

Long noncoding RNAs regulate malignant phenotypes in colorectal cancer

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Abstract: Noncoding RNAs (ncRNAs) are functional RNAs that are transcribed from DNA but are not related to translation. Long noncoding RNAs (lncRNAs) are over 200 nucleotides and are categorized as ncRNAs that affect cell processes, including transcription, remodeling, trafficking, and cell motility. Changes in the expression levels of lncRNAs affect the malignancy phenotype in various types of cancer. Furthermore, some lncRNAs affect the oncogenic pathway and aggravate the potential for malignancy in cancer. Hence, these RNAs are thought to be biomarkers and therapeutic targets for cancer. Because colorectal cancer (CRC) is the third leading cause of deaths from cancer, new diagnostic strategies and therapies for CRC continue to be developed. New drugs, including molecular targeted drugs, have improved the outcome of CRC but remain insufficient. Several studies have shown a correlation between the expression level of lncRNAs and CRC. In this study, we review the lncRNAs that are associated with CRC and describe their potential as novel biomarkers and therapeutic targets.

Keywords: Colorectal cancer (CRC); long noncoding RNAs (lncRNAs); cancer hallmark

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Introduction

Because colorectal cancer (CRC) is the fourth most frequent type of malignancy and because the incidence of CRC is increasing worldwide, this disease is a serious threat to human health (1,2). Researchers have determined the mechanisms of CRC, reducing the mortality from CRC in the past several decades. However, the prognosis of this malignancy remains poor, and the development of new biomarkers and therapeutic strategies is challenging.

Recent advances in sequencing technologies have revealed that protein-coding genes only occupy 3% of the human genome, suggesting that noncoding RNAs (ncRNAs) have a crucial role in process between DNAs and proteins (3,4). Long noncoding RNAs (lncRNAs), which have different biological functions and implications, are a category of ncRNAs that are over 200 nucleotides (5).

Some lncRNAs are evolutionarily conserved, despite having limited sequence similarity. Syntenic genomic sites frequently encode evolutionarily conserved, functional lncRNAs (6,7).

Several lncRNAs are uniquely expressed and exquisitely regulated in cancer cells (8). Although high-throughput studies have provided instructions on how mutations in protein-coding RNAs genetically affect translation, the biology of ncRNAs, including lncRNAs, has been unknown (9). However, accumulated knowledge on lncRNAs and emerging technologies has enabled researchers to annotate cancer-related lncRNAs and their pathways. Furthermore, Batista *et al.* reported the importance of the localization of lncRNAs, which influences cell fates during development, and their dysregulation causes human disorders (10). The regulation of lncRNAs at the chromatin level is a well-reported

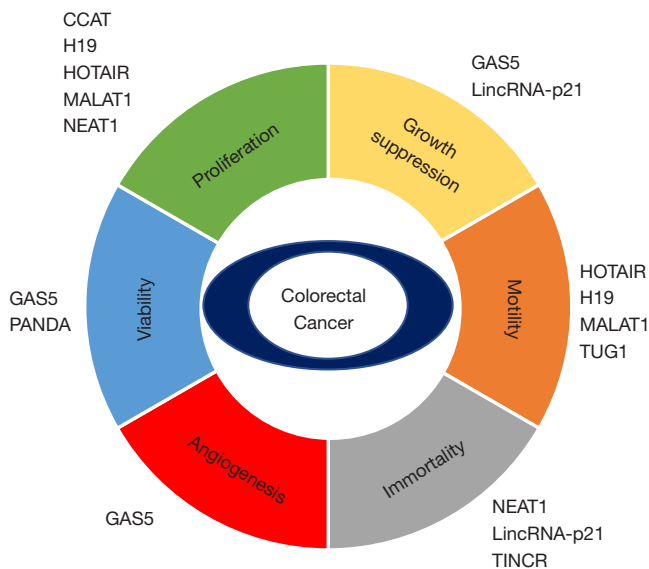


Figure 1 lncRNAs related to CRC in the hallmarks of cancer. This figure illustrates lncRNAs, categorized according to the six hallmarks of colorectal cancer. CRC, colorectal cancer; lncRNAs, long noncoding RNAs.

