

Metastasis-associated long noncoding RNAs in gastrointestinal cancer: Implications for novel biomarkers and therapeutic targets

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Abstract

Long non-coding RNAs (lncRNAs), a newly discovered class of ncRNA molecules, have been widely accepted as crucial regulators of various diseases including cancer. Increasing numbers of studies have demonstrated that lncRNAs are involved in diverse physiological and pathophysiological processes, such as cell cycle progression, chromatin remodeling, gene transcription, and posttranscriptional processing. Aberrant expression of lncRNAs frequently occurs in gastrointestinal cancer and plays emerging roles in cancer metastasis. In this review, we focus on and outline the regulatory functions of recently identified metastasis-associated lncRNAs, and evaluate the potential roles of lncRNAs as novel diagnostic biomarkers and therapeutic targets in gastrointestinal cancer.

Key words: Gastrointestinal cancer; Tumor metastasis; Long noncoding RNAs; Epithelial-to-mesenchymal transition; MicroRNAs

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Core tip: Long non-coding RNAs (lncRNAs), a newly discovered class of non-coding RNA molecules, have been widely identified as crucial regulators of various

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INTRODUCTION

Gastrointestinal cancers (GCs) are among the most lethal cancers worldwide. In 2012, there were estimated more than 2.8 million new cases and 1 817 200 deaths worldwide^[1]. Although multimodal therapeutic regimens have been applied, survival from gastrointestinal cancers remains in a narrow range of 25% to 30% in most countries^[2]. One reason for this poor survival rate is distant metastasis before diagnosis. Metastasis is one of the most significant features of cancer and frequently occurs in multiple sequential steps. Thus, a detailed understanding of the precise molecular mechanisms underlying GC metastasis is urgently required.

Recent studies have found that protein-coding genes and non-protein-coding genes are abundantly transcribed in the human genome, especially ncRNAs, which account for more than 70% of the human genome^[3-5]. A large number of transcripts are ncRNAs, including miRNAs (miRNAs) and lncRNAs, as well as several other types of RNAs. MiRNAs are mostly known ncRNAs, with molecules of around 22 nucleotides in length that regulate target gene expression at the post-transcriptional level^[6]. lncRNAs are roughly defined as molecules greater than 200 nucleotides in length that are devoid of evident open reading frames^[5]. With the development of high-throughput sequencing, increasing numbers of lncRNAs are being revealed and extensively investigated. It is now recognized that lncRNA alterations are highly tumor- and lineage-specific and regulate various stages of cancer, including chromatin remodeling, gene transcription, and post-transcriptional modifications^[7-10]. Over the past decades, multiple studies have demonstrated that lncRNAs are aberrantly expressed in GCs and are associated with tumor metastasis. In this article, we summarize the molecular mechanisms of lncRNAs identified in GCs, especially those that are significantly associated with tumor metastasis, and discuss the potential role of lncRNAs as novel diagnostic

biomarkers and therapeutic targets.

OVERVIEW OF lncRNAs

lncRNAs can be generated at any region of the genome by RNA polymerase II/III, and most of them are polyadenylated and located within nuclear or cytosolic fractions^[3]. Interestingly, lncRNAs can undergo alternative splicing similarly to protein coding RNAs, and develop secondary and even tertiary structures to form specific functional domains. These domains provide greater potential for interaction with DNA, RNA or proteins^[11,12]. The detailed classification of lncRNAs can be complex. According to the genome position with their neighboring protein-coding genes, lncRNAs can be divided into sense, antisense, intronic, intergenic, and divergent lncRNAs (Figure 1). Sense lncRNAs are transcribed from the same strand as protein-coding genes, while antisense lncRNAs are generated from antisense strands. Both can overlap with exonic or intronic regions, or cover entire protein-coding regions. Intronic lncRNAs are entirely generated from introns of protein-coding genes, while intergenic lncRNAs are transcribed from the regions between two protein-coding genes. Divergent lncRNAs are located on the opposite strands of the protein-coding genes, the transcription of which starts within 1000 base pairs. Compared with protein-coding genes, lncRNAs are lower in abundance and poorer in interspecies sequence conservation, and frequently occur in the nucleus^[13]. lncRNAs can be located in the nucleus or cytoplasm, and different biological functions are implicated depending on their subcellular localization (Figure 2).

NUCLEAR lncRNAs

Multiple lines of evidence have indicated that nuclear lncRNAs function by guiding chromatin modifiers to their specific genomic loci^[10]. Genomic DNA is surrounded by histone proteins and packaged into an advanced structure termed chromatin. Histones can be modified in various ways, and as a result can influence the potential DNA functional state. Recent studies have demonstrated that most nuclear lncRNAs function through interacting with and modulating the activity of chromatin regulatory complexes, thereby guiding them to their specific genomic loci^[8,10]. For example, they can recruit protein complexes from the Trithorax group (TrxG) or Polycomb group (PcG), and guide these protein complexes to specific sites for action^[14,15]. Generally, TrxG proteins are essential for active gene expression, while PcG proteins function by repressing expression^[16,17]. Transcriptional activation may be promoted by lncRNAs *via* recruitment of chromatin regulatory complexes such as histone H3K4 methyltransferase, which is frequently located at the promoter regions of the transcribed genes. Furthermore, the common

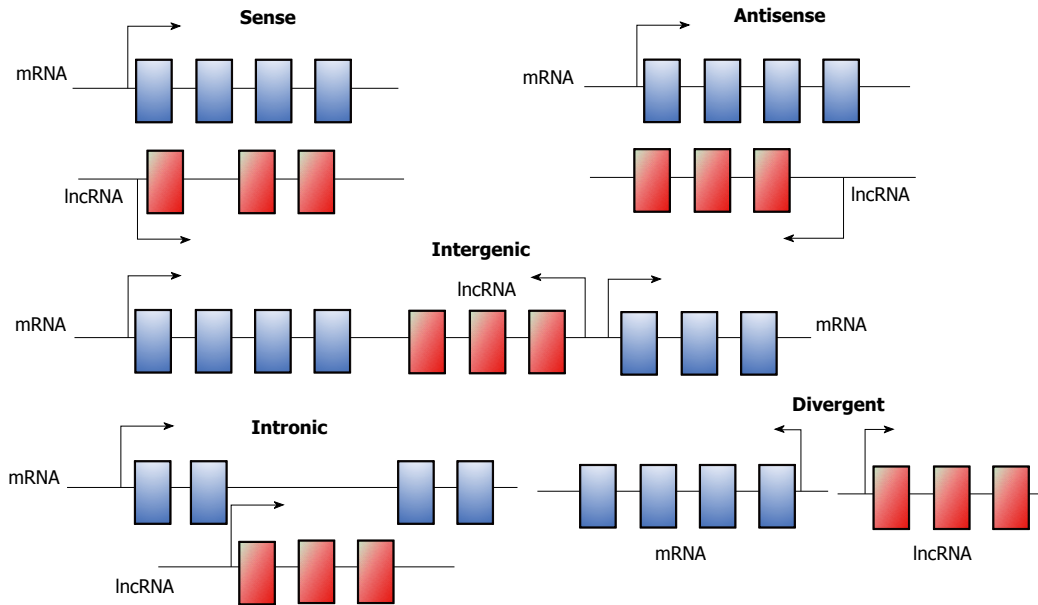


Figure 1 Five brief categories of long noncoding RNAs based on the genome position. lncRNAs: Long noncoding RNAs.

