Review Article

The relevance of long noncoding RNAs in colorectal cancer biology and clinical settings

ABSTRACT

Colorectal cancer (CRC) is one of the most frequent causes of cancer-related death worldwide. The prognosis of the malignancy and patient survival is commonly poor. Therefore, the discovery of pertinent biomarkers is essential to provide an accurate diagnosis and effective therapy. Newly, a group of noncoding RNAs named long noncoding RNAs (lncRNAs) has been found to involve in CRC development and progression. In this review, we highlighted the biological function of lncRNAs and reviewed their potentials as clinical tools in the CRC. A literature search of PubMed, EMBASE, MEDLINE, Web of Science, Scopus, and Cochrane Library using the MeSH terms "CRC," "long noncoding RNA," "lncRNA," and relevant was completed. The review included all articles that reported on the significance and role of lncRNAs in CRC development and clinical settings. All identified articles were cross-referenced for further articles, and any unavailable online were retrieved from hardcopy archive libraries. CRC-related lncRNAs could regulate a number of cellular processes, and their dysregulations have been suggested as potential biomarkers.

KEY WORDS: Colorectal cancer, diagnosis, long noncoding RNAs, prognosis

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INTRODUCTION

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers and considered as the third mainly cause of cancer-related death worldwide.[1-3] The carcinogenesis of CRC involves sequential alterations in genetic and epigenetic genes ultimately resulting in the progression of malignant cells to invasive carcinoma. The developed malignancy usually is detected in the late clinical stage, which prognosis and survival of CRC patients frequently are poor.[2,4,5] The existing clinical and pathological diagnostic and prognostic factors for the cancer have various limitations in evaluating the patient outcome. Hence, it is essential to inspect and develop proficient biomarkers for diagnosis and prognosis of CRC to improve therapeutic strategies and patient survival. Although the current genetic signs have revealed a promising clinical significance, further investigations are needed to confirm these biomolecules as routine clinical biomarkers.[6,7]

Recently, a number of investigations have emphasized the biological function of noncoding RNAs (ncRNA), especially microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) in the pathogenesis of CRC. LncRNAs are known as transcribed RNA molecules with 200 nucleotides in length and without an open reading frame.[8] These RNA molecules are functionally imperative in either transcriptional or posttranscriptional regulation. These nonprotein coding transcripts have been demonstrated to involve in numerous key cellular processes, including cell differentiation, proliferation, migration, and invasion.[9-11] Recently, a number of lncRNAs have been shown to function as oncogenes or tumor suppressors in CRC development. In addition, the expression level of some lncRNAs has been correlated with clinicopathological features, serving them as promising predictors of patient outcomes. Therefore, the potential of these molecules has increasingly been revealed for diagnostic, prognostic, and therapeutic applications.[12,13] In this review, we overview the recent findings about the biological function of CRC-related lncRNAs and their potential applications as biomarkers in

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CRC [Table 1]. We highlighted the biological function of lncRNAs and their potentials as clinical tools in the CRC. A literature search of PubMed, EMBASE, MEDLINE, Web of Science, Scopus, and Cochrane Library using the MeSH terms "CRC," "long noncoding RNA," "lncRNA," and relevant was completed. It was reviewed the latest articles regarding the 82 CRC-related lncRNAs reported up to August 2018. The review included all articles that reported on the significance and roles of lncRNAs in CRC development and clinical settings. All identified articles were cross referenced for further articles, and unavailable online articles were retrieved from hard-copy archive libraries [Figure 1]. This review study may be valuable in understanding the underlying mechanisms in CRC development and progression as well as designing the targeted cancer therapies.

LNCRNAS: BIOGENESIS AND BIOLOGICAL FUNCTIONS

LncRNAs are a family of nonprotein-coding RNAs transcribed by RNA polymerase II enzyme. LncRNAs are characterized by a size of ≥200 nucleotides in length and lack of an open reading frame. These RNA transcripts may be transcribed from a different locus of the whole genome, including intronic, intergenic, even pseudogenes, and retrotransposons. Furthermore, they have a number of binding sites to interact with DNA, proteins, or other RNA molecules.[8] A range of biological functions, including cell differentiation, proliferation, invasion, and apoptosis have identified for various classified lncRNAs. Transcriptome sequencing databases imply that half of the human genome transcribes for lncRNA. Despite the majority of ncRNAs, the function of lncRNAs has not fully been characterized. A range of genetic- or epigenetic-mediated cellular processes is regulated by lncRNAs. Gene transcription and translation, histone modification, and microRNA machinery may be regulated by lncRNAs[9-11] More recently, it has been revealed that this transcribed RNAs potentially function as suppressors or promoters of gene expression to develop human cancers.[12,13] Thus, the expression profile of the functional lncRNAs may alter in cancers. Increasing evidence suggests that the dysregulation of these cancer-associated lncRNAs potentially provide diagnostic, prognostic, and therapeutic biomarkers.[14-27] The experimental confirmation and bioinformatics prediction using the Cancer Genome Atlas database (http://cancergenome.nih.gov/) is especially helpful to validate the underlying mechanisms, as well as evaluate the biological role and diagnostic performance.[28]

