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Long non-coding RNAs as diagnostic and prognostic biomarkers for colorectal cancer (Review)

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Abstract. Colorectal cancer (CRC) ranks as the 3rd most common cancer globally and is the 2nd leading cause of cancer-related death. Owing to the lack of specific early symptoms and the limitations of existing early diagnostic methods, most patients with CRC are diagnosed at advanced stages. To overcome these challenges, researchers have increasingly focused on molecular biomarkers, with particular interest in long non-coding RNAs (lncRNAs). These non-protein-coding RNAs, which exceed 200 nucleotides in length, play critical roles in the development and progression of CRC. The stability and detectability of lncRNAs in the circulatory system make them promising candidate biomarkers. The analysis of circulating lncRNAs in peripheral blood represents a potential option for minimally invasive diagnostic tests based on liquid biopsy samples. The present review aimed to evaluate the efficacy of lncRNAs with altered expression levels in peripheral blood as diagnostic markers for CRC. Additionally, the clinical significance of lncRNAs as prognostic markers for this disease were summarized.

Contents

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1. Introduction

The incidence of colorectal cancer (CRC) in people aged ≥65 in high-income countries has declined since 2012. However, in people <55 years of age, the incidence has increased by 1-2% per year. The death rates in men and women decreased by 1.8% per year from 2012-2021, according to the latest report. Despite these improvements, CRC remains the 3rd most common type of cancer worldwide and the second leading cause of cancer-related deaths globally (1). The survival rate of patients with CRC is significantly influenced by the stage at which the tumor is detected, with an overall 5-year survival rate of ~65% (2). Common diagnostic methods for CRC include the fecal occult blood test (FOBT), the fecal immunochemical test (FIT), colonoscopy and computed tomography (CT) colonography. FOBT and FIT are non-invasive screening methods; the former detects hidden blood in the stool, whereas the latter detects human hemoglobin in the stool. However, neither method can reveal the exact location of the lesions, and they have relatively high false-positive and false-negative rates (3). Colonoscopy is the gold standard for diagnosing CRC, providing direct visualization and allowing for pathological analysis. Although highly accurate, it is invasive, expensive, and requires bowel preparation and anesthesia, which poses some risks (4). CT colonography generates a 3D image of the colon via CT scans. Although it is non-invasive, its resolution and detection sensitivity have limitations (5). The diagnosis of CRC usually begins with a preliminary screening with the FOBT and FIT, followed by imaging tests such as CT scans and magnetic resonance imaging to assess the spread of the cancer. The most effective method of diagnosis is endoscopy, as the lesions can be directly observed through colonoscopy and the cancer can be confirmed by biopsy (6-8). CRC is classified into 4 stages on the basis of the TNM system as follows: i) Stage I, the cancer is confined to the intestinal wall and has not spread to the lymph nodes or beyond; ii) stage II, cancer invades deeper into the intestinal wall or adjacent structures but does not spread far; iii) Stage III, cancer spreads to regional lymph nodes without distant metastasis; and iv) stage IV, the cancer has spread to a distant organ or site. 'Advanced' CRC usually refers to stages III and IV (9,10). Owing to the absence of distinct early-stage symptoms and limitations in early

diagnostic methods, most patients with CRC are diagnosed at an advanced stage. In total, ~50% of the patients with CRC develop metastases, with the liver being the primary metastatic site and the most frequent cause of death (11). Recurrence patterns differ by location: 20% of right-sided colon cancer recurrences exhibited peritoneal dissemination, 42% of left-sided colon cancer recurrences were liver metastases and 33% of rectal cancer recurrences were local (12). CRC is unique in that it can be prevented and cured through the early identification and removal of high-risk adenomas (13). Therefore, implementing early detection screening programs is crucial for reducing the incidence and mortality of this disease. Early detection increases the likelihood of successful treatment and improves patient health outcomes (14). Colonoscopy is a widely accepted and effective screening method for CRC detection, despite certain risks, such as bleeding during sampling or polyp removal, and other potential complications (15). In recent years, advanced molecular techniques have played a significant role in the early diagnosis and treatment of various cancers, including CRC, by revealing the genetic mechanisms underlying CRC (16). Understanding these molecular mechanisms is crucial for addressing colon cancer. Non-coding RNAs (ncRNAs) have been shown to be involved in the onset and progression of colon cancer (17,18). These ncRNAs, which are mostly not translated into proteins, play significant roles in various cellular and physiological processes (19). Long non-coding RNAs (lncRNAs), which are longer than 200 nucleotides, participate in numerous biological processes, including cell proliferation, differentiation, development, apoptosis and metastasis. They often act as competitive endogenous RNAs (ceRNAs) to regulate the expression of specific miRNAs, thereby targeting molecules downstream of these miRNAs (20). lncRNAs can interact with RNA, DNA and proteins to form RNA-RNA, RNA-DNA and RNA-protein complexes that regulate gene expression through by affecting transcription, mRNA stability and translation (21,22). Numerous studies suggest that lncRNAs are crucial in cancer-related biological processes, including apoptosis, cell proliferation, cell invasion and metastasis (23-25).