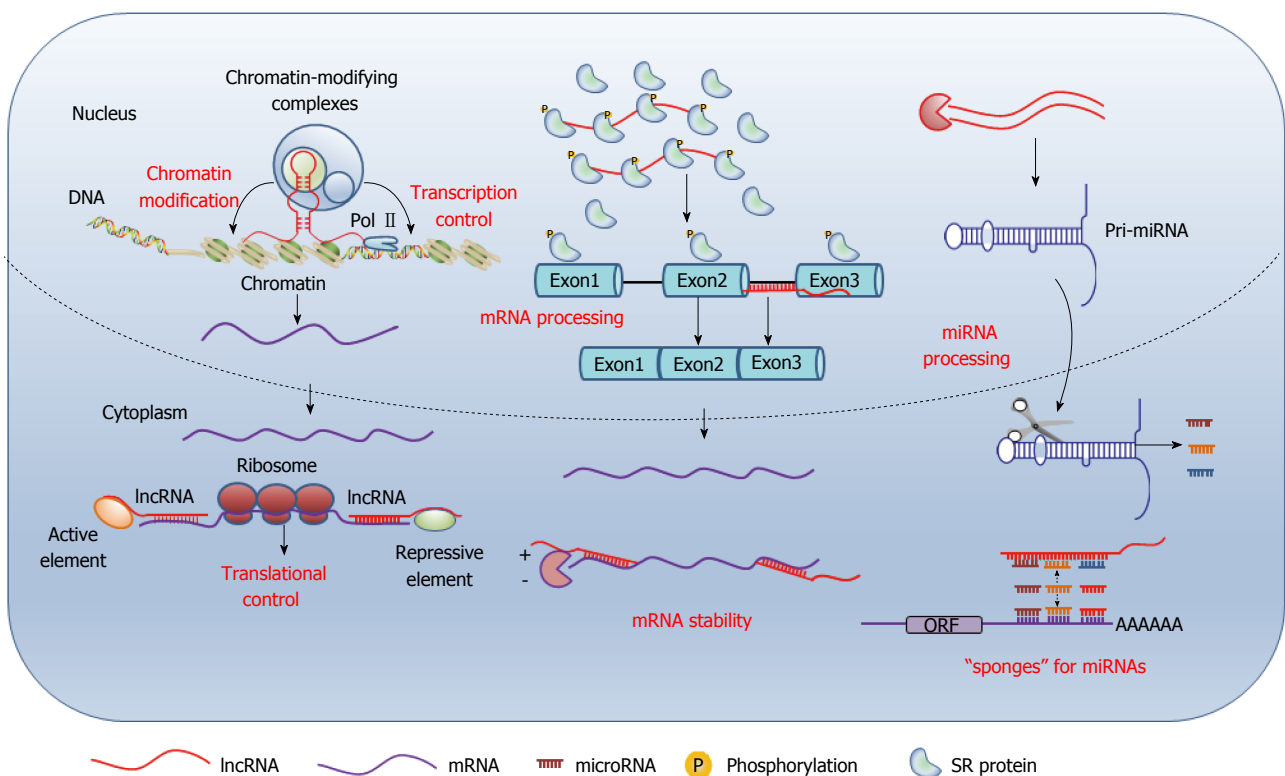


Figure 2 Mechanisms of long noncoding RNAs according to the subcellular localization. lncRNAs in nucleus frequently interact with protein complexes (such as PRC2) to modify chromatin structures. lncRNAs can also recruit transcription factors to promote or repress gene transcription, through regulating SR proteins, or form RNA-RNA duplexes with pre-mRNAs. Some lncRNAs (such as H19) are spliced into pri-miRNAs, which contributed to miRNA processing. In cytoplasm, lncRNAs may form specific structures with mRNA and interact with some active elements or repressive elements to modulate mRNA translation. By forming RNA-RNA complementary sites with mRNA or microRNA, lncRNAs can promote or inhibit mRNA stability and serve as "sponges" for miRNAs. lncRNAs: Long noncoding RNAs; PRC2: Polycomb repressive complex2.

marks of silenced heterochromatin contain di- and trimethylated H3K9, trimethylated H3K27 and Polycomb Repressive Complex 2 (PRC2). PRC2 is composed of four core components including Enhancer of zeste, Suppressor of zeste 12 homolog, Embryonic ectoderm

development and RbAp46/48^[18,19]. As lncRNAs are frequently located in the nucleus, their molecular functions can be divided into three main categories: modification of chromatin structures, transcriptional control, and mRNA/miRNA processing. For example,

the X-inactive specific transcript (*Xist*) gene was the first lncRNA identified to be directly involved in the formation of repressive chromatin domains, which is necessary for reducing X-chromosome gene expression in female genomes^[20]. *Xist* is expressed in the X chromosome targeted for inactivation (Xi), and produces multiple transcripts to “coat” Xi^[21]. As lncRNAs can develop secondary or even tertiary structures, they are proposed to be molecular scaffolds through combinations of regulatory proteins. During X inactivation, one of the steps in initiating the process is the recruitment of PRC2 *in cis* by RepA RNA, which originates from the 5′ end of *Xist*^[22]. Furthermore, the transcriptional repressor Yin Yang 1 (YY1) may be involved in the interaction between the *Xist* and chromatin, because its deletion leads to a loss of *Xist* loading on Xi^[23]. Recent studies have revealed that YY1 can facilitate the loading of PRC2 to DNA and initiate DNA methylation and chromatin silencing, these findings suggest that YY1 is the docking factor for the *cis*-acting nature of *Xist*^[22,23]. Due to the development of RNA technology, increasing numbers of lncRNAs are being discovered, and are verified to be associated with modification of chromatin. HOX transcript antisense intergenic RNA (HOTAIR) is another classical case. HOTAIR is a 2.2 kb lncRNA expressed in the HOXC locus, which cooperates with PRC2 to repress transcription of *HOX* genes^[24]. Tsai *et al.*^[25] demonstrated that besides the 5′ domain of HOTAIR binding to PRC2, the 3′ domain binds to LSD1, resulting in H3K27me3 and H3K4me2 methylation, which in turn leads to HOXD silencing^[25,26].