CRC-associated lncRNAs: Biological and clinical significance

A number of lncRNAs have been reported to function as oncogenes or tumor suppressors in CRC development.[29-58] As well, the expression levels of some lncRNAs correlate with CRC clinicopathological features, serving them as promising predictors of patient outcomes.[59-71] Therefore, the potential of these molecules is increasingly revealed for diagnostic, prognostic, and therapeutic applications. Here, we overview the recent findings about the biological function of lncRNAs and their potentials as prognostic biomarkers in CRC. We searched Scopus, Web of Science, PubMed, MEDLINE, EMBASE, and the Cochrane Library for studies reporting the biological or clinical significance of lncRNAs in CRC. All references from related studies were checked, and any study was not found online was retrieved from archived library sources. The identified original, prospective cohort, and retrospective cohort studies were included in our study.

Oncogenic lncRNAs upregulated in colorectal cancer

Prostate cancer-associated ncRNA transcripts 1

Prostate cancer-associated ncRNA transcripts 1 (PCAT-1), as a long intergenic noncoding RNA, is transcribed from gene at chromosome 8q24. This lncRNA was firstly reported to be overexpressed in prostate cancer and established to relate with a prognosis of the cancer patients.[72] LncRNA PCAT-1 could promote cell proliferation through association with polycomb repressive complex 2 as a transcriptional repressor.[72] The high levels of PCAT-1 associated with cancer patients' survival rate. PCAT-1 also was shown to upregulate in CRC tissues and correlate with the overall survival and lymph node metastasis. It has also been reported a correlation between PCAT-1 overexpression and the progression of CRC. Related findings presented a molecular mechanism by which PCAT-1 is implicated in CRC progression, indicating it as a suitable target[72,73] and an independent prognostic factor for CRC.[73]

Colon cancer-associated transcript-1

Colon cancer-associated transcript-1 (CCAT1) is a lncRNA with 11.88 kb in length that upregulates in CRC tissue.[16] CCAT1 gene is located on chromosome 8q24.21 and is placed within a strong super-enhancer in vicinity of transcription factor c-Myc.[74-76] CCAT1 could regulate Myc transcription and promote chromatin turnover.[17,18] The elevated expression level of CCAT1 was also correlated with the tumor node metastasis (TNM) stage, lymph node metastasis, and survival rate. *In vitro* experiments showed that CCAT1 could function in CRC carcinogenesis and it may be served as a clinical outcome biomarker.[74] The plasma expression level of CCAT1 has also been confirmed it as a predictive biomarker for CRC screening.[19]

MALAT1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a lncRNA with8.75 kb in length transcribed from the nuclear-enriched transcript-2 gene. This lncRNA is also known NEAT2, noncoding nuclear-enriched abundant transcript 2. A number of carcinogenic functions of MALAT1 have been described in various cancers such as pancreatic, liver, cervical, and colon cancers.[77] Moreover, related studies in CRC cell lines demonstrated a range of functional roles for MALAT1 in CRC carcinogenic processes including cell proliferation and invasion.[78] MALAT1 could promote cell colony formation, migration and invasion mediated by PRKA (kinase anchor protein 9).[20] Some researchers showed that the high expression level of MALAT1 is correlated with clinicopathological parameters and poor prognosis in CRC

Table 1: Description of colorectal cancer-related lncRNAs and their biological and clinical significance