2. History of lncRNAs

In 1984, Pachnis *et al* (26) discovered the first eukaryotic lncRNA in mice and named it H19. This lncRNA was identified as a highly abundant fetal transcript in mice. Initially, scientists focused primarily on mRNAs, which encode proteins, whereas ncRNAs were dismissed 'noise' or 'byproducts'. However, as technology has advanced and research has progressed, it has become clear that ncRNAs play crucial roles in gene regulation, epigenetics and disease development. The research on lncRNAs can be traced back to a series of groundbreaking studies in the late 20th and early 21st centuries. In 2002, researchers identified a lncRNA associated with gene silencing on the X chromosome (27). Subsequently, Guttman *et al* (19) discovered HOTAIR, a lncRNA that significantly influences gene locus regulation. In 2009, Rinn *et al* (28) identified HOTTIP, a different lncRNA located in the HOX gene cluster, noting its crucial involvement in gene locus regulation. Additionally, lncRNAs have been reported to play essential roles in embryonic development (29). Previous studies have also highlighted the involvement of lncRNAs in tumor initiation and progression, sparking intense research into their roles in cancer (20,30,31).

3. lncRNA localization and related research techniques

lncRNAs can be found in the cytoplasm (32), nucleus (33), nucleolus (34) and other subcellular regions and vesicles (such as nucleoli and exosomes). The localization of these proteins is associated with their molecular functions (32,35). Certain sequence motifs in their primary sequences are associated with subcellular localization (36). Investigating the localization of lncRNAs is crucial for understanding their roles in gene regulation, disease development and cellular functions. Compared with mRNAs, a greater proportion of lncRNAs are localized in the nucleus. An analysis of the overall characteristics of lncRNAs and mRNAs revealed that lncRNA genes are less evolutionarily conserved, contain fewer exons, and are expressed at lower levels (37-41). Different polyadenylation signals within lncRNAs can also influence their subcellular localization. For example, the CCAT1 lncRNA gene produces two isoforms: The long isoform (CCAT1-L) is expressed in the nucleus and includes an internal polyadenylation site that corresponds to the 3' end of the short isoform (CCAT1-S), which is expressed in the cytoplasm (42). Nuclear lncRNAs can play a regulatory role in gene expression; for example, Xist RNA located on the X chromosome achieves X chromosome inactivation by silencing genes on the X chromosome (43). Numerous lncRNAs in the nucleus interact with chromatin modification complexes, affecting chromatin structure and gene expression; for example, HOTAIR binds to polycomb reactive complex 2 (PRC2), promoting the formation of H3K27me3 marks (29). NEAT1 is an lncRNA located in the nucleolus that plays an important role in paraspeckle formation and mRNA maturation (44). NEAT1 and MALAT1 are well-known nucleolar lncRNAs that play roles in maintaining nucleolar structure and RNA processing (45). Certain lncRNAs regulate mRNA stability and translation efficiency by binding to the target mRNAs in the cytoplasm. For instance, the lncRNA Linc-ROR protects mRNAs from degradation by binding to miRNAs, thereby influencing protein synthesis (46). Cytoplasmic lncRNAs can also act as molecular sponges, sequestering miRNAs and preventing them from binding to their target miRNAs. For example, the lncRNA PTENP1 regulates the expression of PTEN genes by binding to miRNAs, thus impacting the PI3K/Akt signaling pathway (47). H19, located on the cell membrane, is involved in the signal transduction process of the cell membrane, affecting cell proliferation and differentiation (48). Techniques for studying the localization of lncRNAs include *in situ* hybridization (49), RNA immunoprecipitation (50), RNA-seq (51), single-cell RNA sequencing (52) and fluorescence *in situ* hybridization-flow cytometry (53), among others.

