



## A Review of Novel and Significant Long Non-Coding RNAs (LncRNAs) in Colorectal Cancer Progress

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### Abstract

Colorectal cancer (CRC) is the third most prevalent cancer worldwide and represents a significant public health concern. Given its complexity, further research is needed to elucidate the role of signaling pathways, particularly those involving long non-coding RNAs (LncRNAs). LncRNAs, which are non-coding RNAs exceeding 200 nucleotides in length, are transcribed by RNA polymerase II and play a crucial role in gene regulation. Altered expression of LncRNAs has been implicated in multiple diseases, including CRC, where they affect key cellular signaling pathways. In this regard, the upregulation of *C6ORF176*, *CASC9er35e*, *ESCCAL-1*, *FBXL19-AS1*, *FGD5-AS1*, *FOXD3-AS1*, *LBX2-AntisenseRNA1*, *SLCO4A1-AS1*, and *HOTAIRMI*, as well as the downregulation of *RP11-462C24.1* and *RPL34-AS1*, has been linked to CRC progression. The urgency of CRC screening is underscored by its increasing incidence, with 14% of cases diagnosed in individuals under 50 years of age in 2021 and 40–45% of cases reported in adults in 2020 and in 2022, according to the Global Cancer Observatory (GLOBOCAN), there has been 1.14 million new diagnosed colon cancer and this number is projected to reach 1.99 million by 2050. Moreover, the annual global incidence surpasses 1.9 million new cases, particularly in Europe, Oceania, and North America. The development and spread of CRC may be mitigated by targeting key pathways such as cAMP/CREB, AKT/mTOR/EMT, Wnt/ $\beta$ -catenin, and nuclear factor (NF)- $\kappa$ B. In this review, we provide a comprehensive summary of novel LncRNAs associated with CRC, focusing on those that have been relatively underexplored. Our findings highlight their potential as both therapeutic targets and research tools, contributing to selective treatment strategies and further investigations aimed at expanding our understanding of CRC pathogenesis.

**Keywords:** Colorectal cancer, Long non-coding RNAs (LncRNA), Oncogenesis, Biomarkers

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### Introduction

Colorectal cancer (CRC), one of the three most prevalent cancers worldwide, has emerged as a major public health concern. In 2018, more

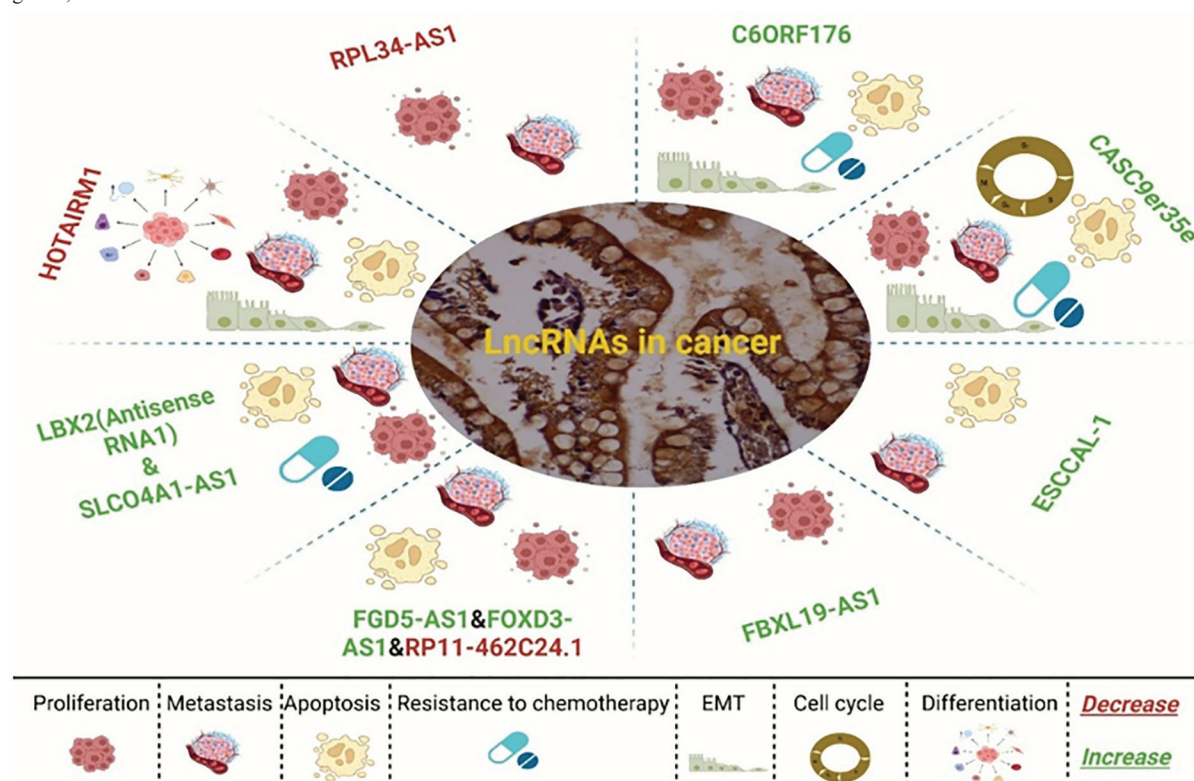
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than 1.8 million individuals were diagnosed with CRC globally, with approximately 150,000 new cases reported that year (1). Consequently, CRC remains one of the most common malignancies and a leading cause of cancer-related mortality in Western industrialized nations (1, 2).