Nuclear lncRNAs also play important roles in transcriptional control. Some lncRNAs can form RNA-protein complexes with transcription factors and modulate gene transcription. For example, the lncRNA heat shock RNA 1 interacts with heat-shock transcription factor 1 to form a protein complex that induces expression of heat-shock proteins during cellular heat-shock stress^[27]. As well as roles in positive regulation, lncRNAs can function as transcription co-repressors. Those transcribed from the Cyclin D1 (CCND1) promoter region are reported to change the RNA-binding protein translocated in liposarcoma (TLS) from an inactive to an active conformation. This causes TLS to bind to and inhibit the enzymatic activities of CBP and p300, which in turn leads to the silencing of CCND^[28].

Interestingly, lncRNAs are not only involved in gene transcription but also in mRNA/miRNA processing. For example, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a cancer-related lncRNA, whose expression is deregulated in many cancers including GCs^[29,30]. MALAT1 regulates the phosphorylation of the serine/arginine-rich (SR) family of nuclear phosphoproteins (SR proteins) and influences the distribution of splicing factors in nuclear speckle domains^[31]. In addition, lncRNA FGFR2

impairs binding of a repressive chromatin-splicing adaptor complex *via* recruitment of PRC2 and KDM2a, leading to the epithelial-specific alternative splicing of FGFR2^[32]. In some cases, lncRNAs are located antisense to their known protein-coding genes. These lncRNAs are also called natural antisense transcripts (NATs). Recent studies indicated that NATs are associated with mRNA processing. For instance, they influence the splicing patterns of mRNAs at v-myc avian myelocytomatosis viral oncogene homolog (MYC)^[33], tyrosine kinase containing immunoglobulin and epidermal growth factor homology domain-1 (Tie-1)^[34], and zinc-finger E-box binding homeobox 2 (ZEB2)^[35]. In these cases, lncRNAs form RNA-RNA duplexes with pre-mRNAs and inhibit splicing. Processing of miRNAs can also be affected by lncRNAs. For example, lncRNA H19 can be spliced into pri-miRNA of miR-675, and miR-675 is derived from nucleotides 1014-1036 of human H19 RNA^[36].

CYTOPLASMIC lncRNAs

Many lncRNAs are located in the cytoplasm, and these lncRNAs often regulate gene expression through sequence complementarity with target genes by base pairing. In the cytoplasm, lncRNAs are responsible for modulating translational control, promoting or inhibiting mRNA stability and serving as molecular “sponges” for miRNAs. For example, ubiquitin carboxy-terminal hydrolase L1 antisense RNA 1 (Uchl1-AS1) lncRNA is produced from the Uchl1 (ubiquitin carboxy-terminal hydrolase L1) locus. The mature lncRNA contains a 73-nucleotide complementary site with the 5′ end of the Uchl1 mRNA, which serves to upregulate translation of Uchl1 mRNA^[37]. By contrast, tumor protein p53 pathway corepressor 1 (Trp53cor1, also known as lincRNA-p21) lncRNA negatively regulates gene translation in human cervical carcinoma^[38]. Similarly, lncRNAs can modulate mRNA stability positively or negatively. The lncRNA-activated by TGF-β (lncRNA-ATB) is upregulated in hepatocellular carcinoma (HCC). It binds IL-11 mRNA and triggers STAT3 signaling, promoting the colonization of organs by disseminated tumor cells^[39]. By contrast, Alu repeat-containing lncRNAs are associated with targeting mRNA transcripts for Staufen-mediated decay, and destabilizing the target mRNA^[40]. Aside from binding to mRNA, lncRNAs can act as decoys to attenuate miRNA regulation. For example, HOTAIR functions as a competing endogenous RNA by “sponging” miR-331-3p, thereby modulating the derepression of human epidermal growth factor receptor 2 (HER2) and promoting GC progression^[41]. Furthermore, another study demonstrated that HOTAIR is involved in the upregulation of human leukocyte antigen (HLA-G) through inhibition of miR-152 in GC^[42]. As increasing numbers of lncRNAs are being identified, we believe that new perspectives on the mechanisms of lncRNA

function will come to light in the near future.

ABERRANT EXPRESSION OF lncRNAs IN GASTROINTESTINAL CANCER

The development of GC is a complex process, although several serum tumor markers such as carcinoembryonic antigen (CEA) and CA19.9 are recommended for clinical applications, their low sensitivity and specificity remain a severe challenge for clinicians. Recent observations demonstrate that lncRNAs are aberrantly expressed in GCs, and have roles in tumorigenesis. Among the most prominent deregulated lncRNAs in gastrointestinal cancer are HOTAIR, MALAT1, and H19, which are upregulated in various cancers and are involved in migration, invasion, metastasis, dissemination and are associated with a more advanced tumor, node, metastasis (TNM) stage. For example, high HOTAIR expression in cancerous tissues closely correlates with poor prognosis in GC^[43-45]. Surprisingly, for colorectal cancer (CRC) patients, plasma levels of HOTAIR were significantly higher than those in healthy controls, and high levels of HOTAIR were associated with an unfavorable prognosis. This indicated that the HOTAIR plasma level could act as a new biomarker for CRC patients^[46]. In GC, circulating H19 in plasma was also higher than in healthy controls, and after surgery, circulating H19 was reduced^[47]. In GC tissues, lncRNA AA174084 expression was found to be downregulated compared to expression in the paired normal tissues, although the AA174084 plasma level was positively associated with invasion and metastasis. Plasma levels of AA174084 dropped after surgical treatment, and A174084 levels in gastric juice were significantly higher in GC patients. These observations provide evidence that A174084 could be a potential biomarker for early diagnosis in GC^[48]. Resveratrol, a monomer extracted from a Chinese herbal medicine *Polygonum cuspidatum*, is known to inhibit metastasis of CRC. Studies have shown that Resveratrol exerts anti-tumor effects *via* MALAT1-mediated Wnt/ β -Catenin signaling; co-repression of MALAT1 led to the enhancement of Resveratrol-induced anti-cancer effects^[49]. These emerging studies elegantly indicate that lncRNAs could be promising future diagnostic markers or therapeutic targets, and that combining lncRNA-based strategies with existing methods would improve the accuracy of diagnosis and efficacy of treatments in a clinical setting. Increasing evidence demonstrates that lncRNA expression levels correlate with GC. A summary of aberrantly expressed lncRNAs, their gene locus, product size, expression status, and biological function are shown in Table 1^[41-46,48-90].

lncRNAs ARE ASSOCIATED WITH CANCER-RELATED PATHWAYS

Cancer-related pathways play essential roles in

cancer metastasis. For example, miR-29b can inactivate the MAPK/ERK and PI3K/AKT pathways *via* dephosphorylation of ERK1/2 and AKT in CRC, which leads to repression of metastatic capacity in cancer cells^[91]. Pathway regulation is mediated not only by miRNAs, but also by lncRNAs. PVT-1 is located at 8q24, whose copy number is amplified in CRC. As observed using gene expression microarray analysis, the TGF- β signaling pathway is upregulated by PVT-1 knockdown^[65]. MALAT1 was first identified in lung cancer, and is an indicator of probability of survival and metastasis in early-stage non-small cell lung cancer^[92]. However, it also plays oncogenic roles in other cancers. MALAT1 was demonstrated to be an independent prognostic parameter in gallbladder carcinoma (GBC); its downregulation reduced phosphorylated MEK1/2, ERK 1/2, MAPK, and JNK 1/2/3, and inactivation of the ERK/MAPK pathway led to the partial impairment of proliferation and metastasis^[76].