4. Classification of lncRNAs

According to a genomic database [Ensembl Release 96 (April 2019); https://www.ensembl.org/info/website/archives/index.html?redirect=no], human lncRNAs are categorized into several types, including 3' overlapping ncRNA, antisense lncRNA, long interspersed ncRNA, retained intron, sense intronic, sense overlapping and macro lncRNAs. Intronic lncRNAs are

Table I. Classification of lncRNAs.

Category	Definition
3' overlapping lncRNA	lncRNA overlapping with the 3' end of coding genes
Antisense lncRNA	lncRNA overlapping with the antisense strand of coding genes, potentially influencing gene expression by forming double-stranded RNA structures with coding regions through complementary base pairing
Long interspersed ncRNA	lncRNA interspersed throughout the genome
Retained intron	lncRNA retained within intron regions
Sense intronic lncRNA	lncRNA located within the intron regions of protein-coding genes, transcribed from these intronic regions, but does not itself participate in encoding proteins
Sense overlapping lncRNA	lncRNA overlapping with the sense strand of protein-coding genes containing exons
Macro lncRNAs	Very long ncRNA
Intergenic lncRNA	lncRNA located between two coding genes, potentially playing a role in the regulation of genes in its region
Messenger lncRNA	lncRNA acting as a regulatory factor, involved in regulating the expression of specific genes
Structural lncRNA	lncRNA that may play an important role in the physical structure within cells or the chromosomal architecture within the nucleus

lncRNA, long non-coding RNA.

transcribed from the introns of protein-coding genes; however, they do not encode proteins themselves (54). Antisense lncRNAs overlap with the antisense strand of coding genes and can influence gene expression by forming double-stranded RNA structures with coding regions through complementary base pairing (55,56). Intergenic lncRNAs are located between two coding genes and may regulate the expression of nearby genes (26). Sense lncRNAs overlap with the sense strand of protein-coding genes containing exons (57). Messenger lncRNAs can act as regulatory factors involved in modulating the expression of specific genes (29). Structural lncRNAs may play crucial roles in regulating the physical structure of cells or the chromosomal architecture within the nucleus (58). The classifications of lncRNAs are shown in Table I.

5. Conservation of lncRNAs

Although lncRNAs are functionally important, most lncRNA sequences exhibit low conservation across different species, making it challenging to identify the same lncRNA in different species through sequence similarity. This low degree of conservation is considered to reflect the diversity and specificity of lncRNA functions, as well as their rapid evolution (41). Despite their low sequence conservation, some lncRNAs exhibit a degree of structural and functional conservation across different species. These lncRNAs may maintain similar three-dimensional structures or play roles in the same gene expression regulation pathways across species (58,59). Moreover, numerous lncRNAs exhibit strong species specificity; that is, they are expressed in certain species but not expressed in others. This species specificity suggests that lncRNAs may play specialized roles in the development and adaptation processes of specific species (41,60). The conservation level of lncRNA promoters is comparable to that of protein-coding genes (37,61).

6. lncRNAs as diagnostic biomarkers for CRC in the blood

Ease of acquisition and detectability are essential criteria for diagnostic biomarkers. For patients that may have early-stage CRC, the option of performing a colonoscopy to obtain tissue samples might be strongly resisted. A genome-wide analysis of lncRNA stability by Clark *et al* (62) revealed that most lncRNAs exhibit high stability, with some having a half-life exceeding 16 h. Additionally, lncRNAs demonstrate greater stability room temperature and greater tolerance to repeated freeze-thaw cycles, making them suitable for clinical applications.Given the long length of lncRNAs, stem-loop primers used for microRNA detection are unnecessary for lncRNA amplification (63). Therefore, biomarkers that can be detected in blood or other body fluids are ideal for broader clinical applications. Over the past decade, numerous studies have demonstrated that lncRNAs are stable in the bloodstream and possess diagnostic potential, making them promising candidates for non-invasive diagnostic tests in CRC (64-67). In certain situations, lncRNAs may not be detectable in blood. These circumstances include improper sample handling (such as insufficient centrifugation, repeated freeze-thaw cycles and prolonged exposure to room temperature), inadequate storage conditions (such as failing to promptly freeze samples or maintain them at appropriate temperatures), and the use of inappropriate anticoagulants (such as heparin), leading to lncRNA degradation. Additionally, insufficient technical sensitivity and specificity can result in undetectable lncRNA levels. Furthermore, the expression levels of lncRNAs can be influenced by the stage of disease, with early-stage diseases potentially having lncRNA levels below the detection limit (63,68,69). lncRNAs are present in various body fluids, such as blood and urine, because they can traverse cellular membranes. This characteristic allows their detection in non-invasive diagnostic tests (70). lncRNAs

Table II. Studies on lncRNAs in blood as diagnostic biomarkers for CRC.