Current treatment strategies for CRC involve a combination of surgical resection, chemotherapy,





Graphical Abstract

radiotherapy, and immunomodulatory therapy. However, nearly 40% of CRC patients eventually experience disease recurrence or late-stage metastasis, reducing the five-year survival rate to less than 15%. Moreover, these treatments are often accompanied by adverse side effects and the emergence of drug resistance (1).

In 2020, CRC accounted for 10% of all cancer diagnoses and 9.4% of cancer-related deaths worldwide, second only to lung cancer, which was responsible for 18% of cancer deaths. By 2040, the number of new CRC cases is projected to reach 3.2 million, with an estimated 1.6 million deaths, based on aging populations, demographic growth, and global development trends (2).

A strong familial component has been identified in CRC, with a high incidence among patients with a family history of the disease. Approximately 25% of CRC patients have been found to have a genetic predisposition (3).

According to the World Health Organization's (WHO) classification of gastrointestinal (GI) tumors, several risk factors contribute to CRC development, including a sedentary lifestyle, obesity, high body mass index (BMI), abdominal fat accumulation, hormone replacement therapy, smoking, alcohol consumption, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) (3).

Chemotherapy resistance in CRC has been linked to epithelial-to-mesenchymal transition (EMT) and enhanced DNA damage repair mechanisms. These processes are influenced by the interplay between *N6-methyladenosine (m6A) modification*—which affects RNA translation, transport, stability, and degradation—and long non-coding RNAs (lncRNAs) (4). The main lncRNAs that are upregulated in CRC include Colon Cancer Associated Transcript 1 (CCAT1), Plasmacytoma variant translocation 1 (PVT-1), Colorectal Neoplasia Differentially



Expressed (CRNDE), Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1), ZNFx1 antisense RNA 1 (ZFAS1), MYC-induced lncRNAs (MYCLO-1, MYCLO-2, MYCLO-3), Antisense noncoding RNA in the INK4 locus (ANRIL), urothelial carcinoma-associated 1 (UCA1) and major lncRNAs that are downregulated in CRC include lncRNA-CTD903, lncRNA TINCR, lncRNA-p21, Loc554202, etc (3). The aim of this study was an overview of lncRNAs association with CRC progress.

### Risk Factors

#### Sex and Age

The risk of CRC increases with age and is higher in men than in women, likely due to the protective effects of estrogen, greater vegetable and fiber intake, and lower alcohol consumption among women (5–8). In recent years, CRC incidence has risen among individuals under 50, a trend attributed to sedentary lifestyles, Western dietary patterns, and genetic predisposition (5, 9).

#### Sedentary Lifestyle

Physical inactivity contributes to fat accumulation and metabolic dysfunction, both of which are associated with an increased risk of CRC (10). Engaging in regular exercise, even once a week, has been shown to reduce CRC risk by 20%, as it promotes bowel motility, regulates metabolic hormones, enhances oxygenation and basal metabolism, and strengthens anti-tumor immune responses through mechanisms involving natural killer (NK) cells, CD8+ T cells, and interleukin (IL)-6 (11–15).

#### Smoking

Smoking is a well-established risk factor for CRC, as it induces both genetic and epigenetic alterations that contribute to carcinogenesis (16).

#### Alcohol Consumption

CRC risk increases in a dose-dependent manner with alcohol consumption (17). Acetaldehyde, the primary metabolite of ethanol, damages the intestinal mucosa, stimulates abnormal cell proliferation, induces DNA damage, and reduces folate absorption—a crucial

factor in DNA synthesis and methylation (18–21).

### Epidemiology of the CRC

A notable rise in CRC incidence, particularly in colon cancer cases compared to rectal cancer, was first observed among individuals born in the 1970s (22). According to GLOBOCAN data (<https://gco.iarc.who.int/en>), CRC ranks third in global cancer incidence and second in cancer-related mortality. In the United States alone, more than 140,000 new cases of CRC were diagnosed in 2021, with 14% occurring in individuals under the age of 50. This trend, referred to as early-onset CRC, mirrors data from previous decades, reflecting a 9% increase between 1995 and 2019, with a continued rise observed from 2011 to 2020 (23, 24).

Countries with the highest age-standardized CRC incidence rates in 2020 included:

- Hungary: 45.3 cases per 100,000
- Slovakia: 43.9 cases per 100,000
- Norway: 41.9 cases per 100,000
- Netherlands: 41.0 cases per 100,000
- Denmark: 40.9 cases per 100,000

Additionally, the Russian Federation, Brazil, Germany, India, the United Kingdom, France, and Italy reported some of the highest overall CRC incidence rates in 2020.

Conversely, countries with the lowest age-standardized CRC incidence rates included:

- Guinea: 3.3 cases per 100,000
- Gambia: 3.7 cases per 100,000
- Bhutan: 3.8 cases per 100,000
- Bangladesh: 3.8 cases per 100,000
- Burkina Faso: 3.8 cases per 100,000 (2)

The stark differences in CRC prevalence across regions may be attributed to several factors, including variations in dietary habits (particularly adherence to a Western diet), levels of physical activity, age distribution, genetic predisposition, and sex-specific risk factors within each population.

### lncRNAs in CRC

lncRNAs are RNA transcripts exceeding 200 nucleotides in length that do not encode proteins.





As functional molecules, they play critical roles in various cellular processes. LncRNAs are known to regulate key biological functions, including the cell cycle, differentiation, metabolism, disease progression, viral infections, transcription, epigenetic modifications, protein-RNA stability, translation, and post-translational modifications. Furthermore, LncRNAs have been shown to directly interact with signaling receptors, influencing various intracellular pathways.