lncRNA	Genomic location	lncRNA expression in CRC	Biological signigicance [references]	Clinical signigicance [references]
			Oncogenic lncRNAs upregulated in CRC	
CCAT1	8q24.21	Upregulated	Super enhancer of c-Myc[14,15] Enhancing the progression and metastasis mediated by c-myc binding to CCAT1 promoter region[16-19]	-
MALAT1	11q13.1	Upregulated	Enhancing the proliferation, migration, and invasion through releasing of proto-oncogene PTBP2, and interaction with AKAP-9 protein, and Wnt/β-catenin signaling pathway proteins[20-23]	Poor prognosis[24] Diagnosis, prognosis and therapy[25] Poor survival, as therapeutic target[26]
GAPLINC	18p11.31	Upregulated	Increasing the invasion and proliferation[27]	Poor prognosis[8]
ROR	18q21.31	Upregulated	Enhancing cell apoptosis and triggering the cell cycle[28] Inhibiting the P53-miR145 pathway[29]	-
ATB	14q11.2	Upregulated	Promoting the invasion and metastasis through interaction with transcription factors ZEB1 and ZEB2, involving in EMT[30,31] Promoting the invasion and metastasis[32]	Poor prognosis[32]
H19	11q15.5	Upregulated	Inducing the resistance to 1,25 (OH) 2D3 by targeting VDR through miR-675-5p[33] Promoting the cell migration and invasion[34] Promoting the cell proliferation by competitively binding to miR-200a Elevating B-catenin expression and activity in CRC cells[35] Targeting the miRNAs[36] Regulating Rb-E2F and CDK8-β-catenin signaling, Regulating RB1-E2F1 Activity[26]	Predicting CRC susceptibility[36] Poor prognosis[37]
GHET1	7q36.1	Upregulated	Inhibits cell proliferation and invasion[38]	-
HOTTIP	7p15.2	Upregulated	Increasing the cell migration and cell proliferation[39] Promoting the progression and metastasis through G1 phase arrest, S phase reduction[40,41]	-
TUG1	22q12.2	Upregulated	Increasing the progression and metastasis mediated by modulation of the expression of EMT related genes[42] Promoting the cell migration ability of colon cancer cells[43]	-
UCA1	19p13.12	Upregulated	Promoting the proliferation of CRC cells through p53/p21 signaling[44] Proliferative and antiapoptotic effect through G0/G1 growth arrest[45]	Early diagnosis[44]
PVT1	8q24.21	Upregulated	Increasing the cell proliferation by promoting the c-Myc expression, as a oncogene coamplified with c-Myc in colorectal cancer[46] Proliferative and antiapoptotic effect through modulation of chromatin remodeling complex SWI/SNF[47]	-
DANCR	4q12	Upregulated	-	Poor prognosis and distant metastasis[48]
PCNCR			Promoting the CRC cell proliferation and migration[49]	-
CLMAT3	14q32.31	Upregulated	Promoting the progression and metastasis[50] Promoting the cell proliferation by targeting regulators of the cell cycle pathway[51]	-
FTX	ChrXq13.2	Upregulated	Promoting the cell proliferation, migration, and invasion mediated by xist upregulation[52]	-
FEZF1-AS1	7q31.32	Upregulated	Promoting the cell proliferation, migration and invasion through S-phase entry[53]	-
UCC	7p15.2	Upregulated	Promoting the cell proliferation and invasion[54]	Associated with lymph node metastasis[54]
Linc00659	20q13.33	Upregulated	Promoting the cell cycle progression and enhancing colon cancer cell growth, by repressing PI3K-AKT signaling[55]	Predicting the prognosis[55]
PINCR	Xp11.3	Upregulated	Promoting the tumor growth and chemotherapeutic resistance Induced by DNA damage and increasing the p53 signaling and apoptosis[56]	-
HOXA-AS2	7p15.2	Upregulated	Promoting the cancer cell proliferation[57]	Associated with a larger tumor size and advanced cancer stages[57]
SPINT1-AS1	15q15.1	Upregulated	Promoting CRC progression[58]	Correlated with shorter survival rate. Predicting the prognosis[58]

Contd...

Table 1: Contd...

lncRNA	Genomic location	lncRNA expression in CRC	Biological signigicance [references]	Clinical signigicance [references]
		Oncogenic lncRNAs upregulated in CRC		
TP73-AS1	1p36.32	Up-regulated	Upregulating the expression of TGFα, promoting the cell growth, proliferation, migration, and invasion[59]	Associated with the advanced cancer stages[59]
LINC01510	7q31.2	Upregulated	Promoting the cell cycle progression and increasing the cell proliferation[60]	Predicting the prognosis[60]
lnc00152	13q32.1	Upregulated	Increasing the cell proliferation and invasiveness, partly by promoting EMT[61]	Correlated with the shorter overall survival; predicting prognosis[61]
		Suppressor lncRNAs downregulated in CRC		
BC0209135	19p13	Downregulated	Decreasing the cell invasion by suppressing Wnt/β-catenin signaling[62]	-
HOTAIRM1	7p15.2	Downregulated	Enhancing the cell proliferation[63]	Early diagnosis[63]
MEG3	14q32.2	Downregulated	Preventing abnormal proliferation by promoting p53 expression[23,64-67]	-
ncRAN	17q25.1	Downregulated	Decreasing the migration and invasion[23,66]	-
RP11-462C24.1	4q25	Downregulation	Decreasing the cell invasion, and metastasis[68]	Poor prognosis[68] Early diagnosis[69]
TUSC7	3q13.3	Down-regulation	Inhibiting the cell proliferation by sponging miR-211 and increased the expression level of CDK6[70]	Early diagnosis[69]

CRC=Colorectal cancer, EMT=Epithelial-mesenchymal transition, lincRNA=Long intergenic noncoding RNA

patients, and suggested MALAT1 as an independent prognostic risk factor.[21,79] Further investigations indicated that the overexpression of MALAT1 could partially be responsible for oxaliplatin-induced EMT and chemoresistant in CRC cells. Altogether, MALAT1 could potentially be a valuable prognostic biomarker and a therapeutic target for CRC.[79]

