Clinical and Translational Oncology (2022) 24:1715–1731
https://doi.org/10.1007/s12094-022-02834-7

REVIEW ARTICLE

Potentials of long non-coding RNAs as biomarkers of colorectal cancer

Yan Lv[1] · Yanhua Wang[1,2] · Zhikai Zhang[3] · Jiarui Bao[1] · Huahua Su[3]

Received: 8 March 2022 / Accepted: 4 April 2022 / Published online: 17 May 2022

Abstract

Colorectal cancer (CRC) is the third most common malignant tumor worldwide and the fourth major cause of cancer-related death, with high morbidity and increased mortality year by year. Although significant progress has been made in the therapy strategies for CRC, the great difficulty in early diagnosis, feeble susceptibility to radiotherapy and chemotherapy, and high recurrence rates have reduced therapeutic efficacy resulting in poor prognosis. Therefore, it is urgent to understand the pathogenesis of CRC and unravel novel biomarkers to improve the early diagnosis, treatment and prediction of CRC recurrence. Long non-coding RNAs (lncRNAs) are non-coding RNAs with a length of more than 200 nucleotides, which are abnormally expressed in tumor tissues and cell lines, activating or inhibiting specific genes through multiple mechanisms including transcription and translation. A growing number of studies have shown that lncRNAs are important regulators of microRNAs (miRNAs, miRs) expression in CRC and may be promising biomarkers and potential therapeutic targets in the research field of CRC. This review mainly summarizes the potential application value of lncRNAs as novel biomarkers in CRC diagnosis, radiotherapy, chemotherapy and prognosis. Additionally, the significance of lncRNA SNHGs family and lncRNA–miRNA networks in regulating the occurrence and development of CRC is mentioned, aiming to provide some insights for understanding the pathogenesis of CRC and developing new diagnostic and therapeutic strategies.

Keywords LncRNAs · MiRNAs · Colorectal cancer · Biomarkers · Treatment

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors. Its incidence rate and mortality rate are incredibly high worldwide, ranking third or fourth in all types of cancers [1]. With rapid advances in medical technology for early screening, diagnosis and treatment, approximately 90% of CRC patients have prolonged survival even more than 5 years [2, 3]. Nevertheless, early diagnosis of CRC remains difficult. 60% of CRC patients are diagnosed at a late stage, resulting in poor treatment outcomes and poor prognosis [4]. Additionally, wide-accepted therapy strategies for CRC chiefly include surgical resection, radiotherapy, chemotherapy, targeted therapy and immunotherapy [5], but the long-term effect is still far from satisfactory. Clinically, due to the insidious symptoms and lack of practical early serological markers, most patients with CRC are diagnosed in the late stage, weakening the effect of postoperative radiotherapy and chemotherapy. Strikingly, radiotherapy resistance and drug resistance make the efficacy of radiotherapy and chemotherapy exceedingly unsatisfactory [6, 7]. Carcinoembryonic antigen (CEA) was unanimously recognized by the College of American Pathologists Consensus Conference as a category I prognostic marker for CRC as early as 1999 [8]. Likewise, CEA is the only tumor-specific marker which is widely recommended for clinical treatment of CRC at this stage [9]. However, with the increasing number of clinical applications of CEA, it is found that the sensitivity and specificity of CEA in practical application are far from the requirements of early diagnosis. Although CEA can occasionally identify patients with CRC, its false positive is too high to be acceptable [10, 11]. It can be seen that CEA still

✉ Yanhua Wang
juddy0921@163.com

1 The Hubei Key Laboratory of Tumor Microenvironment and Immunotherapy, China Three Gorges University, Yichang, China

2 Department of Morphology, Medical College of China Three Gorges University, Life Science Building, No.8 Daxue Road, Yichang, China

3 The Third-Grade Pharmacological Laboratory on Chinese Medicine Approved by State Administration of Traditional Chinese Medicine, China Three Gorges University, Yichang, China

has some limitations in the early screening of CRC. Therefore, in-depth study of the pathogenesis of CRC, improving the accuracy of CRC diagnosis, and seeking promising biomarkers and potential prognostic indicators are of great clinical significance for the development of new targeted therapeutic drugs, reducing radiotherapy resistance and drug resistance, and improving the survival rate of patients.