Wnt/ β -catenin signaling is a classical pathway in cancer, and frequently correlates with cancer metastasis. During Wnt/ β -catenin signaling activation, β -catenin often translocates to the nucleus from the cytoplasm, and cooperates with transcription factors such as TCF/LEF to induce downstream target genes such as *c-Myc*, *MMP-7*, and *CD44*. In CRC, MALAT1 was found to increase the nuclear localization of β -catenin, activating Wnt/ β -catenin signaling to enhance expression of *c-Myc* and *MMP-7*, which are involved in CRC cell metastasis^[49]. HOTAIR cooperates with the PRC2 complex, leading to H3K27me3 and H3K4me2 methylation and HOXD gene silencing^[25,26]. In esophageal squamous cell carcinoma (ESCC), HOTAIR is significantly upregulated, and has been shown to promote migration and invasion of ESCC cells *in vitro*^[43]. Gene microarray analysis indicated that the expression of WNT/ β -catenin associated gene WIF-1 changed most significantly in HOTAIR overexpressing cells. A further study showed that HOTAIR promoted H3K27 methylation in the promoter region of WIF-1 and inhibited WIF-1 expression, and that the low expression of WIF-1 triggered Wnt/ β -catenin signaling, thereby promoting ESCC invasion and migration.

lncRNAs PARTICIPATE IN EPITHELIAL-TO-MESENCHYMAL TRANSITION

The epithelial-mesenchymal transition (EMT) is a biological process in which polarized epithelial cells acquire a mesenchymal cell phenotype. It is a process known to enhance cancer cell metastasis, invasiveness, and chemoresistance. Recent studies have verified that noncoding RNAs are frequently involved in the EMT process, especially miRNAs. For example, miR-187, as a downstream target of TGF- β , inhibits EMT by suppressing the expression of multiple targets in CRC^[93]. The maturation of high throughput genomic tools, such as high-resolution microarray and

Table 1 Aberrant expression of lncRNAs and their gene locus, product size, expression status and biological function

lncRNAs	Cancer type	Gene locus	Size	Expression	Correlation with metastasis	Biological function
91H	CRC	11p15.5 (H19/IGF2 locus)	119392nt	Up	Positive	Migration and invasiveness ^[50]
AK123657	CRC	NA	2126 nt	Down	Negative	Inhibit cell invasion, and serve as promising biomarkers for prognosis ^[51]
BX649059			3967 nt	Down	Negative	
BX648207			5032 nt	Down	Negative	
CCAT1	CRC	8q24.21	2628 nt	Up	Positive	Up-regulated across the colonadenoma-carcinoma sequence and activated by C-myc to promote metastatic process ^[52,53]
CCAT2	CRC	8q24.21	1752 nt	Up	Positive	Interacts with TCF7L2 which leads to genomic instability, cell invasion and forms a feedback loop with WNT signaling ^[54]
FER1L4	CRC	20q11.22	6717 nt	Down	Negative	Suppresses oncogenesis <i>via</i> inhibiting miR-106a-5p ^[55]
HOTAIR	CRC	12q13.13	2370 nt	Up	Positive	Interacts with PRC2 complex and participates in EMT ^[45,56] ; the blood levels of HOTAIR also serves as a negative prognostic factor ^[46]
LOC285194	CRC	3q13.31	2105 nt	Down	NA	Novel biomarker of cancer metastasis ^[57]
MALAT1	CRC	11q13.1	8758 nt	Up	Positive	3' end of MALAT-1 (6918 nt-8441 nt) promotes migration and invasion and AKAP-5 is a downstream target protein ^[58,59] ; Mediates Wnt/ β -catenin signalling ^[49] ; Upregulated by tumor-associated dendritic cells expressed CCL5 and enhances Snail to promote migration, invasion and EMT ^[60]
MEG3	CRC	14q32	1595 nt	Down	NA	Potential marker for prognosis ^[61]
ncRAN	CRC	17q25.1	2538 nt	Up	Positive	Promotes migration and invasion ^[62]
ncRuPAR	CRC	5q13.3	486 nt	Down	NA	Potential biomarker ^[63]
NEAT1	CRC	11q13.1	3756 nt	Up	NA	Indicator of tumor differentiation, invasion and metastasis ^[64]
PVT-1	CRC	8q24	1957 nt	Up	NA	Antiaoptotic activity ^[65]
TUG1	CRC	22q12.2	7598 nt	Up	Positive	Activates EMT and promotes migration, invasion ^[66]
91H	ESCC	11p15.5	119,392kb	Down	Negative	Inhibits IGF2 expression and regulates tumor development ^[67]
AFAP1-AS1	ESCC	(H19/IGF2 locus) 4p16.1 (AFAP1 locus)	6810 nt	Down	Positive	Hypomethylated and overexpressed in ESCC, promotes migration and invasion in a AFAP1 independent manner ^[68]
CCAT2	ESCC	8q24.21	1752 nt	Up	Negative	Potential prognostic biomarker and therapeutic target ^[69]
H19	ESCC	11p15.5	2362 nt	Up	Positive	H19 CBS6 hypermethylation leads to IGF2 overexpression and cancer progression ^[70]
HNF1A-AS1	ESCC	(IGF2 locus) 12q24.31	2455 nt	Up	Positive	Upregulated in primary ESCC , affects assembly of chromatin and the nucleosome process by H19 induction ^[71]
HOTAIR	ESCC	(HNF1A locus) 12q13.13	2370 nt	Up	Positive	Medicates migratory capacity ^[44,72,73] ; promotes histone H3K27 methylation and activates Wnt/ β -catenin signaling and decreases WIF-1, lead to metastasis ^[43]
MALAT1	ESCC	11q13.1	> 8 kb	Up	Positive	Target of miR-101 and miR-217 and promotes migration, invasion and metastasis ^[74]
MALAT1	GBC	11q13.1	8758 nt	Up	Positive	Binds to SFPQ, leading to PTBP2 release from SFPQ/PTBP2 complex ^[75] ; Activates the ERK/MAPK pathway and promotes metastasis ^[76]
AA174084	GC	13q33.1	601 nt	Up	NA	The expression level in gastric juice is a potential marker for the early diagnosis of GC ^[48]
AC130710	GC	2p24.3	984 nt	Up	NA	As a target of miR-129-5p and may be a potential biomarker for GC prognosis ^[77]
AK058003	GC	10q22	1197 nt	Up	NA	Induced by hypoxia and regulates SNCG to promote metastasis ^[78]
BM742401	GC	18q11.2	1788 nt	Down	Negative	Decreases expression of MMP9 and inhibits metastasis-related phenotypes ^[79]
FENDRR	GC	3q13.31	3099 nt	Down	Negative	Downregulates FN1 and MMP2/MMP9 to suppress invasion and migration ^[80]
GAPLINC	GC	18p11.31	924 nt	Up	Positive	Competes to bind with miR-211-3p, which leads to the increased translation of CD44 and promotes proliferation, migration, and angiogenesis ^[81]
H19	GC	11p15.5	2362 nt	Up	Positive	Target of c-Myc and promotes migration, invasion and metastasis by the direct upregulation of ISM1 and indirect suppression of CALN1 <i>via</i> miR-675 ^[82,83]
HOTAIR	GC	(IGF2 locus) 12q13.13	2370 nt	Up	Positive	Novel biomarker for prognosis and promotes metastasis <i>via</i> PCBP1 inhibition ^[61,84-87] ; as a ceRNA of miR-331-3p and modulates the derepression of HER2 ^[41] ; Upregulates HLA-G <i>via</i> inhibiting miR-152 ^[42] ; binds to PRC2 complex and epigenetically represses miR34a, which inhibits HGF/Met/Snail pathway and Snail, leads to EMT and metastasis ^[55]
HULC	GC	6p24.3	About 1.6 kb	Up	Positive	Promotes EMT ^[88]