mechanism that affects intra-chromosomal genes and accordingly targets gene transcription in cis or trans (11,12). lncRNAs have been reported as cis enhancers that regulate transcription through chromatin remodeling, methylation, and transcriptional factor trapping (13-15). For example, the lncRNA X-inactive specific transcript (XIST), which is the master regulator of X chromosome inactivation, accumulates in cis on the X chromosome (16). Chu *et al.* reported that XIST interacts with 81 chromatin modification and RNA remodeling proteins, inducing the transition from pluripotency to differentiation (17).

Further, lncRNAs modulate RNA metabolism by controlling mRNA stability, splicing, and transcription. MALAT-1, also known as NEAT2 and highly conserved in mammals, has been reported to interact with pre-mRNA in the proximal region of the chromatin of a target gene. Through this interaction, MALAT1 regulates gene expression through splicing (18). The lncRNA Staufeu-1 (STAU-1) also binds to the 3'UTR region of the target gene, collapsing mRNA (19). This interaction between STAU-1 and mRNA is regulated by terminal differentiation-induced noncoding RNA (TINCR), promoting epidermal differentiation, and is suppressed in poorly differentiated squamous cell carcinoma (20).

lncRNAs interact with protein, inducing changes in

protein-protein interactions, protein localization, and protein function—this interaction is thought to be a crucial role of lncRNAs (21). As described above, XIST binds to several proteins, inducing X chromatin inactivation (17). Recent RNA chromatography techniques have enabled researchers to detect this interaction genetically and biochemically. By RNA immunoprecipitation, lncRNA pull-down, and RNA-seq, the interaction between lncRNAs and proteins has been studied extensively (22,23).

Thus, lncRNAs have several functions and affect many pathways in human cells. Here, we focus on lncRNAs and their role in human CRC, as these RNAs are thought to be essential targets for next-generation diagnosis and therapy in CRC in the ncRNA field.

lncRNA regulates cancer phenotypes

Currently, cancer is believed to be regulated by intrinsic cellular dysfunction and intercellular connections with the cancer microenvironment. Based on this concept, cancer phenotypes are divided to six categories during the development of human cancer (24)—proliferation, growth suppressor, motility, immortality, and viability—that affect the growth and metastasis of cancers. In this review, we focus on the function of lncRNAs in each cancer hallmark, describing the related cancer pathways in CRC (Figure 1).

Colon cancer-associated transcript (CCAT) family

Current studies have shown an association of multiple genomic variants, including lncRNAs, in chromosome 8q24, which is specific for c-MYC (25). CCAT1 is a recently discovered lncRNA on chromosome 8q24 that is 2,628 nucleotides and has a short isoform, CCAT1-S, and a long isoform, CCAT1-L. Several studies have revealed the function and mechanisms of CCAT1 in CRC. Kim *et al.* reported that CCAT1-S, known as Carlo-5, is significantly associated with the cancer-associated variant rs6983267 in the MYC enhancer region in CRC. They also found that the promoter region of CCAT1-S interacts physically with the MYC enhancer region, regulating CCAT1-S expression (26). Recently, CCAT1 was reported to be a target of the bromodomain and extraterminal (BET) protein and marks the colon cMYC super-enhancer. This result indicates that CCAT1 might be a clinical biomarker for detecting CRC patients who respond to a BET inhibitor as

chemotherapy (27). Furthermore, the other isoform, CCAT1-L, which is transcribed from a super-enhancer region of MYC, modulates chromatin looping between the MYC promoter and its enhancers by interacting with CCCTC-binding factor (CTCF) (28).

Ling *et al.* identified CCAT2 and demonstrated that CCAT2 regulates MYC, miR-17-5p and miR-20a through the regulation of transcription factor 7-like 2. They also revealed that CCAT2 is a downstream target gene of WNT, which means that these genes form a feedback loop, and that SNP status influences CCAT2 expression (29). Moreover, Redis *et al.* showed that CCAT2 regulates cancer metabolism in an allele-specific manner by binding cleavage factor I and affects carcinogenesis in CRC (30).