Long non-coding RNAs (lncRNAs) are mainly located in the nucleus and cytoplasm. They are a class of RNA sequences with a length of more than 200 nucleotides and no protein-coding ability. Moreover, they lack a complete functional open reading frame (ORF) in the humankind genome [12, 13]. The structure of lncRNAs is similar to that of mRNAs, such as a cap structure at the 5 'end, polyadenylated tail at the 3' end, and promoter [14]. There are many kinds of lncRNAs, including long intervening/intergenic non-coding RNAs (lincRNAs), promoter upstream transcripts (PROMPTs), enhancer RNAs (eRNAs), natural antisense transcripts (NATs) and so on [15]. Generally, there are four mechanisms of lncRNAs in the body: (1) as signal molecules, lncRNAs transmit information through corresponding signal pathways; (2) as an inducible molecule, it regulates the expression of target genes through histone modification; (3) as a guiding signal, chromosome-modifying enzymes are recruited, and protein complexes are successively installed on the corresponding cis- or trans-regulatory sites; (4) as a molecular scaffold, it indirectly regulates the transcription of target genes [16]. In addition, lncRNAs are associated with various important physiological activities in cells, such as gene recombination, gene imprinting, chromatin modification, and cell cycle regulation, transcription and translation [17–21]. Interestingly, there is a close relationship between lncRNAs and other non-coding RNAs (such as miRNAs). Various non-coding RNAs interact to form a complex and efficient molecular network. Salmena et al. have proposed the competitive endogenous RNA (ceRNA) hypothesis for the first time to describe the interaction between diverse types of non-coding RNAs (including miRNAs and lncRNAs), and it is believed that the molecular network could regulate multiple physiological processes of various tissues and cells in the body [22].

In recent years, it has been observed in the field of cancer biology that some lncRNAs are closely related to the occurrence and development of cancer, and they may become potential targets for cancer treatment and diagnosis [23, 24]. Therefore, a mounting number of researchers have begun to pour attention into the experimental research of lncRNAs. Previous evidence and investigations have illustrated that lncRNAs play an essential role in the early screening, prevention, prognosis and treatment of CRC. LncRNAs are promising biomarkers for CRC diagnosis, prognosis or treatment [25]. Here, this dissertation reviews (1) lncRNAs related to the occurrence and development of CRC; (2) lncRNA SNHGs associated with the development of CRC; (3) lncRNAs associated with radiotherapy resistance of CRC; (4) lncRNAs associated with chemoresistance of CRC; (5) various lncRNAs that can be used as prognostic biomarkers of CRC (Fig. 1).

LncRNAs are associated with the development of CRC

Abnormal expression of lncRNAs can affect the occurrence and development of CRC. Here, two types of lncRNAs with opposite effects are summarized, one is tumor promoter lncRNAs (Table 1), and the other is tumor-suppressor lncRNAs (Table 2). These lncRNAs may become potential therapeutic targets for CRC and are supposed to be used in the clinical treatment of CRC.

LncRNAs promote the development of CRC

Targeted regulation of lncRNAs

P53 has been demonstrated to be an essential tumor suppressor. Its high expression helps induce tumor cell apoptosis, maintain genomic stability and inhibit tumor angiogenesis. Currently, studies have discovered that P53 mutation exists in more than 50% of malignant tumors (including CRC) [26–28]. Among them, some aberrantly expressed lncRNAs can alter the expression of P53. Wei et al. have found that the expression of lncRNA CACNA1G antisense RNA 1 (CACNA1G-AS1) in CRC tissues and cell lines is abnormally increased, which can interact with enhancer of zeste homolog 2 (EZH2) to form carcinogenic complex, and then target inhibit the expression of p53, and aggravate the malignant progression of CRC [29]. Additionally, FAM83C antisense RNA 1 (FAM83C-AS1) can also interact with EZH2 and exert oncogenic effects. Recent studies from Xue et al. have demonstrated that FAM83C-AS1 could target and regulate semaphorin 3F (SEMA3F). Its expression level is negatively correlated with SEMA3F. Notably, FAM83C-AS1 enhances methylation of SEMA3F promoter H3K27me3 via up-regulating methyltransferase enhancer of zeste 2 polycomb repressive complex 2 subunits. Specifically, FAM83C-AS1 stabilizes EZH2 protein through recruiting the zinc finger RANBP2-type containing 1 (ZRANB1), thus promoting the development of CRC [30].