Similar to messenger RNAs (mRNAs), most LncRNAs are transcribed by RNA polymerase II (Pol II) and undergo capping and polyadenylation. However, a small subset of LncRNAs is inherently unstable. While polyadenylation stabilizes the majority of LncRNAs, some non-polyadenylated LncRNAs achieve stability through secondary structures, such as triple-helix formations at their 3' ends. The expression levels of LncRNAs are generally lower than those of mRNAs. Unlike mRNAs, which exhibit a high degree of sequence conservation across species, LncRNAs typically lack this feature (25).

The dysregulated expression of microRNAs (miRNAs) and LncRNAs has been proposed as a potential prognostic and diagnostic biomarker in various cancers, including CRC (26). There is growing evidence of a relationship between autophagy—the process of degrading and recycling cellular components—and LncRNAs in CRC. By targeting specific LncRNAs involved in autophagy and tumor progression, it may be possible to inhibit metastasis and reduce drug resistance in CRC (27).

Notably, LncRNAs exhibit resistance to degradation by RNase, which contributes to their high stability and extended half-life—some lasting up to 16 hours. Additionally, they demonstrate considerable resistance to repeated freezing and thawing, making them suitable for experimental and clinical applications (28-30). To complement this review, we conducted a literature search using Google Scholar and PubMed, employing relevant keywords and

LncRNA-related terms.

This review aims to introduce novel and highly significant LncRNAs that hold promise for future CRC research. By expanding our understanding of their pathways and molecular functions, these LncRNAs may serve as valuable targets for further investigation. Unlike previous studies, which have either focused on a single LncRNA or provided broad overviews of known LncRNAs, this review specifically highlights newly identified and clinically relevant LncRNAs. Furthermore, it presents the most up-to-date mechanisms and pathways associated with these molecules up to 2024, offering a foundation for future research directions (Table 1).

### **C6ORF176 (LINC00473)**

C6ORF176 (*Chromosome 6 Open Reading Frame 176*), also known as LINC00473 (LNC473), encodes an 1832-bp intergenic long non-coding RNA (LncRNA) (31). The cAMP-induced activation of the C6ORF176 gene locus serves as a valuable model for studying transcriptional regulation by chromatin and RNA polymerase II.

C6ORF176 plays a pivotal role in human ocular ciliary smooth muscle (HCSM) cells, particularly within the cAMP signaling pathway. Following treatment with EP2 (AGN007) and EP4 (AGN008) agonists, C6ORF176 was identified as one of the most highly upregulated genes in these cells. Additionally, C6ORF176 participates in epigenetic regulation, similar to the 2.2-kb LncRNA *HOX transcript antisense RNA (HOTAIR)* (32).

C6ORF176 also promotes the EMT process (31) and is frequently upregulated in multiple cancers, facilitating tumor growth and metastasis. However, its precise role in chemotherapy resistance remains unclear. In CRC, the tumor suppressor miR-15a is significantly downregulated and negatively correlated with LINC00473 expression levels. LINC00473 contains a binding site for miR-15a, reducing its availability in HCT116 CRC cells. Moreover, LINC00473 knockdown leads to increased miR-15a expression.



Table 1. Novel CRC LncRNAs

LncRNA	Pathway	Expression	Functions	Reference
C6ORF176	cAMP/CREB, APAF1-CASP9-CASP3	↑	Proliferation, metastasis, apoptosis, resistance to chemotherapy, EMT	(31, 33, 36)
CASC9er35e	AKT/mTOR/EMT	↑	Proliferation, metastasis, apoptosis, resistance to chemotherapy, EMT, Cell cycle	(40, 42, 121, 122)
ESCCAL-1	Src/FAK/JNK	↑	Metastasis, apoptosis	(51)
FBXL19-AS1	AKT/VEGFA	↑	Proliferation, metastasis	(58)
FGD5-AS1	wnt/ $\beta$ -catenin	↑	Proliferation, metastasis, apoptosis	(123)
FOXD3-AS1	NF- $\kappa$ B	↑	Proliferation, metastasis, apoptosis, Cell cycle	(71)
LBX2AntisenseRNA1	miR-627-5p/RAC1/PI3K/AKT	↑	Proliferation, metastasis, apoptosis, resistance to chemotherapy	(124, 125)
SLCO4A1-AS1	Cdk2/c-Myc, EGFR/MAPK, Wnt/ $\beta$ -catenin	↑	Proliferation, metastasis, apoptosis, resistance to chemotherapy	(109)
HOTAIRM1	miR-17-5p/BTG3	↓	EMT, Proliferation, metastasis, apoptosis, EMT, distinction	(109)
RP11-462C24.1	PI3K/AKT	↓	Proliferation, metastasis, apoptosis	(126)
RPL34-AS1	MDM2-P53	↓	Proliferation, metastasis	(100, 127)

CASC: Cancer Susceptibility Candidate, ESCCAL: Esophageal Squamous Cell Carcinoma-Associated Long Non-Coding RNA, FBXL19-as1: F-Box and Leucine-Rich Repeat Protein 19 Antisense RNA 1, SLCO: Organic anion transporter, HOTAIRM1: HOX Antisense Intergenic Myeloid RNA 1, RPL: Ribosomal protein L

Overall, LINC00473 functions as an oncogene in CRC, influencing tumor proliferation and chemotherapy resistance through the miR-15a/cAMP/CREB signaling axis (33). Elevated LINC00473 expression is associated with poor prognosis in lung cancer patients, while in cervical cancer, *miR-34a* targets and destabilizes LINC00473, leading to interleukin-enhancer-binding factor 2 (*ILF2*) degradation and tumor inhibition (33).