First author, year	Biomarker	Sample type	Diagnostic (AUC)	Potential clinical diagnosis implication	Number of cases (cancer vs. control)	(Refs.)
Dong *et al*, 2016	MAGEA3 and BCAR4 combination	Serum	Combination: 0.936	Distinguish patients with CRC from health controls	76 vs. 76	(64)
Zhao *et al*, 2015	CCAT1, HOATIR	Plasma	CCAT1: 0.836 HOTAIR: 0.777	Predict different CRC stage	32 vs. 32	(77)
Ye *et al*, 2022	LNCAROD, SNHG20, LINC00534, TSPOAP-AS1	Serum	LNCAROD: 0.74 SNHG20: 0.73 LINC00534: 0.73 TSPOAP-AS1: 0.63	Distinguish patients with CRC from health controls	105 vs. 105	(78)
Ye *et al*, 2023	LncGMDS-AS1	Plasma	0.7211	Distinguish between patients with CRC and those with gastrointestinal inflammation	97 vs. 91	(79)
Elabd *et al*, 2022	ASB16-AS1 AFAP1-AS1	Plasma	Plasma, ASB16-AS1: 0.974 Plasma, AFAP1-AS1: 0.965	Distinguish between patients with early CRC and those with colonic lesions	47 vs. 50	(80)
Barbagallo *et al*, 2018	circHIPK3, UCA1	Serum	circHIPK3: 0.771 UCA1: 0.719	Distinguish patients with CRC from health controls	20 vs. 20	(84)
Abd El Fattah *et al*, 2023	CCDC144NL-AS1	Serum	0.994	Predict different CRC stage	60 vs. 30	(85)
Long *et al*, 2024	circRHBDD1	Serum	0.76	Distinguish patients with CRC from health controls	24 vs. 24	(86)
Dai *et al*, 2022	EGFR-AS1	Plasma	0.938	Distinguish patients with CRC from health controls	128 vs. 64	(87)
Gong *et al*, 2017	lncRNA-HIF1A-AS1	Serum	0.96	Distinguish patients with CRC from health controls	151 vs. 160	(88)
Graham *et al*, 2011	CRNDE-h	Serum	0.888	Distinguish patients with CRC from health controls	15 vs. 15	(89)
Li *et al*, 2017	MEG3	Serum	0.784	To distinguish between those who respond to oxaliplatin treatment and those who do not	70 vs. 70	(90)
Liu *et al*, 2019	GAS5, PVT-1, MEG3, 91H, CCAT1-L	Plasma	GAS5: 0.642 PVT-1: 0.786 MEG3: 0.819 91H: 0.870 CCAT1-L: 0.748	Distinguish patients with CRC from health controls	58 vs. 56	(91)

Table II. Continued.