The JAK/STAT3 signaling pathway is associated with numerous critical physiological processes, such as differentiation, cell growth, migration, and hematopoiesis [31]. Currently, there are an increasing number of evidences that JAK/STAT3 signal abnormalities play an indispensable role in the occurrence and development of CRC. For

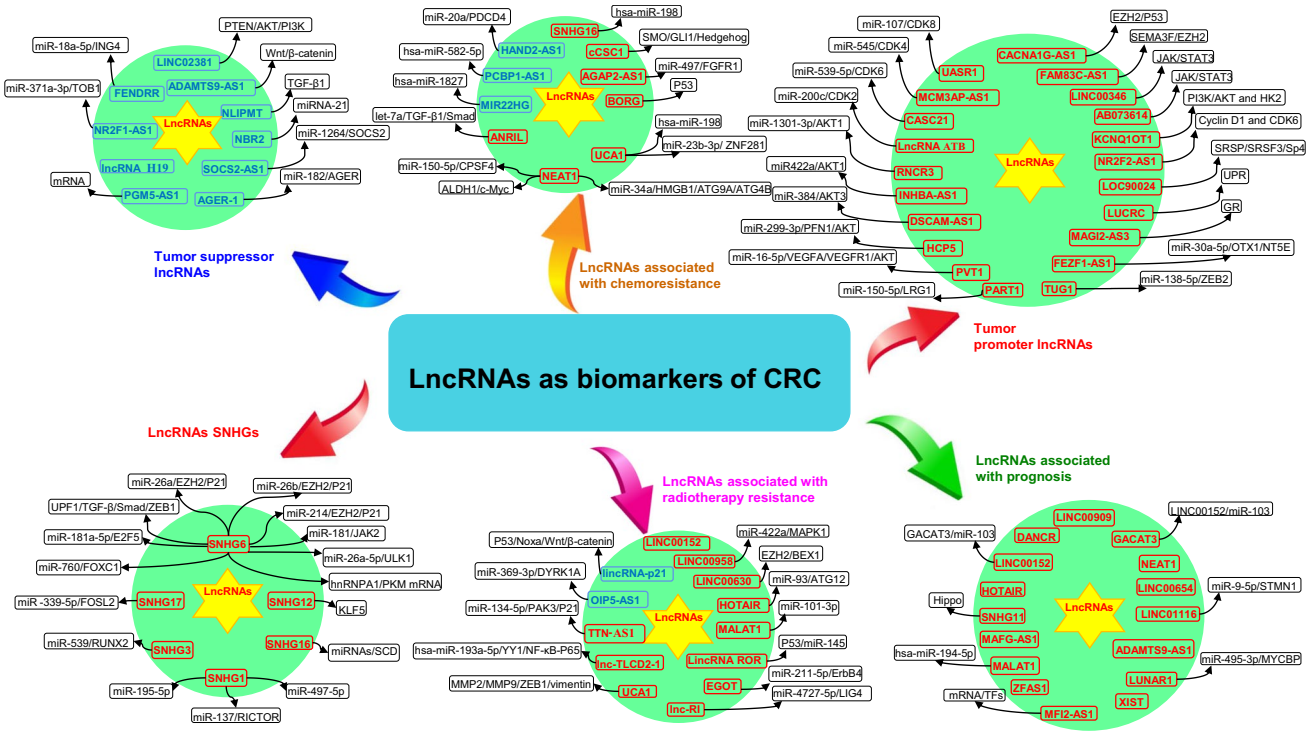

Fig. 1 Schematic graph about lncRNAs as biomarkers in CRC. The lncRNAs depicted in blue color are down-regulated, whereas the red ones are up-regulated. The pathways where these different lncRNAs are involved have been shown in black