Additionally, LINC00473 has been identified as the most dysregulated LncRNA in invasive pituitary adenoma (IPA), acting through the LINC00473/miR-502-3p/KMT5A signaling pathway, which regulates the cell cycle (34). Furthermore, LINC00473 accelerates apoptosis by activating the APAF1-CASP9-CASP3 pathway.

Recent studies have also detected C6ORF176 expression in hepatocellular carcinoma (HCC), non-small cell lung cancer (NSCLC), cervical cancer, and Wilms tumor (31). Notably, LINC00473 levels are significantly higher in CRC

patients with metastasis, contributing to enhanced proliferation, cell cycle progression, and invasion. However, miR-195 has been shown to effectively suppress these oncogenic effects (35, 36).

Moreover, LINC00473 methylation levels in advanced colorectal polyps and CRC significantly differ from those in healthy individuals (37). Another LncRNA, SURC (*specific upregulated LncRNA in CRC*), has been identified as a key CRC-related LncRNA, acting through the SURC/*miR-185-5p/CCND2 axis* (38). Additionally, the transcription factor forkhead box protein O1 (*FOXO1*) has been shown to increase miR-502-5p levels, which in turn represses cyclin-dependent kinase 6 (CDK6), thereby inhibiting CRC cell growth (39).

### Cancer Susceptibility Candidate 9

Cancer Susceptibility Candidate 9 (CASC9) is a recently discovered LncRNA comprising four transcript variants: CASC9-201, CASC9-202, CASC9-203, and CASC9-204 (40). Upregulated CASC9 expression is closely associated with



advanced tumor-node metastasis (TNM) stage and poor CRC prognosis. Quantitative polymerase chain reaction (RT-qPCR) analysis has confirmed CASC9 expression in four CRC cell lines (DLD, HT-29, SW480, and HCT-116), as well as in the normal colon cell line CCD-112CoN. Pathway analysis has revealed that CASC9 silencing induces autophagy, promotes AMP-activated protein kinase (AMPK) phosphorylation, and inhibits both mTOR and AKT signaling pathways. Additionally, CASC9 knockdown alters EMT marker expression, thereby reducing CRC cell proliferation and migration (40).

CASC9 exerts its oncogenic effects through SMAD3 phosphorylation and TGF- $\beta$  signaling. Its silencing has been shown to modulate EMT—a critical step in cancer metastasis—by upregulating the epithelial marker E-cadherin while downregulating the mesenchymal marker vimentin in HCT-116 and SW480 CRC cells (40). Furthermore, the CASC9/miR-576-5p/AKT3 axis has been identified as a key regulatory mechanism governing CRC cell proliferation and apoptosis. CPSF3, a protein significantly upregulated in CRC tissues, has been found to correlate positively with CASC9 and TGF $\beta$ 2 expression levels in CRC patients. Notably, CASC9 and CPSF3 form a functional complex, activating TGF- $\beta$  signaling via direct binding to TGF $\beta$ 2 mRNA (41).

CASC9 silencing has also been shown to downregulate AKT3 expression by reducing its competitive binding to miR-576-5p, thereby inhibiting CRC cell proliferation and promoting apoptosis. MiR-576-5p, a key suppressor of CRC metastasis, negatively regulates CASC9 expression by directly targeting its 3'-UTR (42). The ErbB receptor family activates cytoplasmic tyrosine kinase domains through homo- or heterodimerization. CASC9 indirectly modulates ERBB2 expression by downregulating miR-193a-5p levels. Overexpression of ERBB2 has been strongly implicated in breast cancer

(BC) and gastric cancer (GC) progression and is considered a critical biomarker and therapeutic target in these malignancies. Similarly, ERBB2 has emerged as a potential therapeutic target in CRC. MiR-193a-5p, which directly targets ERBB2, is negatively correlated with CASC9 levels in CRC cells. Thus, miR-193a-5p exerts a tumor-suppressive effect by inhibiting ERBB2-mediated oncogenic signaling (43). Additionally, CASC9-1, a recently identified LncRNA variant, has been shown to function as an oncogene in cervical squamous cell carcinoma (CSCC) via the CASC9-1/miR-383-5p/SIN1 signaling pathway (44).

### **Esophageal Squamous Cell Carcinoma (ESCC)-Associated LncRNA-1**

The *Esophageal Squamous Cell Carcinoma-Associated Long Non-Coding RNA 1* (ESCCAL\_1) was first identified in 2013 (45). ESCCAL\_1 is a long non-coding RNA (LncRNA) with oncogenic potential. The expression of ESCCAL\_1 is significantly increased in esophageal squamous cell carcinoma (ESCC), and the inhibition of ESCCAL\_1 expression has been shown to promote apoptosis and reduce invasion in ESCC cell lines (46). However, the precise molecular mechanisms through which ESCCAL\_1 influences tumor growth in vivo remain poorly understood. The downregulation of ESCCAL\_1 significantly reduces the levels of the anti-apoptotic protein Bcl-2 while increasing the expression of p53, BAX, and caspase-3, though it does not affect the expression of p21. Depletion of ESCCAL\_1 also suppresses tumor growth, potentially by inactivating the Src/FAK/JNK pathway. Specifically, ESCCAL\_1 reduces protein kinase activity, as evidenced by decreased levels of phosphorylated c-Jun N-terminal kinase (p-JNK), phosphorylated focal adhesion kinase (p-FAK), phosphorylated glycogen synthase kinase 3 $\beta$  (p-GSK3 $\beta$ ), and phosphorylated Src proteins (47).