As biomarkers of CRC, high expression of CCAT1 and CCAT2 has been revealed to be significantly associated with poor overall survival and disease-free survival in 300 CRC samples (31). Thus, CCAT1 and CCAT2 regulate several oncogenic genes and pathways, indicating their essential role in CRC.

H19

The lncRNA H19 was discovered as a parentally imprinted gene and is located on human chromosome 11p15.5 (32,33). H19 is abundantly expressed during embryonic development and is nearly completely repressed after birth (34). Since its discovery, several studies have shown that H19 has an essential role in the progression of multiple types of cancers as an oncogene and tumor suppressor (35-38).

H19 is also known as the precursor gene of miR-675 (39). Tsang *et al.* revealed that H19 and miR-675 are highly expressed in CRC tissue compared with normal colon tissue. Furthermore, they found that the tumor suppressor retinoblastoma (RB) was a direct target of miR-675, indicating that H19-derived miRNA-675 regulates cancer development in CRC through downregulation of RB (40). Regarding the H19-miR-675 axis, Chen *et al.* reported that overexpression of H19 increases the resistance to vitamin D treatment by targeting vitamin D receptor through miR-675-5p in CRC (41). H19 recruits the cell cycle-related gene eukaryotic translation initiation factor 4A3 (eIF4A3) and promotes proliferation of CRC cells, based on bioinformatics methods. This study also showed that higher expression of H19 is related to tumor differentiation and advanced TNM stage in CRC patients (42). We reported that H19 is the most significant lncRNA among several cancer-related lncRNAs in The Cancer Genome Atlas

CRC dataset. Furthermore, using two other physical CRC datasets, we confirmed that H19 affects the poor prognosis in CRC. Knockdown of H19 dramatically reduces CRC cell proliferation through cell cycle control and migration. By microarray, as a non-biased approach and a bioinformatics technique, H19 affects RB protein and beta-catenin activity by regulating CDK8 expression (43).

HOX transcript antisense RNA (HOTAIR)

HOTAIR is 2,158 bp and is located on chromosome 12q13.13. HOTAIR was the first lncRNA to be reported as a transcriptional regulator and has also been reported to correlate with polycomb repressive complex 2 (PRC2) (44). Several reports have shown that HOTAIR has essential oncogenic function in breast cancer, pancreatic cancer, liver cancer, gastric cancer, and esophageal cancer (45,46). In CRC, the first report by Kogo *et al.* revealed that cancerous tissue has higher expression of HOTAIR than noncancerous tissue and that high HOTAIR expression correlates with liver metastasis. Furthermore, they showed that the reprogramming of PRC2 function influences HOTAIR expression (47). Following the first report, Svoboda *et al.* evaluated the expression level of HOTAIR in the blood of CRC patients, concluding that this lncRNA might be a prognostic marker in CRC (48). Depletion of HOTAIR is reported to increase E-cadherin expression and decrease matrix metalloproteinase 9, which indicates that HOTAIR is associated with the epithelial-mesenchymal transition (EMT). This study concluded that HOTAIR might promote CRC cell invasion and migration through the EMT (49). Yang *et al.* confirmed that HOTAIR influences the proliferation and invasion of CRC through a clinical analysis and *in vitro* experiments, and they found that HOTAIR also changes the radio-sensitivity of CRC (50). Bhan *et al.* reported that hypoxic conditions induce the expression of HOTAIR through the histone methylase MLL1 and HIF. In CRC, HIF1 α , MLL1, and the histone acetylase p300 are abundant at the promoter site of HOTAIR, indicating that hypoxia-induced HOTAIR might correlate with the carcinogenesis of CRC (51). Thus, HOTAIR affects cancer phenotypes multi-directionally.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1)

MALAT-1, also known as nuclear enrichment autosomal transcript 2, is 8.7 kb and is located on chromosome