Gastric adenocarcinoma predictive long intergenic noncoding

Long intergenic noncoding RNA (lincRNA) named gastric adenocarcinoma predictive long intergenic noncoding (GAPLINC) was firstly identified in gastric cancer. This lincRNA is located on chromosome 18 and its synonym names are TCONS_00026238, LINC01540, and lncRNA-uc002 kmd. 1.[27] The functional and experimental studies confirmed the effect of GAPLINC on CRC cell proliferation, migration, and invasion. It was identified that this lncRNA might play an imperative role in CRC carcinogenesis.[80] Furthermore, the clinical findings showed that the high expression of GAPLINC correlates with invasion, lymph node metastasis, and TNM stage and poor survival rate in CRC patients.[27] Taken together, it was suggested that GAPLINC could promote cell proliferation and metastasis and represents a potential prognostic biomarker and therapeutic target in CRC patients.[8,27,80]

Regulator of reprogramming

A new lncRNA, with 2.6 kb in length named lincRNA-regulator of reprogramming (RoR), was characterized in induced pluripotent stem cells (iPSCs). LincRNA-RoR could play an important role in the biology of iPSCs by regulation of cellular stress pathways.[12,13,81] LincRNA-RoR can act as a p53 repressor in response to DNA damage and hypoxic stress.[10] Furthermore, lincRNA-RoR has been reported to be active as a molecular sponge for miR-145 to modulate the metastasis and drug resistance in breast cancer.[11,71] The regulation of P53/miR-145 pathway by lincRNA-ROR indicated a biological role of this RNA molecule for stress-induced approach in CRC therapy. Interestingly, the altered expression of lncRNA ROR has been reported to determine efficiency of CRC radiotherapy.[29] Experimental studies showed that the expression level of lncRNA-ROR was elevated in CRC cell lines and tissues compared to normal controls and its overexpression significantly promote cell proliferation. *In vitro* studies demonstrated that lncRNA-ROR could regulate cell proliferation, viability, and apoptosis, providing potential and prospective therapeutic targets for CRC.[28]

Activated by transforming growth factor beta

LncRNA-ATB (lncRNA activated by transforming growth factor beta [TGF-β]) is upregulated in several cancers including hepatocellular carcinoma, prostate, and CRC.[82-84] The activation of this lncRNA is mediated by cytokine TGF-β that acts as a moderator in tumor transformation, migration, invasion, and metastasis.[30] lncRNA-ATB increases colonization of migrating cells by promoting the function of interleukin-11-STAT3 signaling pathway.[31] The biological roles of lncRNA-ATB in regulating E-cad and other EMT-related markers expression in CRC were elucidated *in vitro*.[32] The expression levels of lncRNA-ATB in CRC tissues also are correlated with clinicopathological features.[32] According to related evidences, lncRNA-ATB is involved in the progression of CRC and may be served as a novel indicator of poor prognosis in patients.[32]

H19

The lnc-H19, an antisense long noncoding RNA with a 120 kb, is located on the H19 gene locus. It has been found that lnc-H19 overexpress in range of malignancies including breast cancer,[85] esophageal squamous cell carcinoma,[86] and CRC.[87] H19 overexpresses in CRC tissues and cell lines.

This lncRNA could play a key role in the progression of CRC by promoting cell motility, migration, and aggression. This lnc-RNA could mediate CRC metastasis through upregulating metastasis-related proteins. Furthermore, a H19-miR138-HMGA1 pathway in regulating the migration and invasion of CRC was validated, providing new insight for the treatment of CRC.[35] Moreover, the functional studies represented a potential mechanism underlying the resistance to treatment with 1,25 (OH) 2D3 in CRC.[33] The high expression of H19 in CRC associated with poor prognosis and metastasis of the disease.[87] In addition, rs2839698 in H19 was related to increased risk of CRC, which may be used as a potential prognostic biomarker.[36]

Gastric carcinoma high-expressed transcript 1

LncRNA gastric carcinoma high-expressed transcript 1 (lncRNA-GHET1) was first found to upregulate in gastric cancer.[88] GHET1 could play an essential role in cell proliferation through increasing c-Myc mRNA expression and stability.[89] The expression of GHET1 in CRC tissues was established to considerably increase compared to normal epithelial cells and tissues.[38] GHET1 overexpression in CRC cell lines has been confirmed to have a biological role in cell proliferation, cell cycle progression, migration, and invasion.[88] GHET1 also could regulate EMT-related gene expression to progress CRC.[89] Taken together, the experimental and clinical findings suggest the potential use of GHET1 as a prognostic marker and therapeutic target of CRC.