example, when LINC00346 is overexpressed in CRC cells, it can significantly up-regulate the expression level of JAK and STAT3, promote cell proliferation and inhibit apoptosis [32]. Another study has found that lncRNA AB073614 can activate JAK/STAT3 signaling pathway and induce the epithelial–mesenchymal transition (EMT) process in CRC cells [33]. In addition, PI3K/AKT signaling pathway also plays a crucial role in the growth and metastasis of CRC. Duan et al. have found that when the KCNQ1OT1 gene in CRC cells is knocked out, the expression of PI3K and AKT proteins decreases dramatically, the PI3K/AKT signaling pathway is blocked. At the same time, the proliferation, migration and invasion of CRC cells decrease evidently. It is appeared that KCNQ1OT1 can regulate PI3K/AKT signaling pathway and participate in the further deterioration of CRC [34].

It is worth mentioning that tumor promoter lncRNAs are highly expressed in most tumor tissues, and are also closely related to various vital physiological activities in tumor cells. They are expected to be biomarkers for cancer monitoring. As an example, the level of KCNQ1OT1 in CRC tissues is remarkably higher than that in adjacent normal colorectal tissues. KCNQ1OT1 directly binds to and stabilizes hexokinase 2 (HK2), which increases aerobic glycolysis and thus promotes the proliferation of CRC cells [35]. Additionally, NR2F2 antisense RNA 1 (NR2F2-AS1) is also highly expressed in CRC cells and plays an energetic role in the occurrence and development of CRC by promoting the expression of cyclin D1 and inducing G0/G1 phase [36]. Another study has revealed that lncRNA LOC90024 could promote splicing regulatory small protein (SRSP). When the content of SRSP increases, SRSP increases the binding of serine- and arginine-rich splicing factor 3 (SRSF3) to exon 3 of transcription factor Sp4, resulting in the inclusion of Sp4 exon 3 to induce the formation of the "cancerous" long Sp4 isoform (L-Sp4 protein) and inhibit the formation of the "noncancerous" short Sp4 isoform (S-Sp4 peptide), which lacks the transactivation domain, to promote the occurrence of CRC [37]. In addition, Tang et al. have conducted transcriptome analysis and functional screening of lncRNA up-regulated in colorectal cancer (LUCRC) tissue and cells. It is found that LUCRC could regulate the target gene expression of unfolded protein response (UPR) in the endoplasmic reticulum (ER), activate the UPR signaling pathway, and accelerate the folding and unfolded protein clearance in the cytoplasm. Thus, it can resist the adverse effects of endoplasmic reticulum stress and promote the survival of tumor cells [38]. It can be seen that some lncRNAs can regulate the expression levels of tumor-related proteins through the regulation of endoplasmic reticulum stress response, thus promoting the process of tumor development.

Nevertheless, it is noteworthy that the anomalous expression of lncRNAs in cancer cells is also influenced by

Table 1 Tumor promoter lncRNAs in CRC

LncRNAs	Expression[1]	Genes and pathways	Functions[2]	References
CACNAIG-ASI	↑	EZH2/P53	Proliferation (+), invasion (+)	[29]
FAM83C-AS1	↑	SEMA3F/EZH2	Tumor growth (+), proliferation (+), metastasis (+)	[30]
LINC00346	↑	JAK/STAT3 pathway	Proliferation (+), apoptosis (–)	[32]
AB073614	↑	JAK/STAT3 pathway	EMT (+)	[33]
KCNQ1OT1	↑	PI3K/AKT pathway	Proliferation (+), migration (+), invasion (+)	[34]
		HK2	Proliferation (+), aerobic glycolysis (+)	[35]
NR2F2-AS1	↑	Cyclin D1	Tumor growth (+), metastasis (+)	[36]
		CDK6	Tumor growth (+), proliferation (+)	[65]
LOC90024	↑	SRSP/SRSF3/Sp4	Tumor growth (+), proliferation (+)	[37]
LUCRC	↑	UPR	Gene translation (+), tumor growth (+), apoptosis (–)	[38]
MAGI2-AS3	↑	GR	Gene transcription (+), tumor growth (+)	[40]
FEZF1-AS1	↑	muR-30a-5p/OTX1/NT5E	EMT (+)	[49]
TUG1	↑	miR-138-5p/ZEB2	EMT (+), metastasis (+)	[50]
PARTI	↑	miR-150-5p/LRG1	EMT (+), proliferation (+), migration (+)	[51]
PVT1	↑	miR-16-5p/VEGFA/VEGFR1/AKT	Proliferation (+), metastasis (+)	[55]
HCP5	↑	miR.299-3p/PFN1/AKT	Proliferation (+), tumor growth (+)	[56]
DSCAM-ASI	↑	miR-384/AKT3	Proliferation (+), transdifferentiation (+)	[57]
INHBA-AS1	↑	miR422a/AKT1	Proliferation (+), invasion (+), apoptosis (–)	[58]
RNCR3	↑	miR-1301-3p/AKT1	Proliferation (+), invasion (+), apoptosis (–)	[59]
LncRNA ATB	↑	miR-200c/CDK2	Tumor growth (+), proliferation (+)	[63]
CASC21	↑	miR-539-5p/CDK6	Proliferation (+), metastasis (+), tumorigenesis (+), apoptosis (–)	[64]
MCM3AP-ASI	↑	miR-545/CDK4	Proliferation (+), apoptosis (–), migration (+), invasion (+)	[66]
UASR1	↑	miR-107/CDKS	Tumorigenesis (+),proliferation (+)	[67]