LEIGC	GC	2q14.1	2659 nt	Down	Negative	Inhibits EMT ^[89]
OR3A4	GC	17p13.3	1202 nt	Up	Positive	Promotes migration, invasion, tubule formation, vasculogenic mimicry, angiogenesis by regulating PDLIM2, MACC1, NTN4, and GNB2L1 ^[90]

CRC: Colorectal cancer; GBC: Gallbladder carcinoma; GC: Gastric cancer; ESCC: Esophageal squamous cell carcinoma; NA: Data not available.

massively parallel sequencing technology, has led to the discovery of an extensive range of lncRNAs. There is a growing understanding that lncRNAs and their associated signaling networks may participate in the induction and regulation of EMT to modulate cancer metastasis^[94]. Esophagus epithelial intergenic specific transcript (Epist) acts as a tumor suppressor by inhibiting EMT^[95], and TGF- β stimulation significantly suppresses the expression of Epist. These findings reveal a new plausible mechanism by which TGF- β -induced EMT could take place.

Taurine upregulated gene 1 (TUG1) was originally reported as a transcript that is upregulated by taurine, and it was also observed to be up-regulated in CRC^[66]. TUG1 overexpression was shown to enhance the migration and invasion capacity of CRC cells significantly. A decrease in the epithelial hallmark E-cadherin combined with an increase in the mesenchymal markers N-cadherin, vimentin, and fibronectin, indicated that TUG1 promoted CRC metastasis by mediating EMT. Another two studies suggested that HOTAIR^[56] and highly upregulated in liver cancer (HULC)^[88] promoted metastasis of CRC by participating in EMT, although the underlying mechanisms require further investigation. In GC, microarray and quantitative real-time PCR identified a new, specific, differentially expressed lncRNA termed LEIGC^[89]. LEIGC is a 2659 nt transcript located at 2q14.1, and contains two exons. Intriguingly, LEIGC knockdown in MGC803 cells induced them to assume a spindle-shaped morphology, whereas LEIGC-overexpression induced a cobblestone-like phenotype, suggesting that LEIGC may be involved in EMT. Further investigation revealed that LEIGC knockdown reduced E-cadherin expression while increasing expression of vimentin, Snail, Slug, Zeb, and Twist. These data indicated that LEIGC may be a potential EMT inhibitor in GC.

Mounting evidence suggests that tumor-associated dendritic cells and the tumor microenvironment are critical factors for cancer metastasis. Many inflammatory factors such as chemokines and cytokines have been implicated as being strongly associated with EMT and metastasis. Increasing numbers of studies support the hypothesis that tumor-associated dendritic cells (TADCs) influence the inflammatory cancer microenvironment and contribute to an aggressive cancer phenotype. Kan *et al.*^[60] found that TADCs secreted high levels of Chemokine (C-C motif) ligand 5 (CCL5), and that CCL5 stimulation upregulated MALAT1 expression in CRC cells. This in turn led to an increase in Snail expression, resulting in enhanced EMT and cancer progression.

HOTAIR is known to play important roles in epigenetic regulation^[24-26]. In GC tissue, HOTAIR expression was shown to correlate negatively with E-cadherin expression^[96]. Western blot assays confirmed that HOTAIR could promote EMT. Bioinformatics analysis showed that miR-34a, which is known to be involved in the C-Met (HGF/C-Met/Snail pathway) and Snail pathway and to repress EMT, was a downstream microRNA of HOTAIR. RNA immunoprecipitation (RIP) assays indicated that HOTAIR could recruit and bind to the PRC2 complex and repress miR-34a epigenetically in GC. This research provided a new insight into the RNA regulatory network, and supported the hypothesis that chromatin modification not only affects protein levels, but also controls miRNA expression.

MALAT1

MALAT1 is a highly conserved lncRNA that was originally identified and is highly expressed in metastatic non-small-cell lung cancer. Recent studies have demonstrated that MALAT1 is overexpressed in other human malignancies, including CRC, GC, and ESCC, and is associated with tumor metastasis. The underlying mechanism of MALAT1 in promoting metastasis is complex. One fragment (6918 nt-8441 nt) of MALAT1 located at the 3' end of the *MALAT1* gene has biological functions in CRC, providing an excellent example for MALAT1 as an accurate therapeutic target in CRC^[58]. Using genome-wide expression profiling analysis, a novel downstream target, PRKA kinase anchor protein 9 (AKAP-9) was identified, providing a novel insight into the mechanism of MALAT1 involvement in CRC development^[59]. MALAT1 can activate several cancer-related pathways such as the ERK/MAPK pathway^[76] and Wnt/ β -catenin pathway^[49]. MALAT1 can also interact with other proteins, such as splicing factor proline/glutamine rich (SFPQ), leading to the release of polypyrimidine tract binding protein 2 (PTBP2) from the SFPQ/PTBP2 complex^[75]. In addition to proteins, MALAT1 also interacts with RNAs, such as the tumor suppressor miRNAs miR-101 and miR-217, and affects their post-transcriptional regulation^[74]. One study also showed that MALAT1 is regulated by tumor-associated dendritic cells (TADCs)^[60], providing a novel insight into the interaction between TADCs and cancer metastasis, and indicating that targeting MALAT1 is a potential strategy to improve immunotherapeutic efficacy. Taken together, the results of these studies support an oncogenic role for MALAT1 in GC (Figure 3), presenting it as a promising biomarker and therapeutic target for metastatic cancers.