11q13.1. In several types of cancer, MALAT-1 is known to be associated with cancer metastasis and recurrence (52-55). The first MALAT-1 report that correlated it with CRC was reported by Zheng *et al.*, which revealed that high expression of MALAT-1 is significantly associated with a poor prognosis in CRC and concluded that MALAT-1 might be a negative prognostic marker in CRC (56). Mechanistically, MALAT-1 is thought to influence the tumor microenvironment in CRC. Tumor-associated dendritic cells (TADCs), which secrete inflammatory cytokines, regulate migration, invasion, and the EMT. Cancer cell invasion and migration in the CRC cell lines SW480 and SW620 are increased through MALAT-1 overexpression with TADC-conditioned medium and chemokine (C-C motif) ligand 5 (57). Using microarray, Jie *et al.* found that MALAT-1 regulates miR-129-5p, inducing high expression of high motility group box protein 1 (HMGB1). Their results concluded that the MALAT-1/miR-129-5p/HMGB1 axis induces cancer development in CRC (58).

Nuclear-enriched abundant transcript 1 (NEAT1)

NEAT1 is a novel lncRNA that has two isoforms: NEAT1_1 and NEAT1_2. NEAT-1 was identified as a component of nuclear paraspeckles and was reported to regulate transcription (59,60). Li *et al.* evaluated NEAT-1 expression in CRC using CRC clinical samples and showed that high expression level of NEAT-1 was an independent prognostic factor of a poor outcome (61). Although there are few reports of NEAT-1 in CRC, the current study revealed a relationship between NEAT-1 and Akt signaling. Knockdown of NEAT-1 in CRC cell lines resulted in cell growth arrest and cell apoptosis by suppressing the phosphorylation of AKT at Ser473 (62).

Growth arrest-specific 5 (GAS5)

GAS5 regulates cell growth arrest by blocking target gene expression through activation of glucocorticoid receptor (63). GAS5 has been studied extensively, and recent reports have shown that this gene has important roles in cancer phenotypes by affecting proliferation, the EMT, and apoptosis (64,65). GAS5 has been identified as a biomarker in bladder cancer, non-small cell lung cancer, breast cancer, hepatocellular carcinoma, ovarian cancer, gastric cancer, cervical cancer, and head and neck squamous cell carcinoma (66-72). In CRC, Yin *et al.* revealed its clinical significance

by evaluating CRC samples. Furthermore, they showed that overexpression of GAS5 inhibits cell proliferation *in vitro* and *in vivo* (73). Interestingly, another study by Kong *et al.* found that GAS5 and the lncRNA Yiya correlate with a poor prognosis and predict the risk of liver metastasis in early-stage CRC patients (74). Moreover, GAS5 was revealed to inhibit interleukin-10 and vascular endothelial growth factor expression, resulting in suppression of CRC carcinogenesis. Because few reports have described the relationship between lncRNA and angiogenesis, this study could provide insights into the development of CRC diagnosis and therapy (75). Thus, GAS5 broadly regulates CRC phenotypes and is a potential biomarker and therapeutic target.

LincRNA-p21

LincRNA-p21 is a P53 transcriptional target that represses the expression of its target genes by associating with hnRNP-K (12). Functionally, two reports have shown an association between LincRNA-p21 and β -catenin signaling (76,77). Wang *et al.* revealed that LincRNA-p21 increases radio-sensitivity, which is induced through the suppression of β -catenin (76). Another study showed that the tumorigenicity of CRC stem cells is mitigated by LincRNA-p21 through suppression of β -catenin signaling and concluded that LincRNA-p21 could be a possible target for cancer stem cell-targeting therapy (77).

Promoter of CDKN1A antisense DNA damage-activated RNA (PANDAR)

PANDAR is located at 6p21.2 and is upregulated by doxorubicin (78). Chen *et al.* determined the mechanisms of PANDAR in CRC. Changes in PANDAR expression could not alter proliferation, apoptosis, and senescence. However, using curcumin-treated CRC cells, knockdown of PANDAR induced apoptosis and increased senescence (79). Lu *et al.* reported that high expression of PANDAR is related to a poor prognosis in CRC and promotes metastasis via the EMT (80).