[1]lncRNAs either up-regulated (↑) or down-regulated (↓) in CRC cells

[2] lncRNAs either promote (+) or inhibit (−) various physiological processes of CRC

Table 2 Tumor-suppressor lncRNAs in CRC

LncRNAs	Expression[1]	Genes and pathways	Functions[2]	References
LINC02381	↓	PTEN/AKT/PI3K pathway	Apoptosis (+), proliferation (−), tumor growth (−)	[70]
NLIPMT	↓	TGF-β1	Migration (−), invasion (−)	[71]
ADAMTS9-AS1	↓	Wnt/β-catenin pathway	Gene transcription (−), proliferation (−)	[72]
lncRNA H19	↓	——	Metastasis (−), tumor growth (−)	[73]
PGM5-AS1	↓	mRNA	Apoptosis (+), tumor growth (−)	[74]
NBR2	↓	miRNA-21	Migration (−), invasion (−)	[75]
AGER-1	↓	miR-182/AGER	Apoptosis (+), tumor growth (−)	[76]
NR2F1-AS1	↓	miR-371a-3p/TOB1	Proliferation (−), metastasis (−)	[77]
FENDRR	↓	miR-18a-5p/ING4	Proliferation (−), tumorigenesis (−)	[78]
SOCS2-AS1	↓	miR-1264/SOCS2	Proliferation (−), tumor growth (−), metastasis (−)	[79]

[1]lncRNAs either up-regulated (↑) or down-regulated (↓) in CRC cells

[2]lncRNAs either promote (+) or inhibit (−) various physiological processes of CRC

several biomolecules. For example, transforming growth factor-β can activate lncRNA ATB, and the activated lncRNA ATB can be regulated by down-regulating the transcriptional activity of the β-catenin pathway. Finally, the reduced expression of β-catenin is conducive to the colony formation, growth and development of CRC cells [39]. More interestingly, polymorphisms in lncRNAs genes also affect the occurrence and development of CRC. Studies have illustrated that single nuclear polymorphisms (SNPs) in lncRNAs are associated with susceptibility to CRC. MAGI2 antisense RNA 3 (MAGI2-AS3) is a kind of lncRNAs. The gene rs7783388 on it increases the binding affinity between the transcription factor glucocorticoid

receptor (GR) and the MAGI2-AS3 promoter, resulting in increased transcriptional activity and risk of CRC [40].

Therefore, the above lncRNAs are highly expressed in CRC cells and tissues, which may be promising prognostic indicators and potential therapeutic targets for CRC. Clearly, compared with a single lncRNA, the combined application of various lncRNAs in diagnosis and treatment may show more superior sensitivity and specificity. However, the current research on the combined treatment of lncRNAs has not been studied in sufficient depth, and its mechanism remains to be confirmed. Clinical samples are insufficient to make use of research and exploration.