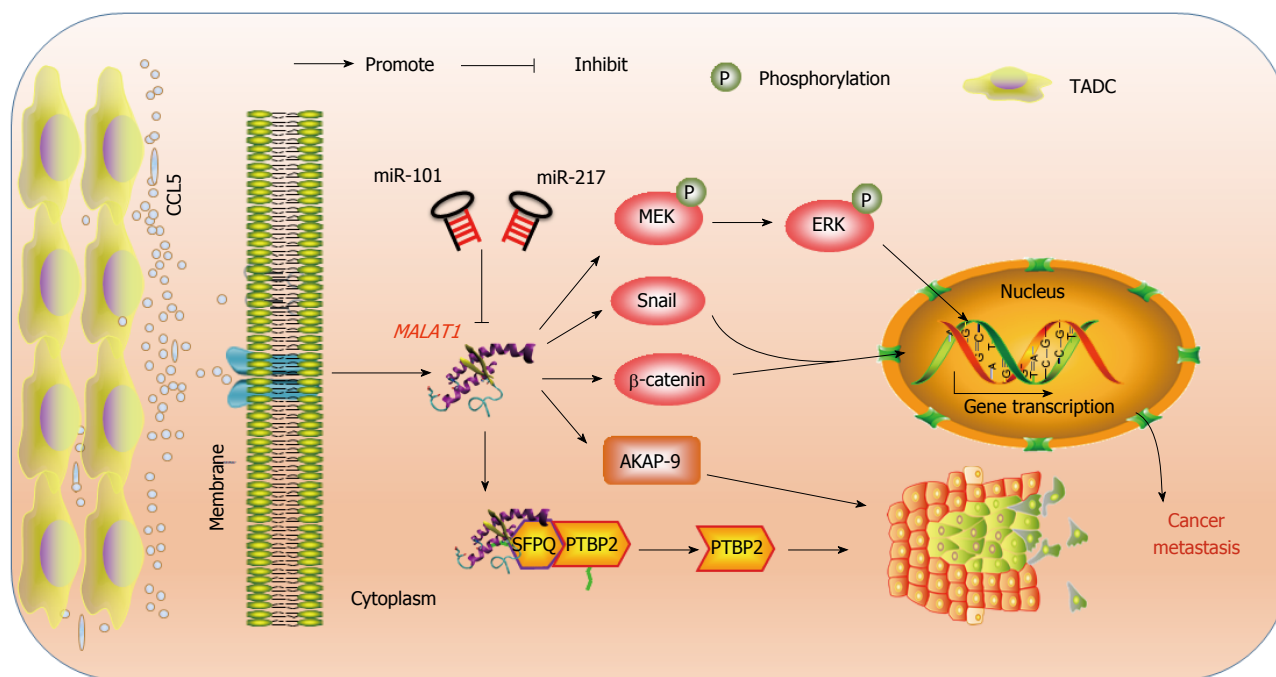


Figure 3 Regulating function of metastasis-associated lung adenocarcinoma transcript 1 in gastrointestinal cancer. CCL5 secreted by tumor-associated dendritic cells (TADCs) can promote MALAT1 expression. MALAT1 activates the ERK/MAPK pathway and Wnt/β-catenin pathway. Snail and AKAP-9 are downstream targets of MALAT1. miR-101 and miR-217 can regulate MALAT1 in 3'UTR region. MALAT1 can also bind to SFPQ/PTBP2 complex and promote the release of PTBP2. MALAT1: Metastasis-associated lung adenocarcinoma transcript 1.

HOTAIR

HOTAIR is a 2.2 kb lncRNA expressed in HOXC locus, which is known to participate in epigenetic regulation in cooperation with the PRC2 complex, leading to H3K27me3 and H3K4me2 methylation and gene silencing^[24]. Overexpression of HOTAIR has been observed in GC^[84,85], ESCC^[72], gastrointestinal stromal tumor^[97] and CRC^[56]. Notably, the level of HOTAIR expression in the blood as well as within the primary tumors was also a reliable biomarker for metastasis in CRC and GC^[46,47]. Although HOTAIR is known to cooperate with the PRC2 complex, it is still not known whether this regulation exists in CRC. A cDNA microarray and gene set enrichment analysis provided evidence for a correlation between HOTAIR and PRC2 complex expression in CRC^[45]. HOTAIR can also modulate HER2 and HLA-G expression by competitively binding to their miRNAs, such as miR-331-3p and miR-152^[41,42]. Therefore, HOTAIR could be a promising prognostic biomarker and a therapeutic target for GC (Figure 4).

H19

H19 is localized at 11p15.5, where a highly conserved cluster of imprinted genes is encoded, such as paternally expressed insulin-like growth factor 2 (IGF2) and maternally expressed H19. The oncogenic role of H19 has been found in a number of cancers. A case-control study in the Chinese Han

population revealed that the presence of H19 single nucleotide polymorphisms (SNPs) rs217727C>T and rs2839698C>T significantly correlated with susceptibility to GC^[98]. These findings indicated an important role for H19 variants in gastric carcinogenesis. In ESCC, Gao *et al.*^[70] found that hypermethylation of CBS6 on H19 was related to loss of imprinting (LOI) of IGF2, which indicated overexpression of the gene. Enhanced expression of IGF2 was closely correlated with cancer metastasis, suggesting that H19 CBS6 methylation might be a novel, clinically relevant epigenetic marker for poor prognosis and ESCC metastasis. In GC, H19 was a novel target of c-Myc, in SGC-7901 and in BGC-823 cells. Exogenous c-Myc significantly induced H19 expression to increase by approximately 3-folds compared to controls. However, the underlying molecular mechanisms remain to be fully elucidated^[82]. Investigations showed that H19 is a precursor of miR-675, and that H19 is involved in biological functions that are partly dependent on the activity of miR-675. Li *et al.*^[83] developed a H19/miR-675 knockdown model in the GC cell line MKN45, and found that calneuron 1 (CALN1) was a target of miR-675. H19 suppressed CALN1 by promoting the generation of miR-675. Conversely, H19 also upregulated expression of its binding protein isthmin 1 (ISM1) directly, suggesting that this function of H19 could be independent of miR-675 activity. In addition, recent reports confirmed that eukaryotic translation initiation factor 4A3 (eIF4A3) also binds to H19 in CRC^[99], and that H19 recruits eIF4A3, resulting in