ESCCAL\_1 interacts with miR-590 and restricts its expression. Functionally, the





knockdown of ESCCAL\_1 or the overexpression of miR-590 inhibits ESCC cell growth, invasion, and migration *in vitro*. Overexpression of miR-590 increases the levels of N-cadherin and Vimentin while decreasing the level of E-cadherin, thereby suggesting an inhibitory role of miR-590 in the EMT process and tumor progression (48). Additionally, the expression of ESCCAL\_1 and ITGBL1 (Integrin beta-like 1) is elevated in CRC tissues, whereas miR-874 levels are notably reduced. ESCCAL\_1 is known to promote CRC progression by regulating the miR-874/ITGBL1 axis (49). Furthermore, the ESCCAL\_1/miR-590/LRP6 pathway has been identified as a key contributor to the progression of ESCC. Notably, targeting LRP6 effectively inhibits the malignant phenotype of ESCC (50).

#### **FBXL19 Antisense RNA 1 = FBXL19-AS1**

The inhibition of *F-Box and Leucine-Rich Repeat Protein 19 Antisense RNA 1* (FBXL19-AS1) is associated with tumor-suppressive effects, including the inhibition of cell proliferation, migration, and invasion *in vitro* as well as the suppression of tumor growth and metastasis *in vivo*. FBXL19-AS1 acts as an oncogene in CRC and is significantly correlated with advanced tumor-node-metastasis (TNM) stages and lymph node metastasis (LNM) in CRC (51). The FBXL19-AS1/miR-203 regulatory pathway plays a pivotal role in CRC progression. Notably, the inhibition of miR-203 abrogates the effects of FBXL19-AS1 knockdown on LoVo cell proliferation and invasion. FBXL19-AS1 expression is markedly elevated in CRC tissues compared to adjacent non-tumor tissues, with higher expression levels observed in advanced-stage tumors. Consequently, upregulated FBXL19-AS1 has been strongly associated with cancer progression (51).

In recent years, the role of FBXL19-AS1 has also been investigated in breast cancer (52), hepatocellular carcinoma (53), and cervical cancer (54). FBXL19-AS1 promotes proliferation and metastasis by interacting with miR-718,

E-cadherin, and N-cadherin, and it influences proliferation, apoptosis, and angiogenesis in various cancers through miR-876-5p and miR-431-5p (55). MiR-718, which is inversely correlated with FBXL19-AS1 expression in breast cancer (BC) tissues, inhibits thyroid cancer cell proliferation, metastasis, and glucose metabolism by negatively regulating the Akt-mTOR signaling pathway (56). In osteosarcoma, FBXL19-AS1 is negatively regulated by miR-346 and is therefore considered a potential therapeutic target (57).

#### **FGD5 Antisense RNA 1=FGD5-AS1**

FGD5 antisense RNA 1 (FGD5-AS1) is a novel non-coding RNA that has been implicated in various cancers, including renal cell carcinoma and periodontitis-associated clear cell carcinoma. In CRC, FGD5-AS1 is overexpressed in tumor cells compared to normal tissues, and its inhibition suppresses cell proliferation, migration, and invasion while promoting apoptosis (58). FGD5-AS1 is also associated with the activity of 14 distinct transcription factors (59). In glioma, FGD5-AS1 accelerates tumorigenesis by activating the Wnt/ $\beta$ -catenin pathway (60). Moreover, it regulates gastric cancer cell function through its downstream epigenetic association with the hsa-miR-153-3p/CITED2 axis (61). The knockdown of FGD5-AS1 reduces migration, survival, and invasion of non-small cell lung cancer (NSCLC) cells by modulating the miR-944/MACC1 axis (62). In CRC, caspase-3 assays have demonstrated that FGD5-AS1 depletion significantly enhances apoptosis (58).

FGD5-AS1 is recognized as a critical regulator of N6-methyladenosine (m6A), which plays a vital role in cancer development and tumorigenesis. It also influences the therapeutic efficacy of cisplatin (63). FGD5-AS1 exerts its effects by binding to miR-142-3p/5p, which functions as a tumor suppressor (64). As a result, FGD5-AS1 is considered a diagnostic and prognostic marker in CRC (65). Furthermore, FGD5-AS1 competes with miR-302e for binding to CDCA7, a known



cancer-promoting gene, thereby contributing to cancer progression (66). It reduces the expression of the HK2 oncogene and inhibits glycolysis through the release of miR-330-3p. FGD5-AS1 also influences SMAD6 via miR-196a-5p, thereby affecting the transforming growth factor- $\beta$  (TGF- $\beta$ ) pathway and the EMT process. Additionally, FGD5-AS1 promotes ERK/AKT phosphorylation through miR-5590-3p, further driving proliferation and EMT. Finally, FGD5-AS1 modulates the Wnt/ $\beta$ -catenin signaling pathway via miR-129-5p and increases the expression of PD-L1, an immunosuppressive protein, through the miR-454-3p/ZEB1 signaling axis or miR-142-5p (67).

### **FOXD3 Antisense RNA 1 (FOXD3-AS1)**

The *LncRNA FOXD3 antisense RNA 1* (FOXD3-AS1) has been identified as a promoter of tumorigenesis in several types of cancer, including CRC, thyroid cancer, cutaneous malignant melanoma, and glioma (68, 69). Knocking down FOXD3-AS1 suppresses cell proliferation, migration, and cell cycle progression, while promoting apoptosis in vitro. In vivo experiments have confirmed that FOXD3-AS1 affects tumor growth. The expression of FOXD3-AS1 is predominantly localized in the cytoplasm of CRC cells.