Taurine-upregulated gene 1 (TUG1)

TUG1 was initially reported to be associated with eye development in mice (81). Additionally, dysregulation of TUG1 regulates carcinogenesis in a variety of tumors (82-84). Regarding CRC, two studies showed that TUG1

promotes invasion and migration via the EMT pathway. These studies also concluded that knockdown of TUG1 could be a therapeutic strategy for CRC (85). Li *et al.* noted that TUG1 regulates the sensitivity of CRC cells to methotrexate (MTX). Knockdown of TUG1 re-sensitized the MTX resistance in MTX-resistant CRC cell lines. Furthermore, using a bioinformatics technique, they revealed that TUG1 binds directly to miRNA-186 and regulates its target, CPEB2 (86).

TINCR

TINCR is a 3.7-kb lncRNA and has been reported as a suppressor of CRC metastasis. Zuo-Yang revealed the clinical significance and mechanisms of TINCR in CRC. Evaluating cancer tissue and adjacent tissues in 44 CRC patients, they found significantly lower expression of TINCR in CRC samples. Additionally, they observed that the loss of TINCR induced Wnt- β -catenin signaling via hydrolysis of EpCAM (87). As with CCAT2, SNP status might influence the development of CRC. Yongbin *et al.* found that genetic variations in TINCR might contribute to the susceptibility to and progression of CRC, analyzing three SNPs in TINCR. They concluded that two SNPs, rs2288947 and rs8105637, might be independent biomarkers that are related to the occurrence and progression of CRC (88).

Concluding remarks and future perspectives

Surgical techniques and chemotherapies have improved the outcomes of CRC patients. Especially, anti-PD-L1 therapy has been reported to be effective in solid tumors, and the US Food and Drug Administration has approved the anti-PD-L1 agent nivolumab (OPDIVO, Bristol-Myers Squibb Company) for CRC patients with mismatch repair-deficient (dMMR) and microsatellite instability-high (MSI-H) metastatic CRC that has progressed following combination treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Thus, new therapeutic strategies for CRC have appeared and had favorable results; however, they are thought to remain insufficient.

Clinical studies that are targeting miRNA are still going. For example, miravirsin, which is a nucleic acid-modified DNA phosphorothioate oligonucleotide complementary to miR-122, suppresses hepatitis C virus (HCV) RNA and clear phase I trials and is now in phase II trials (89). In cancer, miR-34 mimics (MRX34) against primary liver

carcinoma, solid tumors, and hematological malignancies have been evaluated in a phase I trial, but this clinical study has been terminated, due to immune-related severe adverse events (ClinicalTrials.gov). Furthermore, since miRNAs are short RNAs (~22 nucleotides), one miRNA targets numerous genes, indicating that it is difficult for miRNA-based drugs to target specific oncogenes or tumor suppressors. Thus, new therapies targeting miRNAs remain underdeveloped. In contrast, lncRNAs bind to chromatin, DNA, RNA, and proteins directly or indirectly, which indicates that the target genes of lncRNAs might be specific compared with those of miRNAs (90).

Although carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are broadly used as CRC markers, more specific biomarkers are eagerly anticipated. As mentioned above, many studies have reported the possibility of using lncRNA as biomarkers for several types of cancers, including CRC, in tumor samples and blood samples. Like H19, some lncRNAs are abundant in and specific to CRC, rendering them good biomarkers for CRC. Intriguingly, Liang *et al.* found that lncRNA expression profiles discriminate several types of microbes in the gut (91). These results indicate that fecal lncRNAs could be possible biomarkers for screening CRC.

Other than the representative oncogenic lncRNAs described above, several lncRNAs contribute to proliferation, invasion, and metastasis in CRC, which could aid its early diagnosis. As possible targets of CRC, many studies have focused on determining the clinical importance of lncRNAs. Several clinical studies targeting lncRNAs have just begun. Hence, further research is necessary to identify the oncogenic mechanisms and pathways of lncRNAs. lncRNAs affect the hallmarks of CRC, implying that they will undoubtedly lead to discoveries that are relevant to the diagnosis and treatment of CRC.

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Footnote

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