First author, year	Biomarker	Sample type	Diagnostic (AUC)	Potential clinical diagnosis implication	Number of cases (cancer vs. control)	(Refs.)
Liu *et al*, 2016	CRNDE-h	Serum (exoso-mal)	0.892	Distinguish patients with CRC from health controls	104 vs. 44	(92)
Dong *et al*, 2022	ARST	Plasma	0.934	Separated patients with CRC from patients with CP, patients with colitis and patients with hemorrhoids	60 vs. 60	(93)
Zhang *et al*, 2023	CACClnc	Plasma	0.846	Predict the chemotherapy effect of patients before treatment	59 vs. 22	(94)
El-Sheikh *et al*, 2023	NNT-AS1	Serum	0.964	Distinguish patients with CRC from health controls	60 vs. 28	(95)
Dai *et al*, 2017	BLACAT1	Serum	0.858	Distinguish patients with CRC from those without	30 vs. 30	(96)
Shaker *et al*, 2017	HULC, CCAT2	Serum	HULC: 0.72 CCAT2: 0.73	Distinguish patients with CRC from health controls	120 vs. 96	(97)
Shi *et al*, 2015	XLOC_006844, LOC152578, XLOC_000303	Plasma	XLOC_006844: 0.783 LOC152578: 0.783 XLOC_000303: 0.891	Distinguish patients with CRC from health controls	220 vs. 180	(98)
Bakr *et al*, 2023	TERC	Serum	0.982	Distinguish patients with CRC from cancer-free controls	70 vs. 35	(99)
Salman *et al*, 2023	ZFAS1	Serum	0.95	Predict different CRC stage	60 vs. 28	(100)
Lin *et al*, 2022	circALG1	Blood	0.676	Distinguish patients with CRC from health controls	20 vs. 15	(101)
Shen *et al*, 2022	Linc01836	Serum	0.809	Distinguish patients with CRC from health controls	137 vs. 138	(102)
Wan *et al*, 2016	HOTAIRM1	Plasma	0.780	Distinguish patients with CRC from health controls	100 vs. 67	(103)
Wang *et al*, 2016	RP11-462C24.1, LOC285194 and Nbla12061 combination	Serum	Combination:0.793	Distinguish patients with CRC from health controls	30 vs. 31	(104)
Wang *et al*, 2018	NORAD	Serum	0.8	Distinguishing CRC from benign diseases	142 vs. 136	(105)

Table II. Continued.

First author, year	Biomarker	Sample type	Diagnostic (AUC)	Potential clinical diagnosis implication	Number of cases (cancer vs. control)	(Refs.)
Wang *et al*, 2016	BANCR, NR_026817, NR_029373, NR_03411	Serum	BANCR: 0.638 NR_026817: 0.708 NR_029373: 0.812 NR_03411: 0.724	Distinguish patients with CRC from health controls	120 vs. 120	(106)
Wu *et al*, 2015	NEAT1	Blood	NEAT1_v1: 0.787 NEAT1_v2:0.871	Distinguish patients with CRC from health controls	100 vs. 100	(107)
Ye *et al*, 2016	lnc-GNAT1-1	Serum	lnc-GNAT1-1: 0.720	Distinguish patients with CRC from health controls	62 vs. 37	(108)

CRC, colorectal cancer.

in body fluids directly reflect the expression levels of certain genes and can distinguish between patients with cancer and healthy individuals (71). Additionally, a key feature of circulating lncRNAs is their ability to resist degradation by RNase enzymes (68,72). Apoptotic bodies, microvesicles and exosomes are vesicles encapsulated by a phospholipid bilayer containing DNA, RNA, lipids, proteins, polysaccharides and metabolites. These vesicles are released into the human circulatory system to facilitate the transfer of materials between cells (73-75). Owing to its notable sensitivity and specificity, reverse transcription-quantitative PCR is frequently employed to detect circulating lncRNAs (76). CCAT1 and HOTAIR were the first lncRNA markers reported to be present at significantly higher levels in the plasma of patients with CRC than in that of healthy individuals (77). lncRNAs also exhibit CRC specificity, which is reflected mainly in the difference in the expression of certain lncRNAs in the blood of patients with CRC compared with healthy individuals or those with other gastrointestinal diseases (78-80). Furthermore, these lncRNAs may be involved in key biological processes such as cell proliferation, invasion and metastasis in CRC. These findings not only contribute to understanding the molecular mechanisms of CRC but also provide new potential targets for the clinical diagnosis of CRC (81-83). Numerous other circulating lncRNAs have also been identified as potential biomarkers for detecting CRC (Table II) (64,77-79,80,84-108).

7. lncRNAs as prognostic biomarkers for CRC

lncRNAs can serve as diagnostic markers for CRC, and changes in their expression can also predict patient prognosis. lncRNAs play multifaceted roles in CRC, impacting various biological processes, including cell cycle control, cell proliferation, epithelial-mesenchymal transition, migration, invasion, drug resistance, apoptosis and cellular stemness (109). These processes influence the malignancy of the tumor and ultimately affect patient prognosis. This section summarizes lncRNAs related to the prognosis of CRC and highlights their associated regulatory signaling pathways, enhancing our understanding of their mechanistic impact on the pathophysiology of CRC (Table III) (79,81-83,110-158).