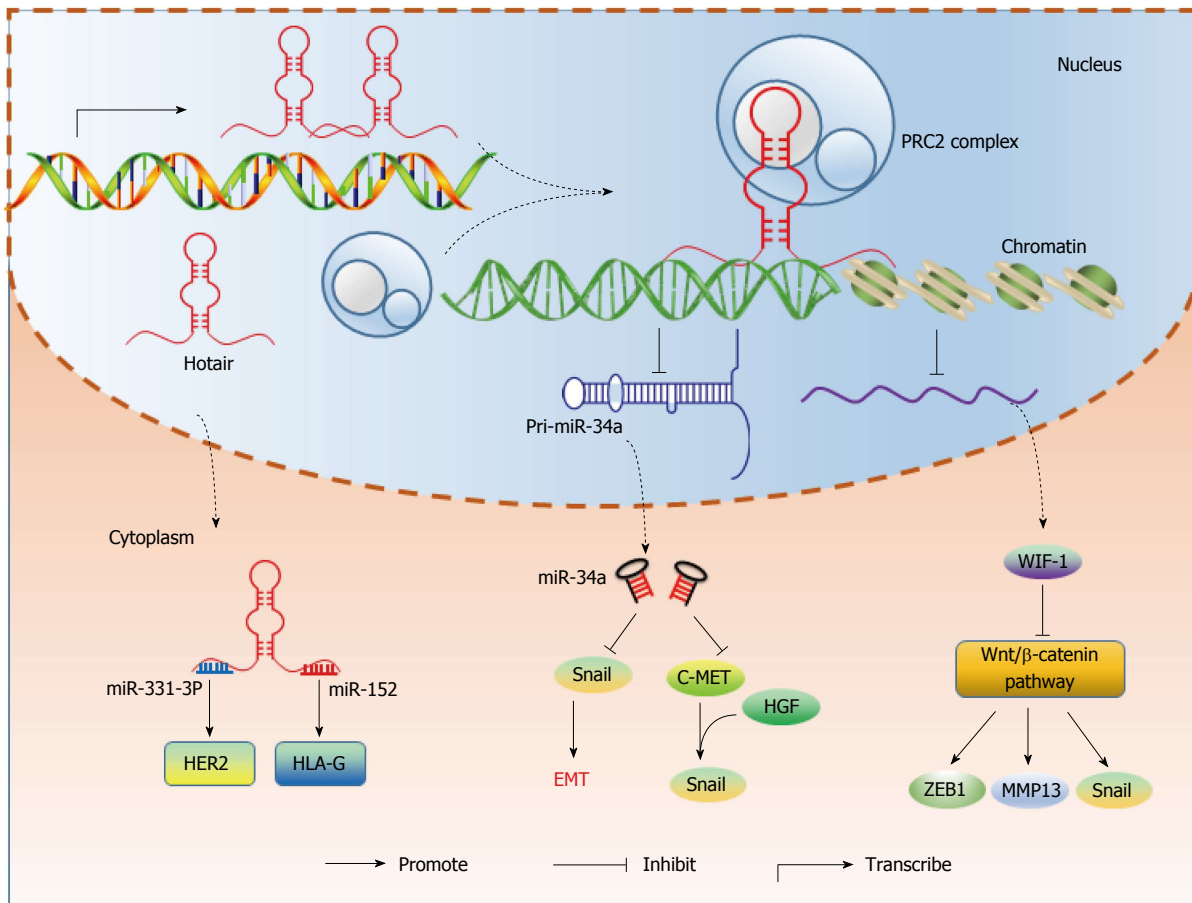


Figure 4 Regulating function of HOTAIR in gastrointestinal cancer. In nucleus, HOTAIR recruits PRC2 complex and represses pri-miR-34a transcription epigenetically. By inducing histone H3K27 methylation in WIF-1's promoter region, HOTAIR decreases WIF-1 expression. In cytoplasm, HOTAIR serves as "sponges" for miR-331-3p and miR-152, leading to the increase of target genes HER2 and HLA-G. PRC2: Polycomb repressive complex2.

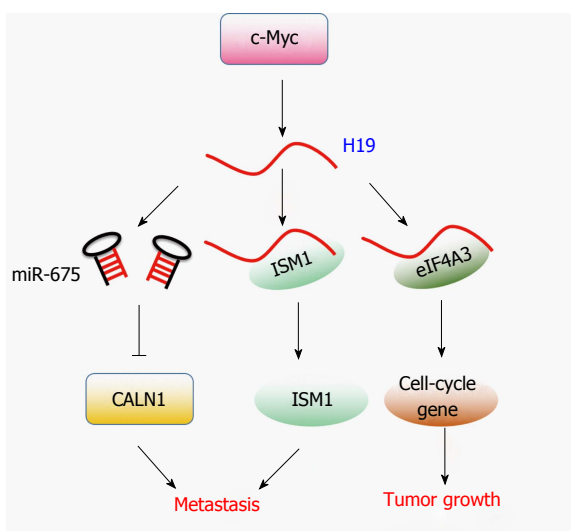


Figure 5 Regulating function of H19 in gastrointestinal cancer. H19 is transcribed by transcription factor c-Myc. H19 can be spliced into pre-miRNA of miR-675, and suppresses miR-675 target gene CALN1. H19 also binds with its binding protein ISM1 or Eif4A3 and promotes metastasis or growth.

obstructing the interaction between eIF4A3 and cell-cycle gene mRNA (Figure 5).

OTHER POTENTIAL METASTASIS-ASSOCIATED lncRNAs

lncRNA 91H is located in the H19/IGF2 locus, and low expression of 91H is associated with imprinting control region methylation of H19^[67], which is known to cause IGF2 overexpression *via* loss of genomic imprinting^[70]. Through the indirect inhibition of IGF-2 in ESCC, 91H inhibits the occurrence, progression, and prognosis of ESCC. Conversely, another study suggested that 91H was overexpressed in CRC tissues as well as cell lines^[50], and might be associated with copy number variation (CNV) in the 11p15.5 region. These findings showed that lncRNAs are highly tumor and lineage specific, and that different regulatory mechanisms might lead to different biological functions in cancer.

A novel specific lncRNA expressed in GC is termed gastric adenocarcinoma predictive long intergenic noncoding RNA (GAPLINC). High expression of GAPLINC indicates severe lymph node invasion and poor prognosis. Ectopic expression of GAPLINC in MGC803 and SGC901 cell lines significantly enhances

their invasive capacity. GAPLINC regulates CD44 mRNA at post-transcriptional level, and miR-221-3p targets both GAPLINC and CD44. GAPLINC increases CD44 expression by competing for miR-221-3p, which contributes to a reduced rate of degradation of CD44 mRNA in cytoplasm^[81].

Olfactory receptor, family 3, subfamily A, member 4 (OR3A4) is a novel lncRNA overexpressed in GC. High OR3A4 expression levels are significantly associated with metastasis. Functional experiments performed in SGC7901 and NCI-N87 indicated that OR3A4 promotes GC cell proliferation, migration, invasion, tubule formation, vasculogenic mimicry, angiogenesis, and tumorigenicity. Four target genes of OR3A4 have been identified: PDLIM2, MACC1, NTN4, and GNB2L1. These results suggest that OR3A4 might play an important role in GC progression^[90].

In order to search lncRNA signatures to predict prognosis of CRC, Hu *et al.*^[51] analyzed lncRNA expression in large CRC cohorts obtained from Gene Expression Omnibus databases. Six of the identified lncRNAs included two genes with enhanced expression in CRC, AK024680, AK026784, and four lower expressed genes with reduced expression, AK123657, CR622106, BX649059, and BX648207. These six genes were significantly correlated (positively or negatively) with disease free survival. Among them, functional experiments demonstrated that three downregulated lncRNAs, AK123657, BX648207 and BX649059, were required for suppressing invasion and proliferation in CRC cell lines. The lncRNAs identified in this study could be potential biomarkers and therapeutic targets for CRC in the future^[80].