HOXA transcript at the distal tip

LncRNAHOXA transcript at the distal tip (HOTTIP) with 3.8 kb, is located at the 5' end of HOXA cluster and regulates HOXA genes.[90,91] A more recent study confirmed fundamental role of HOTTIP in CRC development. HOTTIP is overexpressed in CRC tissues in comparison with normal tissues.[40] Moreover, the expression level of HOTTIP has been reported to be correlated positively with advanced pathological tumor stage, tumor size, and distant metastasis. *In vivo* experiments showed that HOTTIP can promote the growth of tumor, suggesting it may be served as a prognosis predictor and candidate for CRC therapy.[40]

Taurine upregulated gene1

Taurine upregulated gene1 (TUG1) is a 9.7 kb and highly conserved gene locating on chromosome 22q12.[92-94] TUG1 was shown to involve in CRC progression and metastasis, thus it was proposed as a prognostic biomarker and therapeutic target for the malignancy.[94] Previous studies showed the expression levels of TUG1 were elevated in CRC tumor tissue and strongly correlated with the survival rate of the CRC patients. Furthermore, TUG1 overexpression could stimulate EMT-related gene expression and promote colony formation, migration and metastasis in CRC. Accordingly, it has been confirmed that TUG1 could increase the cell proliferation and migration and inhibit colon cancer cell apoptosis.[93]

Urothelial cancer associated1

Urothelial cancer associated 1 (UCA1) with 7.37 kb is located on chromosome 19p13. LncRNA UCA1 could regulate cell proliferation, apoptosis, and cell cycle progression of CRC cells.[45] Furthermore, a correlation between UCA1 expression and clinicopathological features of CRC patients, including larger tumor size, less differentiated histology, and greater tumor depth has been found. Furthermore, the expression level of UCA1 in CRC patients was associated with poor prognosis. Multivariate analysis indicated that UCA1 over-expression could be as an independent predictor for CRC.[95] UCA1 upregulates in CRC and negatively correlates with survival rate of the patients. Functional studies revealed a function of UCA1 in promoting cell growth and decreasing the apoptosis of CRC cells. The findings confirmed UCA1 as a new potential oncogene and prognostic factor for CRC.[96]

Plasmacytoma variant translocation 1

LncRNA plasmacytoma variant translocation 1 (PVT1) gene is located on 8q24. The overexpression of lncRNA PVT1 has been suggested as a powerful predictor of tumor progression and patient survival in a diverse range of cancer types, such as pancreatic cancer,[97] gastric cancer,[98] hepatocellular cancer,[99] ovarian and breast cancer.[100] PVT1 can promote CRC cells proliferation and reduce apoptosis. The high PVT1 expression correlates with poor prognosis of CRC patients. Further analyses showed that PVT1 expression level was an independent prognostic factor of overall survival in CRC patients.[100] This lncRNA can regulate cell proliferation and cell apoptosis by affecting c-Myc expression. Taken together, the findings indicated that the overexpression of PVT1 predicts the prognosis of CRC patients, providing insights into future investigations on CRC therapeutic strategies.[47]

Differentiation antagonizing nonprotein coding RNA

Differentiation antagonizing nonprotein coding RNA (DANCR) is a 7.94 kb transcript that its gene is located on chr4q12. LncRNA DANCR play a fundamental role in maintenance of stemness features of stem cells.[101] Recent studies have shown this lncRNA involves in CRC carcinogenesis.[48] The high expression levels of DANCR were shown to be associated with TNM stage and distant metastasis in CRC. LncRNA-DANCR overexpression also was associated with aggressive progression and poor prognosis in CRC. Multivariate analysis showed that lncRNA-DANCR might be considered as an independent predictor for clinical outcome of CRC patients.[101]

PCNCR1

The novel lncRNA prostate cancer noncoding RNA 1 (PRNCR1) is located in a susceptible area of human genomic. More recently, one investigation confirmed the biological function and clinical significance of PRNCR1 in CRC. The expression profiling of PRNCR1 and functional studies by antisense oligonucleotide in CRC tissues and cell lines revealed that PRNCR1 could promote cell proliferation. Furthermore, diagnostic value of PRNCR1 has been suggested by finding

a correlation between the lncRNA expression levels and CRC clinicopathologic characteristics.[49]

Cancer liver metastasis associated transcript-3

Cancer liver metastasis associated transcript-3 (CLMAT3) or TR05005298 gene is mapped on chromosome 14. An *in vitro* study demonstrated that lncRNA-CLMAT3 expression was significantly elevated in CRC cells proliferation. As well, it was observed that lncRNA CLMAT3 could affect cell proliferation and apoptosis by inducing G0/G1 cell-cycle arrest.[102] The high expression levels of CLMAT3 are significantly associated with liver metastasis and lymph node metastasis. Besides, the overexpression of lncRNA-CLMAT3 was shown to be correlated with reduced overall survival. Altogether, this lncRNA was considered as a potential independent prognostic factor in CRC patients with liver metastasis.[49]