Regulation of lncRNA–miRNA networks

MicroRNAs (miRNAs, miRs) are small molecule non-coding RNAs (ncRNAs) with a size of 18–24 nucleotides, which can bind to the 3 'UTR region of the target gene and play a post-transcriptional regulatory role in gene expression and RNA silencing [41, 42]. LncRNA–-miRNA networks formed between miRNAs and lncRNAs can affect the proliferation, invasion and metastasis of CRC cells. In this process, lncRNAs can be competitively bind with the shared miRNA response elements (MREs), down-regulate the expression level of miRNAs, or inhibit the maturation process of miRNAs, resulting in overexpression of downstream target genes and affecting the development process of CRC [43–45]. Such molecular mechanism has been confirmed in a large number of experiments.

EMT is a unique and complicated physiological process in cells, which may be the leading cause of the metastasis of CRC. EMT can be adversely affected by quite a few factors [46–48]. Previous studies have demonstrated that the interactions between lncRNAs and miRNAs can regulate the formation of EMT at the transcriptional or post-transcriptional level. For example, FEZF1 antisense RNA 1 (FEZF1-AS1) is highly expressed in the nucleus and cytoplasm of CRC cells. It can specifically bind and regulate the expression of miR-30a-5p. Furthermore, the FEZF1-AS1–miR-30a-5p axis can regulate orthodenticle homeobox 1 (OTX1) and 5'nucleotidase ecto (NT5E) to activate the EMT process [49]. Surprisingly, miR-138-5p is an anti-metastasis factor in CRC. It is negatively regulated by taurine up-regulated gene 1 (TUG1), which induces high expression of zinc finger E-Box-binding homeobox 2 (ZEB2) and promote cancer cell metastasis and EMT process [50]. Another study has shown that the expression level of prostate androgen-regulated transcript 1 (PART1) is significantly higher in CRC tissues and cell lines than that in adjacent normal tissues and cells. High expression of PART1 can inhibit the expression of miR-150-5p, regulate the expression of leucine-richα-2-glycoprotein-1 (LRG1), and then promote CRC cell proliferation, migration, and EMT [51].

It is well known that the AKT serine/threonine kinase 1 (AKT1) signaling is usually one of the critical factors implicated in the development of a variety of cancers [52]. AKT is activated by phosphorylation. Activated AKT can affect various biological processes including cell proliferation and apoptosis [53, 54]. Plasmacytoma variant translocation 1 (PVT1) is expressed up-regulated in CRC. It promotes AKT phosphorylation and activation by targeting the miR-16-5p/vascular endothelial growth factor A (VEGFA)/vascular endothelial growth factor receptor 1 (VEGFR1) axis and accelerates cancer metastasis. Down-regulation of miR-16-5p expression can improve the metastatic ability of CRC, while overexpression of miR-16-5p can inhibit the expression of lncRNA PVT1 and then inhibit the growth of CRC [55]. Additionally, lncRNA human primary histocompatibility complex P5 (HCP5) is another oncogene, which is highly expressed in CRC tissues and cells. The ceRNA of miR-299-3p improves the proliferation rate of CRC and accelerates the cycle process of cancer cells by regulating the miR-299-3p/profilin 1 (PFN1)/AKT axis [56]. As a negative regulator, Down syndrome cell adhesion molecule antisense RNA 1 (DSCAM-AS1) inhibits the expression of miR-384, induces activation of downstream target AKT3, and affects the proliferation and differentiation of CRC cells [57]. In addition, INHBA antisense RNA 1 (INHBA-AS1) and retinal non-coding RNA3 (RNCR3) in the lncRNAs family could be involved in colorectal carcinogenesis via the miR422a/AKT1 axis and miR-1301-3p/AKT1 axis, respectively. Meanwhile, the latter could inhibit the expression of cyclin A1, PCNA, N-cadherin and Bcl-2 and promote the expression of E-cadherin and Bax, further promoting the proliferation and invasion while inhibiting apoptosis of CRC cells [58, 59].