Mechanistic experiments have revealed that FOXD3-AS1 acts as a competing endogenous RNA (ceRNA), upregulating Sirtuin 1 (SIRT1) by sponging miR-135a-5p. The FOXD3-AS1/miR-135a-5p/SIRT1 axis plays a pivotal role in CRC progression. Furthermore, SIRT1 dysfunction results in cell cycle arrest in the G0/G1 phase, promotes apoptosis, and significantly inhibits migration and invasion, highlighting the oncogenic role of SIRT1 in CRC progression (70). Patients with high FOXD3-AS1 expression exhibit lower overall survival rates, underscoring its prognostic significance. FOXD3-AS1 exerts oncogenic functions in CRC both in vitro and in vivo (70). FOXD3-AS1 overexpression elevates levels of CK, CK-MB, cTnI, TNF- $\alpha$ , IL-1 $\beta$ , IL-

6, reactive oxygen species (ROS), and nitric oxide (NO). It also increases apoptosis rates by reducing Bcl-2 expression and upregulating Bax and caspase-3 expression (71). The inducible role of FOXD3-AS1 has been implicated in the all-trans retinoic acid-mediated therapeutic effects on neuroblastoma (NB) (72). In melanoma, FOXD3-AS1 contributes to tumor progression through the miR-127-3p/FJX1 axis (73, 74). Similarly, in cutaneous malignant melanoma, it regulates the miR-325/MAP3K2 functional pathway (75). FOXD3-AS1 suppresses invasion and EMT in H1229 cells via the PI3K/Akt and miR-150/SRCIN1 axes (74–76). In thyroid cancer, FOXD3-AS1 regulates the TGF- $\beta$ 1/SMAD signaling pathway by inhibiting miR-296-5p. In cervical cancer, it contributes to cell proliferation by clearing miR-296-5p and binding to miR-128-3p (77). In breast cancer, FOXD3-AS1 mediates miR-363 clearance to promote cell proliferation, and in cervical cancer, it enhances cell proliferation by interacting with miR-128-3p (78).

### **HOX Antisense Intergenic Myeloid RNA 1 = (HOTAIRM1)**

Zhang et al. identified a novel LncRNA, HOTAIRM1, located between the human HOXA1 and HOXA2 genes (79). HOTAIRM1 was initially recognized as a key factor in granulocyte differentiation in NB4 promyelocytic leukemia (80). Recently, HOTAIRM1 has been implicated in various cancers, including CRC (81), head and neck tumors (82), retinoblastoma (83), gastric cancer (84), hepatocellular carcinoma (HCC) (85), and lung cancer (86). In glioblastoma multiforme (GBM), HOTAIRM1 mediates the demethylation of histone H3K9 and H3K27 and reduces DNA methylation levels by sequestering epigenetic modifiers such as G9a and EZH2 (87). Silencing HOTAIRM1 suppresses EMT, and the HOTAIRM1/miR-148a/DLGAP1 axis has been shown to play a role in the initiation and progression of head and neck tumors (88). Downregulating HOTAIRM1 decreases the





expression of Bcl-2 or Bid while increasing Bax expression, thereby promoting apoptosis in HCC cells (81). HOTAIRM1 overexpression, along with miR-107, impairs tumorigenic potential in mouse xenografts. Furthermore, miR-107 inhibits the proliferation, invasion, and migration of papillary thyroid carcinoma (PTC) cells *in vitro* (81). One study revealed that HOTAIRM1 exhibits high exon inclusion in early-onset CRC (EOCRC) tumors compared to normal tissues, a phenomenon attributed to age differences among CRC samples (89). In CRC, HOTAIRM1 regulates B-cell translocation gene 3 (BTG3) via the miR-17-5p axis (90).

HOTAIRM1 is also implicated in head and neck cancer and thyroid cancer through the HOTAIRM1/miR-148a/DLGAP1 and HOTAIRM1/miR-107/TDG pathways. In HCC cells, HOTAIRM1 reduces the levels of Akt1, phosphorylated GSK-3 $\beta$  (pGSK-3 $\beta$ ), and  $\beta$ -catenin proteins, further supporting its role in cancer progression (82, 91, 92).

### **Ladybird Homeobox 2 Antisense RNA 1**

*Ladybird Homeobox 2* (LBX2)-AS1 is located in the chr2p13.1 region. LBX2-AS1 has been implicated in tumorigenesis across various cancers, including hepatocellular carcinoma (HCC), esophageal squamous cell carcinoma (ESCC), and gastric cancer (GC). However, its role in CRC tumorigenesis remains poorly understood. The expression level of LBX2-AS1 is significantly higher in CRC cell lines compared to normal colon mucosal cell lines. Knocking down LBX2-AS1 in CRC cells reduces their proliferative ability *in vitro*. This suggests that LBX2-AS1 plays a crucial role in CRC tumorigenesis and represents a potential therapeutic target for CRC patients. Deletion of LBX2-AS1 suppresses CRC cell proliferation, and its reduced expression significantly decreases the mRNA and protein levels of CCND1, CDK3, and CDK6, while increasing the mRNA and protein levels of CDKN1A. Thus, LBX2-AS1 is involved in the regulation of proliferation markers in

CRC cell lines (93). Additionally, LBX2-AS1 increases AKT1 levels by sponging miR-422a. The expression of LBX2-AS1 is regulated through RNA methylation. Induced by the transcription factor ELK1, LBX2-AS1 potentially facilitates CRC cell proliferation, migration, invasion, and angiogenesis while suppressing apoptosis. Mechanistically, LBX2-AS1 regulates the miR-491-5p/S100A11 axis, promoting the proliferation and invasion of CRC cells (94).