MOLECULAR MECHANISMS OF lncRNAs IN GASTROINTESTINAL CANCER

Previously, we have categorized the molecular mechanisms of lncRNAs into modification of chromatin structures, transcriptional control, mRNA/miRNA processing, translational control, mRNA stability control, and roles as molecular “sponges” for miRNAs. However, these mechanisms are not absolutely independent of each other, and one lncRNA may use several processing controls. In this section, we will focus on the molecular mechanisms of metastasis-associated-lncRNAs in GC, and provide insights into interpreting results of previous investigation of lncRNAs.

ROLE OF lncRNAs IN CHROMATIN MODIFICATION

Many lncRNAs are located in the nucleus and form secondary or tertiary structures. They can interact with specific chromatin regulatory complexes and

participate in chromatin modification, leading to DNA methylation and gene control, including expression of miRNAs. HOTAIR is known to cooperate with the PRC2 complex and repress transcription of HOX genes^[24-26]. In ESCC, WIF-1 expression is decreased by HOTAIR^[43]. Mechanistically, HOTAIR promotes histone H3K27 methylation in the promoter region of the WIF-1 gene, and directly decreases WIF-1 expression. In GC, HOTAIR recruits and binds to the PRC2 complex and epigenetically represses miR34a, leading to the enhancement of C-Met (HGF/C-Met/Snail pathway) and Snail activation, and thus contributes to EMT and metastasis^[55]. This work provided a new insight into the RNA regulation network, and demonstrated that chromatin modification not only affects protein levels, but also controls miRNA expression. Another study showed that HNF1A antisense RNA 1 (HNF1A-AS1), a 2455 nt lncRNA located at chromosomal band 12q24.31, is markedly upregulated in esophageal adenocarcinoma (EAC) and that HNF1A-AS1 knockdown significantly inhibits cell proliferation, migration, and invasion. Microarray analysis and GO enrichment analysis revealed that HNF1A-AS1 knockdown affected chromatin/nucleosome assembly by inhibiting lncRNA H19, which contributed to cancer metastasis^[71].

ROLE OF lncRNAs IN TRANSLATIONAL CONTROL

Colon cancer associated transcript 2 (CCAT2), a novel lncRNA encompassing the rs6983267 SNP, is highly overexpressed in microsatellite-stable (MSS) CRC, and promotes cancer growth and metastasis. Genomics analysis showed that the oncogene MYC is located in the same region as CCAT2. CCAT2 regulated MYC expression and affected MYC downstream genes such as miR-17-5p and miR-20a. Transcription factor 7 like 2 (TCF7L2) was confirmed as the promoter of MYC, and physical interaction between CCAT2 and TCF7L2 enhanced TCF7L2 transcriptional activity. This resulted in an increase in MYC and a change in downstream gene expression and pathway activity^[54]. Notably, CCAT2 itself was a downstream target of TCF7L2-mediated WNT signaling, indicating existence of a feedback loop during carcinogenesis.

ROLE OF lncRNAs IN mRNA/miRNA PROCESSING

H19 was reported to be the precursor of miR-675, a regulator of CALN1. H19 promoted metastasis of GC via regulation of the miR-675/CALN1 axis. However, H19 banded to ISM1 and upregulated ISM1 expression directly, which suggested that H19 could also work in an miR-675 independent manner^[83].

ROLE OF lncRNAs AS “SPONGES” FOR miRNAs

lncRNAs and mRNAs may share some of the same response elements of miRNAs. In these cases, lncRNAs may serve as competing endogenous RNAs (ceRNAs) to sponge miRNAs, regulating target gene expression in post-transcriptional regulation. The function of ceRNAs is one of the most commonly investigated mechanisms of lncRNA activity, and completes the post-transcriptional regulatory network.

miR-331-3p and miR-124 directly target HOTAIR, which is reported to play a critical role in GC metastasis. Moreover, miR-331-3p also targets HER2 at the 3'-UTR region, providing compelling evidence that targeting HOTAIR would be a useful therapeutic strategy in GC^[41]. HOTAIR competitively binds to miR-152 and attenuates its expression in GC, leading to the release of HLA-G, which has been identified as a target of miR-152 and is associated with cancer metastasis^[42].

lncRNA AC130710 is overexpressed in GC, and its expression is significantly associated with tumor size, TNM stage, and distal metastasis. Bioinformatics analysis uncovered that AC130710 had nine complementary binding sites to miR-129-5p. A miR-129-5p mimic significantly decreased AC130710 expression, suggesting that miR-129-5p could regulate AC130710 expression through binding with complementary sites^[77].

A newly described lncRNA, termed gastric adenocarcinoma associated, positive CD44 regulator, long intergenic non-coding RNA (GAPLINC) is associated with CNV and expression of oncogenic transcription factors in GC^[81]. In GC cells, GAPLINC and CD44 were identified as common targets of miR-211-3p^[81]. GAPLINC regulated CD44 as a decoy for miR-211-3p.

MALAT1, an acknowledged metastasis-associated lncRNA, was predicted as a target of miR-101, miR-217, miR-383, and miR-503 using bioinformatics analysis. Among them, miR-101 and miR-217 mimics decreased MALAT1 expression and were identified as tumor suppressor genes in GC. This was proposed as the mechanism involved in MALAT1 suppression at a post-transcriptional level^[74].

Through combining lncRNA microarray, bioinformatics algorithm databases such as miRcode, and the miRNA target database TarBase, Xia *et al.*^[100] constructed an lncRNA-miRNA-mRNA network in GC. Furthermore, *in vitro* experiments showed that lncRNA-FER1L4 promoted the target gene RB transcriptional corepressor 1 (RB1) expression by binding to miR-106a-5p. Based on the previous report, FER1L4 suppresses oncogenesis by inhibiting miR-106a-5p expression^[55].

CONCLUSION

GCs are still one of the greatest challenges to human

health, and metastasis is the leading cause of death from these cancers worldwide. Recently, lncRNAs have attracted remarkable attention from researchers, and increasing evidence suggests that lncRNAs are frequently aberrantly expressed in cancers, and play vital roles in various biological processes including cancer metastasis. In this review, we focus on the metastasis-associated lncRNAs in GCs. Characterization of their deregulated expression, especially in blood or other fluids, could provide novel biomarkers for cancer diagnosis and prognosis, including early diagnosis and observation of cancer progression^[46-48]. Many lncRNAs have been demonstrated to participate in cancer metastasis by influencing the process of EMT and affecting pathways required for cancer metastasis. The molecular mechanisms of lncRNA involvement in cancer include chromatin modification, transcriptional control, mRNA/miRNA processing, translational control, mRNA stability control and acting as “sponges” for miRNAs. However, the roles and mechanisms of metastasis-associated lncRNAs in GC still require further investigation and evaluation. Through promoting the understanding of lncRNAs in cancer, lncRNAs may be implicated as new targets for biological therapeutics.

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