Cancer cells commonly have the characteristics of rapid proliferation and immune escape. Cell cycle regulation is generally mediated by the change of cyclin-dependent kinase (CDK) activity [60–62]. When CDK is highly expressed, the proliferation ability of CRC cells is improved, and the apoptosis ability is weakened. For instance, lncRNA ATB, a transformation growth factor-β activated long non-coding RNA, is highly expressed in CRC. Meanwhile, it can be utilized as ceRNA of miR-200c, reduce the level of miR-200c, induce prominent expression of CDK2 and accelerate the cell cycle process [63]. CASC21 plays a key role in the occurrence and development of CRC. CASC21 gene cleavage reduces the level of CDK6 and inhibits the proliferation of cancer cells by targeting miR-539-5p. Up-regulation of CDK6 in CRC can promote proliferation, metastasis and tumorigenesis [64]. Additionally, NR2F2-AS1 can also promote the expression of CDK6 and accelerate the process of the G1 phase [65]. Recent studies by Ma et al. have shown that MCM3AP antisense RNA 1 (MCM3AP-AS1) can directly target miR-545 and down-regulate the expression

of miR-545 to activate CDK4, thereby shortening the time required for CRC cell proliferation. MCM3AP-AS1 down-regulation and miR-545 up-regulation can reverse the effects of CDK4 down-regulation on proliferation, apoptosis, migration, and invasion of CRC cells [66]. LncRNA UASR1 has a carcinogenic effect and is a research hotspot related to CRC. One study has shown that the silencing of UASR1 increases apoptosis of CRC cells, and the cell cycle is blocked in the G1 phase. Mechanically, miR-107 is a direct target of UASR1, and CDK8 is a direct target of miR-107. The inhibition of UASR1 inhibits the development of CRC through the miR-107/CDK8 axis, which may be an innovative signaling pathway for the treatment of CRC [67].

LncRNAs act as ceRNAs of miRNAs, which participate in the occurrence and development of CRC by regulating the expression of multiple miRNAs. At the same time, lncRNA–miRNA networks closely related to CRC may be promising biomarkers and potential therapeutic targets. However, the gold standard for early detection of CRC remains the classical biomarkers and derived scores. It can be observed that a large number of experimental and clinical studies of novel biomarkers represented by lncRNAs are significant and prospective [68].

LncRNAs inhibit the development of CRC

It has been confirmed that PTEN is a tumor-suppressor gene, which can inhibit the activation of AKT and negatively regulate the PI3K signaling pathway, which plays an indispensable role in inhibiting tumor development [69]. Jafarzadeh et al. have found that LINC02381 has DNA methylation in various malignancies (including CRC), resulting in transcriptional silencing and down-regulation. When LINC02381 is overexpressed, it can target to increase the expression level of PTEN, decrease the phosphorylation level of AKT, and inhibit the development process of CRC by regulating the PI3K signaling pathway [70]. Transforming growth factor β1 (TGF-β1) can promote the migration and invasion of cancer cells. An et al. have identified NLIPMT as a tumor-suppressor lncRNA. When its expression is up-regulated, it can be significantly down-regulate TGF-β1 and inhibit the migration and invasion of CRC cells [71]. Similarly, another study has illustrated that ADAMTS9 antisense RNA 1 (ADAMTS9-AS1) could inhibit the Wnt/β-catenin signaling pathway involved in gene transcription regulation, thereby suppressing the occurrence of CRC [72]. Interestingly, some lncRNA gene polymorphisms are also engaged in regulating the development of CRC. For example, the rs2839698 polymorphism of the lncRNA H19 gene can reduce the risk of CRC, and its expression is negatively correlated with lymph node metastasis and tumor size [73].