8. Conclusions

CRC poses significant global health challenges and is characterized by high mortality rates, particularly when it is diagnosed at advanced stages. Improving treatment success and patient survival hinges on the development of reliable early detection biomarkers. In recent years, researchers have increasingly explored the potential of lncRNAs as non-invasive molecular biomarkers in CRC.

lncRNAs exhibit diverse functions in CRC, influencing processes such as cell cycle regulation, proliferation, apoptosis and metastasis. By acting as ceRNAs, they modulate the expression of specific miRNAs and downstream targets while also exerting control over gene expression through mechanisms such as transcriptional regulation, mRNA stability and translation. Interactions with RNA, DNA and proteins enable lncRNAs to form complex regulatory networks that impact CRC initiation and progression.

Table III. Studies on lncRNAs as prognostic biomarkers for colorectal cancer.

First author, year	lncRNA	Sample	Prognostic indicator	Expression and prognostic role	Functions	Related regulatory axes	(Refs.)
Ye *et al*, 2023	LncGMDS-AS1	Tissue	OS DFS	Up-poor prognosis	Promotes proliferation and stemness	GMDS-AS1/HuR-STAT3/ Wnt	(79)
Yue *et al*, 2016	ATB	Tissue, cell line	OS DFS	Up-poor prognosis	Promotes invasion, induces EMT	E-cadherin	(81)
Wang *et al*, 2018	B3GALT5-AS1	Tissue	OS	Down-poor prognosis	Inhibits proliferation, promotes migration, inhibits invasion, induces EMT	B3GALT5-AS1/miR-203/EMT	(82)
He *et al*, 2014	CCAT1	Tissue	OS	Up-poor prognosis	Promotes proliferation and invasion	c-Myc/CCAT1	(83)
Zhang *et al*, 2022	CCDC144NL-AS1	Tissue, cell line	OS DFS	Up-poor prognosis	Promotes proliferation and cell cycle	CCDC144NL-AS1/miR-363-3p/GALNT7	(110)
Li *et al*, 2023	CCL14-AS	Tissue	OS	Down-poor prognosis	Inhibits migration and invaion	CCL14-AS/MEP1A	(111)
Yue *et al*, 2018	CYTOR	Cell line	OS	Up-poor prognosis	Promotes migration, invasion and EMT	CYTOR/β-catenin/TCF complex	(112)
Li *et al*, 2023	DICER1-AS1	Tissue	OS DFS	Up-poor prognosis	Promotes proliferation, migration and invasion	DICER1-AS1/miR-650/ MAPK/ERK	(113)
Wang *et al*, 2022	ENST00000543604	Tissue	OS	Up-poor prognosis	Promotes proliferation, migration and drug resistance	lncRNA 604/miRNA 564/ AEG-1/EMT or lncRNA 604/ ZNF326/EMT	(114)
Bin *et al*, 2021	EPB41L4A-AS1	Tissue	OS	Up-poor prognosis	Promotes proliferation, migration, invasion and EMT	EPB41L4A-AS1/Rho/Rh	(115)
Wu *et al*, 2018	FAL1	Tissue	OS	Up-poor prognosis	Promote proliferation, invasion and inhibits apoptosis	Bcl-2, TGF-β1,p65	(116)
Song *et al*, 2022	FAM222A-AS1	Tissue, cell line	OS DSS	Up-poor prognosis	Promote proliferation, migration and invasion	FAM222A-AS1/miR-let-7f/MYH9	(117)
Yang L *et al*, 2019	FAM83H-AS1	Tissue	OS	Up-poor prognosis	Promotes tumorigenesis	SMAD1/5/9, TGF-βsignaling	(118)
Yue B *et al*, 2015	FER1L4	Tissue	OS DFS	Down-poor prognosis	Inhibits proliferation, migration and invasion	FER1L4/miR-106a-5p	(119)
Yang X *et al*, 2023	FEZF1-AS1	Tissue	OS	Up-poor prognosis	Promote proliferation, migration and invasion	FEZF1-AS1/miR-92b-3p/ZIC5	(120)

Table III. Continued.