FTX

The gene of lncRNA FTX is located in chrXq13.2 at an intron within the X-inactivation center region.[52] LncRNA FTX is notably overexpressed in CRC tissues and correlated with differentiation grade, lymphvascular invasion, and clinical stage. Another study showed the high expression of FTX in CRC patients with poor prognosis.[103] Supplementary analysis showed that the upregulated expression of lncRNA FTX was correlated with overall survival, suggesting it as a valuable prognostic biomarker for CRC patients.[52]

FEZ family zinc finger 1 antisense RNA 1

FEZ family zinc finger 1 antisense RNA 1 (FEZF1-AS1) is located in chr7q31.32 on the opposite strand of gene FEZF1. The expression levels of FEZF1-AS1 are positively correlated with lymphatic metastasis, designating the lncRNA as a possible effector in CRC metastasis. The high expression levels of FEZF1-AS1 in CRC were significantly correlated with shorter survival rate.[53] Further analyses indicated that the upregulation of FEZF1-AS1 was an independent prognostic factor of outcomes in CRC patients.

Upregulated in colorectal cancer

A lincRNA termed upregulated in CRC (UCC) was newly reported to be overexpressed in CRC tissues and cell lines. Experimental findings in CRC cell lines and xenograft tumors confirmed the roles of UCC in cell proliferation and invasion. The expression levels of UCC associate with tumor stage and lymph node metastasis. Upregulation of UCC was shown to promote cell growth and invasion, indicating UCC as a valuable molecular target for CRC therapy.[54]

Linc00659

Linc00659 has been characterized as an oncogenic lncRNA that its expression level is considerably increased in CRC. This lncRNA could promote cell cycle progression and enhance colon cancer cell growth, by repressing PI3K-AKT signaling. The high expression levels of linc00659 are also correlated with poor survival in patients with CRC, pointing to a value of this lncRNA for CRC therapy.[55]

P53-induced noncoding RNA

P53-regulated lncRNA also named p53-induced noncoding RNA (PINCR), is upregulated followed by DNA damage in CRC cells and promotes tumor growth and chemotherapeutic resistance. Molecular investigations on CRC cells confirmed a function of PINCR in response to DNA damage in CRC cells through p53 signaling network. PINCR could induce some p53 signaling-related genes involved in G1 and apoptosis, suggesting an oncogenic role for this lncRNA.[56]

HOXA cluster antisense RNA 2

HOXA cluster antisense RNA 2 (HOXA-AS2), an lncRNA with a length of 1048 bp locating in the HOXA region, was found to be upregulated in CRC and associated with a larger tumor size and advanced cancer stages. HOXA-AS2 was also revealed to promote cancer cell proliferation. HOXA-AS2 could repress a number of transcription factors involved in CRC proliferation, including p21 (CDKN1A) and KLF2, and exert an oncogenic function. Therefore, this lncRNA may be served as a therapeutic target for CRC.[57]

Serine peptidase inhibitor, Kunitz type 1 antisense RNA1

Serine peptidase inhibitor, Kunitz type 1 antisense RNA1 (SPINT1-AS1) is a newly lncRNA overexpressed in CRC tissues compared to adjacent normal tissues. The high expression of SPINT1-AS1 was correlated with distant metastasis, and shorter survival rate of CRC, indicating it as a potential prognostic factor. Altogether, related findings demonstrated a critical role of lncRNA SPINT1-AS1 in CRC progression, designating it as a candidate prognostic biomarker and therapeutic target.[58]

TP73 antisense RNA 1

Long noncoding RNA TP73 antisense RNA 1 (TP73-AS1) has been reported as an upregulated lncRNA in CRC patients. Overexpression of TP73-AS1 was associated with advanced stages of the cancer. TP73-AS1 can upregulate the expression of TGFα in CRC cells, promoting the cell growth, proliferation, migration, and invasion *in vitro*. These findings indicated that TP73-AS1 is involved in CRC progression by modulating TGFα expression.[59]

LINC01510

lncRNA LINC01510 was identified as a lncRNA with a high expression in CRC tissues and cell lines. LINC01510 could promote cycle progression and increase cell proliferation. LINC01510 also was demonstrated to contribute to upregulation of oncogene MET expression. Clinical investigations revealed that the high expression levels of LINC01510 were associated with the clinicopathological features and advanced stages. Overall, related data suggested LINC01510 as a candidate prognostic biomarker and a molecular target for CRC therapy.[60]

lncRNA 00152

Lnc00152, as a newly identified lncRNA, upregulates in CRC and increase the cell proliferation and invasiveness of CRC cells *in vitro,* partly by promoting EMT. The overexpression of lnc00152 was found to be correlated with the shorter overall survival of CRC patients. Cooperatively, these findings revealed a critical role of lnc00152 in CRC cell growth, indicating it as a potential therapeutic target.[61]