LBX2-AS1 is overexpressed in ESCC, where it interacts with the RNA-binding protein heterogeneous nuclear ribonucleoprotein C to regulate the expression of ZEB1 and ZEB2. This interaction promotes cell migration and induces epithelial-to-mesenchymal transition (EMT) in ESCC cells. In HCC cells, LBX2-AS1 sponges miR-384, thereby enhancing the expression of insulin receptor substrate 1, which accelerates proliferation, migration, and invasion while inducing apoptosis *in vitro* (93). In GC cells, LBX2-AS1 binds to miR-4766-5p to regulate CXCL5 expression. Overexpression of CXCL5 abrogates the tumor-suppressive effects of miR-4766-5p, while the LBX2-AS1/miR-4766-5p/CXCL5 axis promotes proliferation, migration, and invasion. This regulatory axis provides a theoretical foundation for developing LBX2-AS1-directed therapies for GC. LBX2-AS1 contains a binding site for miR-4766-5p, which acts as a tumor suppressor in GC tissues and cells (95). Suppression of LBX2-AS1 reduces the levels of Notch1, p21, and Hes1, suggesting that LBX2-AS1 influences the activation of the Notch signaling pathway (96). Furthermore, LBX2-AS1 is highly expressed in clear cell renal cell carcinoma (ccRCC), where it contributes to tumor progression through the mitophagy pathway (97).

### **Retinitis Pigmentosa 11-462C24.1**

*Retinitis pigmentosa* (RP) 11-462C24.1 is located on chr4q25 and consists of four exons. The expression of LncRNA RP11-462C24.1 is significantly reduced in CRC tissues compared to



healthy tissues. RP11-462C24.1 regulates CRC cell growth and invasion *in vitro* as well as *in vivo*. It mediates the proliferation and migration of CRC cells by modulating HSP70 and the PI3K/AKT signaling pathway *in vitro*. HSP70 is significantly upregulated in several types of cancer, including oral squamous cell carcinoma (OSCC), ESCC, GC, lung cancer, and CRC (98). LncRNA RP11-462C24.1 has been reported to exhibit lower expression in cancer tissues than in adjacent normal tissues from CRC patients, indicating its potential as a novel prognostic marker for CRC. RP11-462C24.1 functions as a tumor suppressor in CRC (98). Ribosomal protein L34 (RPL34), a leukemia-associated protein, is transcribed head-to-head with RP11-462C24.1. While RPL34 is highly expressed in metastatic breast cancer and CRC, RP11-462C24.1, as an antisense transcript of RPL34, negatively regulates its expression. This regulation occurs through chromatin modification, transcriptional control, and post-transcriptional processing, implicating RP11-462C24.1 in CRC metastasis (99).

#### **RPL34-AS1= RPL34 Antisense RNA 1**

The *long non-coding RNA* (LncRNA) ribosomal protein L34 antisense RNA 1 (RPL34-AS1) is localized to human chromosome 4q25 and is downregulated in CRC and gastric cancer tissues. RPL34-AS1 is transcribed opposite to RPL34, which functions as an oncogene in lung cancer, oral cancer, GC, pancreatic cancer, osteosarcoma, and esophageal cancer (100). RPL34-AS1 suppresses the oncogenic effects of miR-3565, which promotes cell proliferation; however, mutations in RPL34-AS1 do not influence cell behavior or the role of miR-3565 in proliferation. In CRC, RPL34-AS1 is downregulated and may act as a molecular sponge for miR-3656, thereby suppressing cell proliferation (101). RPL34-AS1 plays a critical role in regulating various malignant tumors. For instance, its expression is decreased in patients with ischemic stroke, where RPL34-AS1 overexpression reduces ischemic brain

injury (102). Additionally, RPL34-AS1 inhibits the proliferation, migration, and invasion of esophageal squamous cell carcinoma (ESCC) cells by reducing RPL34 expression. Consequently, RPL34-AS1 acts as a tumor suppressor in ESCC by modulating RPL34 levels. RPL34, on the other hand, serves as an oncogene by regulating the PI3K/Akt signaling pathway (100). However, in CRC, RPL34 functions as a tumor suppressor and is downregulated, inhibiting the proliferation, migration, and invasion of CRC cells (103). In cervical cancer, elevated RPL34 levels decrease MDM2 expression and increase p53 levels. Furthermore, eukaryotic initiation factor 4A3 (EIF4A3) binds to RPL34 and influences its expression (104). RPL34-AS1 plays an essential role in the growth and metastasis of ESCC cells (105). In CRC, it inhibits the JAK2/STAT3 signaling pathway, while cullin-associated NEDD8-dissociated protein 1 (CAND1) reduces RPL34 ubiquitination, thereby increasing cell proliferation and metastasis (106). Additionally, RPL34-AS1 reduces oxygen-glucose deprivation and simulated reperfusion-induced neuronal injury via the miR-223-3p/IGF1R axis (107).