First author, year	lncRNA	Sample	Prognostic indicator	Expression and prognostic role	Functions	Related regulatory axes	(Refs.)
Han *et al*, 2021	FLVCR1_x005f_x001e_AS1	Tissue, cell line	OS	Up-poor prognosis	Enhances vitality, promotes migration and invasion	FLVCR1-AS1/miR-381/RAP2A	(121)
Chen *et al*, 2022	GAS6-AS1	Cell line	OS	Up-poor prognosis	Promote proliferation, migration, invasion and EMT	GAS6-AS1/TRIM14	(122)
Fang *et al*, 2017	HNF1A-AS1	Tissue	OS DSS	Up-poor prognosis	Enhances vitality, promotes migration, invasion and xenotransplantation	HNF1A-AS1/miR-34a/SIRT1/p53	(123)
Huang *et al*, 2021	HOTAIR	Tissue	OS	Up-poor prognosis	Promotes stemness	HOTAIR/miR-211-5p/FLT-1	(124)
Wu *et al*, 2014	HOTAIR	Tissue	MFS OS	Up-poor prognosis	Promotes EMT	Vimentin, MMP9, E-cadherin	(125)
Zhang *et al*, 2022	HOXC-AS3	Tissue	OS	Down-poor prognosis	Inhibits migration and invasion	HOXC-AS3/miR-1269/TGF-β2	(126)
Fang *et al*, 2022	LBX2-AS1	Tissue	MFS OS	Up-poor prognosis	Promote growth, proliferation, migration and inhibits invasion	LBX2-AS1/miR-627-5p/RAC1/PI3K/AKT	(127)
Liang *et al*, 2023	LINC00174	Tissue, cell line	OS DFS	Up-poor prognosis	Promote proliferation, migration, invasion and inhibits apoptosis	LINC00174/miR-2467-3p/USP21	(128)
Guo *et al*, 2024	Linc00239	Tissue	OS DFS	Up-poor prognosis	Promotes proliferation, migration and invasion	linc00239/miR-182-5p/MTDH	(129)
Li *et al*, 2021	LINC00485	Tissue, cell line	OS	Down-poor prognosis	Inhibits proliferation, migration and invasion	LINC00485/miR-581/EDEM1	(130)
Zheng *et al*, 2023	LINC00543	Tissue	OS	Up-poor prognosis	Promotes EMT and migration	LINC00543/pre-miR-506-3p/FOXQ1	(131)
Ren *et al*, 2023	LINC00955	Tissue	OS	Down-poor prognosis	Promotes growth	TRIM25/Sp1/DNMT3B/PHIP/CDK2	(132)
Liang *et al*, 2021	LINC00958	Tissue, cell line	OS DFS	Up-poor prognosis	Promotes proliferation, drug resistance and growth and inhibits apoptosis	LINC00958/miR-422a/MAPK1	(133)
Wu *et al*, 2022	LINC01021	Tissue, cell line	OS DFS	Up-poor prognosis	Promotes proliferation, colony formation, migration and inhibits apoptosis	LINC021/IMP2/MSX1/JARID2	(134)

Table III. Continued.

First author, year	lncRNA	Sample	Prognostic indicator	Expression and prognostic role	Functions	Related regulatory axes	(Refs.)
Zhang *et al*, 2022	LINC01094	Tissue, cell line	OS PFS	Up-poor prognosis	Promotes proliferation, migration and invasion	LINC01094/miR-1266-5p	(135)
Fu *et al*, 2021	LINC01287	Tissue	OS	Up-poor prognosis	Promotes proliferation, migration, invasion and EMT	LINC01287/miR-4500/ MAP3K13	(136)
Li *et al*, 2022	LINC01436	Tissue	OS	Up-poor prognosis	Promotes proliferation	LINC01436/miR-466	(137)
Liu *et al*, 2020	Linc01578	Tissue	OS DSS	Up-poor prognosis	Enhances metastasis	NF-κB, YY1	(138)
Luo *et al*, 2022	LINC01606	Tissue	OS DFS	Up-poor prognosis	Promote growth, invasion and stemness	LINC01606/miR-423-5p	(139)
Xu *et al*, 2024	LINC01836	Tissue, cell line	OS	Up-poor prognosis	Promote proliferation, migration and invasion	LINC01836/miR-1226-3p/ SLC17A9	(140)
Tian *et al*, 2020	Linc02418	Tissue	OS	Up-poor prognosis	Promotes proliferation, migration invasion and development	LINC02418/miR-34b-5p/BCL2	(141)
Zhou *et al*, 2022	MHENCR	Tissue	OS	Up-poor prognosis	Promotes proliferation, migration and invasion	MHENCR/miR-532-3p	(142)
Zhou *et al*, 2022	MIR155HG	Tissue	OS	Up-poor prognosis	Promotes proliferation, migration invasion and drug resistance	MIR155HG/miR-650/ANXA2	(143)
Guo *et al*, 2021	MIR31HG	Tissue	OS	Up-poor prognosis	Promotes proliferation, growth, invasion, migration and angiogenesis	MIR31HG/miR-361-3p/YY1	(144)
Sun *et al*, 2022	MNX1-AS1	Tissue, cell line	OS	Up-poor prognosis	Promotes stemness, proliferation and migration and inhibits invasion	MNX1-AS1/PFIA4/AKT/ HIF-1α	(145)
Liu *et al*, 2023	PROX1-AS1	Tissue, cell line	OS DSS	Up-poor prognosis	Promotes proliferation, migration and invasion	PROX1-AS1/miR-326/ FBXL20	(146)
Yin *et al*, 2023	PVT1	Cell line	OS	Up-poor prognosis	Promotes proliferation and migration	PVT1/miR-24-3p/NRP1	(147)
Zhou *et al*, 2016	ROR	Tissue, cell line	OS DFS	Up-poor prognosis	Promotes proliferation, migration and invasion	lincRNA-ROR/miR-145	(148)
Pu *et al*, 2022	SKAP1	Tissue, cell line	OS DFS	Up-poor prognosis	Promotes proliferation, migration and invasion	THUMPD3-AS1/miR-218-5p/ SKAP	(149)