Small nucleolar RNA host gene 20

Small nucleolar RNA host gene 20 (SNHG20) is mapped to chromosome 17q25.2. Biological and clinical significance of long noncoding transcript SNHG20 is inadequately realized in oncology. LncRNA SNHG20 is up-regulated in human CRC tissues and cell lines. Functional studies revealed that lncRNA SNHG20 promotes CRC cell proliferation, invasion and migration, and cell cycle progression. The experimental data suggested that SNHG20 involves in carcinogenesis and functions as a potential therapeutic target in CRC.[104] The high expression levels of SNHG20 associate with poor prognosis of patients with CRC. Moreover, the expression pattern of SNHG20 was presented as an independent prognostic factor for overall survival in CRC patients.[104]

Suppressor lncRNAs downregulated in the colorectal cancer

Growth arrest-specific transcript 5

Growth arrest-specific transcript 5 (GAS5) is transcribed from a gene located in chromosome 1q25.[105] LncRNA GAS5 could bind the glucocorticoid receptor, regulating cell metabolism,[104] and apoptosis.[105] The suppressor activity of GAS5 has been revealed in various malignancies such as breast,[106] prostate,[107] renal,[108] and gastric cancer.[109] *In vitro* and *in vivo* studies showed that overexpression of GAS5 reduces cell proliferation.[110] In human CRC, the expression levels of GAS5 are reversely associated with larger tumor size and advanced TNM stage and overall survival time.[110] Multivariate analysis showed that GAS5 expression was a significant independent predictor of poor survival of CRC patients.[110] The results demonstrated a potential value for GAS5 as a prognostic and diagnostic marker and a therapeutic target of CRC.[111]

BC029135

lncRNA BC029135 is a newly recognized lncRNA that was reported to be downregulated in CRC tissues than in adjacent normal tissues. The high expression of lncRNA BC029135 can decrease the invasion of cells by suppressing Wnt/β-catenin signaling in CRC cells. Related findings could provide new insights for CRC clinical settings and new evidence for targeted therapy.[62]

HOXA transcript antisense RNA, myeloid-specific 1

HOXA transcript antisense RNA, myeloid-specific 1 (HOTAIRM1 gene) is located in the HOX gene cluster on chromosome 7p15 between HOXA1 and HOXA2 genes.[63] Other names for the lncRNA HOTAIRM1 gene are C00U924339 and GC07P027137.[112] HOTAIRM1 regulates the CRC cell proliferation as a tumor suppressor. In addition, the downregulation of circulating HOTAIRM1 could be served as a biomarker for CRC.[63] The authors also suggested the combined HOTAIRM1 and CEA assay as a valuable tool for the early diagnosis of CRC.[63]

GNAT1

More recently, some researchers identified a new functional lncRNA known as lnc-GNAT1. The overexpression of lnc-GNAT1 could reduce the liver metastasis of CRC cells. A correlation between lnc-GNAT1-1 and Raf kinase inhibitor protein (RKIP) expression both in CRC cell lines and in patients' tissues was found. It was suggested that lnc-GNAT1-1 could act as a tumor suppressor via regulating RKIP-NF-κB-Snail circuit in CRC.[113] The expression levels of lnc-GNAT1-1 in primary tissue and plasma was shown to decrease in CRC patients and correlate with clinicopathological features. Taking the information together, lnc-GNAT1 could predict poor prognosis and act as an independent prognostic factor for CRC patients.[113]

ncRAN

Noncoding RNA expressed in aggressive neuroblastoma (ncRAN) is a RNA transcript locating in chromosome 17q25.[114] The biological functions of the lncRNA shown in cell proliferation, migration and invasion functions of lncRNA-ncRAN in bladder and CRC were.[115] The expression pattern of ncRNA was revealed to be tumor dependent. Recent studies reported a downregulation of ncRAN in CRC tumors and cell lines compared to normal samples. The decreased expression of ncRAN was associated with liver metastasis, poor differentiation and overall survival rate. Thus, related studies identified ncRAN as a new potential early diagnostic biomarker for CRC.[64]

ncRuPAR

lncRNA ncRuPAR is a lately discovered noncoding transcript, mapping on chromosome 5q13. LncRNA ncRuPAR could implicate in tumor growth, invasion, and metastasis in a number of cancers including gastric[116] and colon cancers.[117] NcRuPAR is overexpressed in CRC tissues in comparison with adjacent normal tissues. Moreover, the expression levels of ncRuPAR were significantly associated with differentiation status,[118] TNM stage and lymph node metastasis.[119] Taken together, ncRuPAR was suggested as a potential biomarker for prognosis of CRC.