#### **SLCO4A1 Antisense RNA 1 = SLCO4A1-AS1**

SLCO4A1 antisense RNA 1 (SLCO4A1-AS1) is located on the opposite strand of SLCO4A1, which is significantly expressed in various cancers, including CRC (108, 109). Although limited studies have explored SLCO4A1-AS1's role, evidence suggests it promotes tumorigenesis and metastasis through diverse mechanisms, particularly miRNA regulation (110). Increased SLCO4A1-AS1 expression has been observed in bladder cancer (111), lung cancer (112), and laryngeal squamous cell carcinoma (LSCC) (113). SLCO4A1-AS1 has been shown to regulate tumor cell proliferation, apoptosis, autophagy, and metastasis in several cancers, including bladder cancer, CRC, and lung cancer. In CRC, SLCO4A1-AS1-induced Cdk2 elevation activates the c-Myc signaling pathway by promoting c-Myc phosphorylation at Ser62. Consequently,



SLCO4A1-AS1 functions as an oncogene by modulating the Hsp90/Cdk2/c-Myc axis (110). SLCO4A1-AS1 facilitates tumor growth and metastasis by potentially influencing the  $\beta$ -catenin/Wnt and EGFR/MAPK signaling pathways. Specifically, SLCO4A1-AS1 inhibits GSK $\beta$ -mediated  $\beta$ -catenin phosphorylation, thereby stabilizing  $\beta$ -catenin and driving CRC progression (110, 114, 115). Additionally, SLCO4A1-AS1 regulates MYC protein stability in CRC (116). Knockdown of SLCO4A1-AS1 significantly suppresses CRC cell multiplication, migration, and invasion while inducing apoptosis *in vitro* and *in vivo* (115).

In lung cancer, SLCO4A1-AS1 acts as an antagonist of the TOX4/NTSR1 signaling axis, while in LSCC, it is implicated in Wnt/ $\beta$ -catenin signaling via SETD7 (113, 117). In CRC, SLCO4A1-AS1 is associated with aberrant EGFR/MAPK pathway activation, which contributes to cancer cell proliferation, migration, and invasion (110). The SLCO4A1-AS1/miR-508-3p/PARD3/autophagy axis plays a significant role in CRC cell proliferation. A positive correlation has been observed between SLCO4A1-AS1 and PARD3 expression, where PARD3 serves as a key initiator of autophagy in CRC patients (109). SLCO4A1-AS1 competitively binds to miR-150-3p, altering SLCO4A1 expression and inhibiting CRC progression (108). It also regulates gastric cancer (GC) progression by interacting with miR-149-5p. SLCO4A1-AS1 appears to affect GC tumor growth and metastasis by targeting STAT3 through the competitive binding of miR-149-5p (118). In lung adenocarcinoma (LUAD), SLCO4A1-AS1 enhances cell growth and chemotherapy resistance by activating the Wnt pathway through the miR-4701-5p/NFE2L1 axis (119). Moreover, SLCO4A1-AS1 and the ABC flux pump ABCC3 are associated with higher SLCO4A1 expression, indicating their involvement in inflammation-related pathways downstream of the prostaglandin E2/cAMP axis (120).

### Future insights and Challenges

CRC is one of the most common cancers

worldwide, with its incidence rising significantly in recent years among individuals under the age of 50 years. To enhance and improve the success of treatment, the development of reliable biomarkers for the early and accurate diagnosis of CRC is of paramount importance (23, 128). LncRNAs have emerged as reliable biomarkers due to their diverse functions, including regulating the cell cycle, proliferation, metastasis, growth, and transcription. By interacting with miRNAs, LncRNAs regulate or disrupt key pathways involved in CRC progression.

Research indicates that LncRNAs form intricate regulatory axes and networks with DNA, RNA, and proteins, thereby influencing the initiation, progression, and inhibition of CRC. Currently, colonoscopy, tissue biopsy, and serum tumor markers are used to diagnose CRC; however, these methods have significant limitations and disadvantages. For instance, colonoscopy may result in intestinal damage and patient discomfort (129), along with sampling limitations and potential diagnostic errors (130, 131). Similarly, serum tumor markers, such as CEA and CA19-9, lack sensitivity and reliability, often producing false-positive results. Although surgical interventions can remove tumors, challenges such as surgical errors, metastasis (132), chemotherapy- and radiotherapy-induced side effects (e.g., nausea, vomiting, and drug-resistant anemia), and the high costs associated with these treatments remain problematic (133). LncRNAs, however, address many of these issues due to their stability in the bloodstream and their non-invasive nature (134-136). In CRC treatment, LncRNAs represent a promising and innovative therapeutic target, as they regulate the expression of genes involved in proliferation, metastasis, growth, and apoptosis (Table 1). LncRNA-based therapies offer more precise targeting with fewer side effects and lower rates of drug resistance (137, 138).

Despite these advantages, challenges persist





in the clinical application of LncRNAs. These include the need for the standardization and optimization of LncRNA assay methods (e.g., qPCR), the limited sample sizes of most studies (often fewer than 100 samples), the complexity of analyzing results, and the lack of comprehensive information on the mechanisms and functional pathways of LncRNAs (139-142).

## Conclusion

In summary, research on LncRNAs provides valuable insights into the molecular mechanisms and pathways underlying CRC, paving the way for the development of novel diagnostic and therapeutic strategies. This study introduces significant and novel LncRNAs (C6ORF176, CASC9er35e, ESCCAL-1, FBXL19-AS1, FGD5-AS1, FOXD3-AS1, LBX2AntisenseRNA1, SLCO4A1-AS1, HOTAIRM1, RP11-462C24.1, RPL34-AS1) implicated in CRC and highlights future directions for research in this field.

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## Conflict of interest

The authors declare no conflicts of interest.

## Authors' Contribution

M. Javad Tahmasebi and Behnoosh Miladpour contributed to data collection, manuscript drafting, writing, and editing, as well as providing support for the study. All authors consent to the publication of this manuscript in the journal.

## Code of Ethics

IR.FUMS.REC.1400.051

## Data availability statement

The data supporting the findings of this study are available from the corresponding author

upon reasonable request.

## Human and animal rights and informed consent

This article does not include any studies involving human or animal subjects conducted by the authors.

## Consent for publication

The authors guarantee that once the material is accepted for publication by the journal, it will not be submitted to another journal, either in whole or in part.

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