be conducted to investigate the clinical therapeutic interventions of lncRNAs in DSCs.

4. Conclusion

Accumulating evidence suggests that lncRNAs function as oncogenes or tumor suppressors in DSCs. A group of lncRNAs including H19, HOTAIR, MALAT1, HULC, MEG3, GAS5, ANRIL, PVT1, CCAT1, and lncRNA-ATB generally share consistent functions in different types of DSCs. The dysregulated expression of these lncRNAs affects tumor development, progression, and metastasis in DSCs. Moreover, lncRNAs exhibit clinical significance in serving as potential diagnostic and prognostic biomarkers and therapeutic targets in DSCs.

The convenient detection of circulating lncRNAs in blood and body fluids such as gastric juice can reflect the malignancy of cancer, which is valuable in distinguishing DSC patients from benign diseases and healthy individuals with the advantages of non-invasiveness and cost-effectiveness. However, the use of lncRNAs for diagnosis still has several issues of concern. First, the concentration of measured circulating lncRNAs may not represent the actual amount in the diagnosed patients. The stability of circulating lncRNAs, which may result in unreliable diagnostic accuracy, needs further validation. Second, as one certain lncRNA can be involved in various types of DSCs, the diagnostic specificity and sensitivity need to be explored and improved. One feasible solution is combined diagnosis. The combined diagnosis of

different lncRNAs, or with other biomarkers such as traditional biomarkers and circulating miRNAs, may increase the diagnostic accuracy. Third, the cohort size presented in current studies is generally too small for the validation steps. Therefore, prospective studies with large cohort size should investigate the practicability of using circulating lncRNAs, as well as combination with miRNAs or other molecules, as diagnostic biomarkers for DSCs.

The study of lncRNAs as therapeutic targets is still in its early stage and has not reached the clinical practice for DSCs. Several challenges are hindering the development of lncRNA-oriented therapeutics. First, the large size of lncRNAs frequently generates secondary structures, which makes it difficult for the design of siRNAs. Besides, the obstacles for RNA therapies such as side effects and lack of delivery methods and appropriate vectors also impede the clinical use of lncRNAs (147). Moreover, most lncRNAs are not conserved evolutionarily, which makes animal models unavailable prior to clinical applications. Ultimately, the role of DSC-related lncRNAs in interacting with other molecules, including DNA, RNA, and proteins remains not completely understood. Identifying the pivotal role of lncRNAs in DSCs and elucidating their mechanisms will help to block malignant signaling and to specifically eliminate DSC cells.

Therefore, great efforts should be continuously made to further elucidate the lncRNA-based regulatory network in DSCs. Large scaled clinical trials are required to select candidate lncRNAs as novel biomarkers with sufficient sensitivity and specificity, as well as to evaluate the effect of combined diagnosis along with other biomarkers. Further studies focusing on improving the therapeutic effect while minimizing the side effect of lncRNA-based therapy should also be conducted. Thus, better understanding of the functional roles of lncRNAs in DSCs would provide new strategies for the early diagnosis and targeted therapy of DSCs.

Acknowledgements

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