Maternally expressed gene3

Maternally expressed gene3 (MEG3) is located on chromosome14q32 at maternally imprinted DLK1-MEG3 locus.[120] The downregulation of MEG3 has been reported in a range of cancers including bladder, brain, breast, colon, liver, lung, and prostate.[65,121-124] Increasing evidences support MEG3 as a lncRNA tumor suppressor and regulator of cell proliferation.[64] MEG3 expression is downregulated in CRC tissues in comparison with normal tissues.[124] Further experiments revealed that MEG3 could inhibit CRC cell proliferation *in vitro*. In addition, MEG3 expression level is

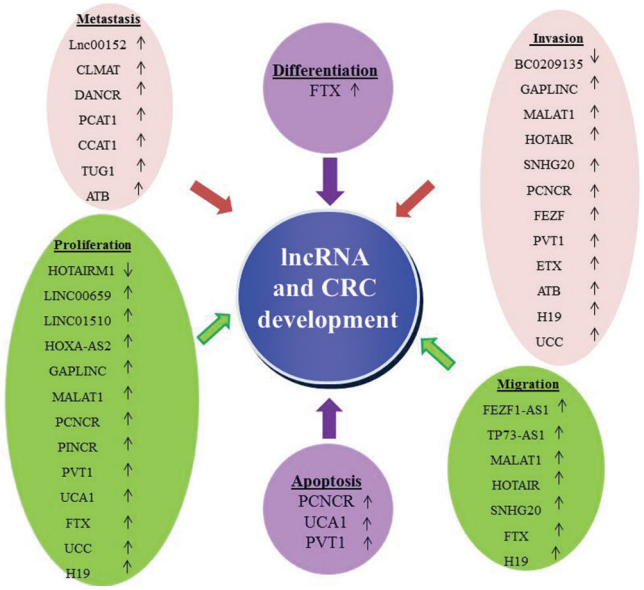

Figure 1: LncRNAs as potential effectors in colorectal cancer development

reversely correlated with high histological grade, tumor invasion, and advanced TNM stage. Taken all together, MEG3 is involved in the development and progression of CRC by regulating cell proliferation and may be considered as a potential diagnostic and prognostic biomarker.[64]

RP11-462C24.1

Long noncoding RNARP11-462C24.1, with a length of 1136 bp, is located on chromosome 4q25. RP11-462C24.1 may function in CRC development and progression.[68,69] Moreover, the decreased expression of RP11-462C24.1 was significantly correlated with lymph node metastasis and poor disease-free survival. Multivariate analysis demonstrated RP11-462C24.1 could act as an independent prognostic factor for CRC. Significant difference of serum levels of RP11-462C24.1 also was shown in CRC patients compared to normal individuals. Statistical analysis also implied this lncRNA has a potential value as diagnostic marker for CRC.[68]

Tumour suppressor candidate 7

Lnc RNA tumour suppressor candidate 7 (TUSC7), known as LOC285194, is located on chr3q13.31.[125] Current studies revealed a potential tumor-suppressor role of lncRNA TUSC7 in several cancers such as pancreatic ductal adenocarcinoma and CRC.[126,127] *In vitro* and *in vivo* investigations showed that TUSC7 could be a potential target of p53 by which suppresses tumor cell growth.[128] Furthermore, the expression levels of TUSC7 are lower in tumor tissues from CRC patients and CRC cell lines compared to adjacent normal tissues and normal intestinal mucous cell line.[126,127] More analysis identified that the expression level of TUSC7 is reversely correlated with tumor size, tumor stage, distant metastasis, and poorer prognosis. In addition, TUSC7 inhibits CRC cell proliferation partly by targeting miR-211-3p-related signaling pathway. TUSC7 also was shown to induce cell cycle arrest and inhibit CRC cell invasion.[128] Thus, lncRNA TUSC7 was suggested as a potential biomarker candidate for CRC prognosis.

CONCLUSIONS

The biological functions of lncRNAs in gene regulation at various levels have been shown in CRC. In addition, the expression levels of circulating lncRNAs may be correlated with clinical TNM stage, lymph node metastasis, and overall survival. Thus, their promising applications as noninvasive tumor biomarkers have been demonstrated in CRC diagnosis and prognosis. However, further understanding the underlying molecular mechanisms and regulation of lncRNAs for the better characterization supports their clinical use to improve cancer settings including early diagnosis and prognosis. So far, only a few numbers of lncRNAs have been characterized as defined biomarkers and there are numerous unsettled issues as clinical biomarkers. For instance, the expression level of some circulating lncRNAs is too low to detect by routine amplification techniques. The discovery of specific and sensitive biomarkers among diverse cancer-related lncRNAs is also a massive challenge. However, determining the value of lncRNAs by supplementary functional studies in animal models and human clinical trials may create a milestone in oncology in the near future.

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Conflicts of interest

There are no conflicts of interest.

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