Table III. Continued.

First author, year	lncRNA	Sample	Prognostic indicator	Expression and prognostic role	Functions	Related regulatory axes	(Refs.)
Zhang *et al*, 2022	SLCO4A1-AS1	Tissue	OS DFS	Up-poor prognosis	Promotes growth	SLCO4A1-AS1/Hsp90/Cdk2/c-Myc	(150)
Jiang *et al*, 2018	SNHG15	Cell line	OS	Up-poor prognosis	Promotes proliferation and migration	Slug	(151)
Xiang *et al*, 2022	SNHG16	Cell line	OS PFS	Up-poor prognosis	Promotes colony formation, proliferation, migration, invasion and EMT	SNHG16/YAP1/TEAD1	(152)
Bian *et al*, 2021	SNHG17	Tissue	OS DFS	Up-poor prognosis	Promotes proliferation and migration	SNHG17/miR-339-5p/FOSL2	(153)
Zhao *et al*, 2023	SOX9-4	Tissue, cell line	OS	Up-poor prognosis	Promotes proliferation and migration	Lnc-SOX9-4/YBX1	(154)
Fang *et al*, 2022	SPINT1-AS1	Cell line	OS	Up-poor prognosis	Promotes proliferation and migration and inhibits apoptosis	SPINT1-AS1/miR-214/HDGF	(155)
Zhou *et al*, 2022	STEAP3-AS1	Tissue	OS	Up-poor prognosis	Promotes proliferation and migration	STEAP3-AS1/STEAP3/Wnt/β-catenin	(156)
Li *et al*, 2022	USP30-AS1	Tissue	OS	Down-poor prognosis	Inhibits development	USP30-AS1/miR-765	(157)
Ma *et al*, 2022	XLOC_006390	Tissue, cell line	OS	Up-poor prognosis	Inhibits apoptosis, promotes migration and invasion	XLOC_006390/miR-296/ONECUT2	(158)

lncRNA, long non-coding RNA; OS, overall survival; DFS, disease-free survival; EMT, epithelial to mesenchymal transition; DSS, disease-specific survival; MFS, metastatic-free survival.

Owing to their stability in blood and potential for early detection, lncRNAs represent promising non-invasive biomarkers for CRC. Research highlights their pivotal roles in regulating pathological processes associated with CRC, including the modulation of cancer cell aggressiveness and metastatic potential through specific regulatory axes.

In conclusion, the study of lncRNAs offers novel insights into the molecular mechanisms of CRC and has potential to guide the development of innovative diagnostic and therapeutic approaches. Further investigations are essential for delineating their precise functions in CRC and exploring their clinical applications with the ultimate goals of increasing treatment efficacy and improving survival outcomes for patients with CRC.

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Availability of data and materials

Not applicable.

Authors' contributions

YuL designed and supervised the study, collected and analyzed data, wrote and revised the manuscript, acquired funding, performed project administration and guidance. WZ, RP, ZL, HX and YiL collected data and revised the manuscript. ZZ conducted project administration, supervised the study and provided guidance, wrote and revised the manuscript and participated in data collection and organisation. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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