It is worthwhile noting that tumor-suppressor lncRNAs can form a co-expression network with other RNAs (such as miRNAs and mRNAs) to regulate the development of CRC jointly. As an example, PGM5 antisense RNA 1 (PGM5-AS1) is a crucial tumor-suppressor gene in CRC, which induces CRC cell apoptosis and cell cycle arrest by regulating the mRNA expression [74]. In addition, Bai et al. have found that the low expression of NBR2 and high expression of miRNA-21 in CRC tissues and cell lines are closely related to the poor prognosis and lymph node metastasis of CRC patients. NBR2 can act as the ceRNA of miRNA-21, inhibit the expression of miRNA-21, and then inhibit the metastasis of cancer cells [75]. Similarly, lncRNA AGER-1 in CRC cells is also inhibited, acts as a molecular sponge for miR-182, reduces the expression of regulatory gene AGER, induces cancer cells to block the G0/G1 phase, and promotes cancer cell apoptosis. MiR-182 also inhibits the expression of lncRNA AGER-1. These two molecules interact and participate in regulating the cell cycle of CRC [76]. NR2F1 antisense RNA 1 (NR2F1-AS1) has been previously confirmed to play a carcinogenic role in liver cancer, but interestingly, NR2F1-AS1 plays a tumor-suppressive role in CRC. Wang et al. have found that NR2F1-AS1, which is lowly expressed in CRC cells, acts as the ceRNA of miR-371a-3p, promotes up-regulation of TOB1 expression and considerably reduces the proliferation rate and metastasis rates of CRC cells [77]. In addition, FENDRR can regulate the expression of miR-18a-5p, promote the expression of inhibitor of growth 4 (ING4) in CRC tissues and cell lines, and exert anti-cancer effects [78]. SOCS2 is a cytokine signaling inhibitor. Its high expression inhibits the progression and metastasis of CRC. Zheng et al. have found that SOCS2 antisense RNA 1 (SOCS2-AS1) promotes and stabilizes the expression of SOCS2 by inhibiting miR-1264, which in turn inhibits further tumor progression. Meanwhile, SOCS2 silencing can eliminate the tumor-suppressive effect of SOCS2-AS1 overexpression, which may play an essential role in the pathogenesis of CRC [79].

Therefore, the above lncRNAs may be valuable biomarkers and potential therapeutic targets, providing original ideas for early screening, early prevention, prognosis, and treatment of CRC. Nevertheless, there remain a large number of non-studied lncRNAs in CRC tissues and cell lines. The related mechanism of lncRNAs in CRC is unclear and has yet to be explored.

LncRNA SNHGs are associated with CRC

Small nuclear RNA host genes (SNHGs) are an integral part of the lncRNAs family. SNHGs are host genes for small nuclear RNAs (snoRNAs) present in the cytoplasm and nucleus [80]. To date, 22 members of the SNHGs family

have been identified, from SNHG1 to SNHG22 [81]. These SNHGs play an indispensable role in the occurrence and development of human cancers and other diseases. SNHGs are closely associated with the development of CRC, and their expression levels are positively correlated with tumorigenesis. They are expected to be biomarkers for CRC diagnosis and potential therapeutic targets (Table 3).

SNHG6 and CRC

SNHG6 is an integral part of the SNHGs family. It is the main type of SNHGs studied and has been most intensively studied in the field of CRC. SNHG6 has been confirmed to be an oncogenic lncRNA. It has been indicated that the up-regulation of SNHG6 expression in CRC patients helps predict poor prognosis for patients. When SNHG6 is knocked out, the proliferation and differentiation of CRC cells are significantly reduced, the cell cycle is blocked, the apoptosis is exacerbated, and the survival time of CRC patients is prolonged [82]. Additionally, the expression level of SNHG6 in CRC tissues and cell lines is positively correlated with a low survival rate, high tumor stage and distant metastasis in various solid tumors [83]. Similarly, SNHG6 can regulate the process of aerobic glycolysis. Recent studies by LAN et al. have shown that SNHG6 could regulate heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1), which specifically acts on the 3′ UTR of pyruvate kinase M (PKM) precursor mRNA, inducing hnRNPA1 to specifically splice PKM precursor mRNA and increasing the proportion of PKM2/PKM1, in order to enhance the intensity of aerobic glycolysis in CRC cells, and promote the growth and development of CRC cells [84].

In addition, SNHG6 can inhibit the expression of miR-26a, induce the up-regulation of EZH2 levels, and promote migration, invasion and EMT of CRC cells [85]. Except for acting as a ceRNA of miR-26a, SNHG6 can also act as a molecular sponge for miR-26b and miR-214, inhibit the expression of miR-26b and miR-214, and then up-regulate the expression level of EZH2 [86]. Further research has found that high expression of EZH2 could inhibit the gene transcription process of P21, reduce the expression level of the cyclin-dependent kinase inhibitor P21, and thus promote tumor growth [87]. Studies have shown that the overall survival (OS) of CRC patients with high SNHG6 levels is significantly lower than that of CRC patients with low SNHG6 level, and the proliferation and metastasis rates of cancer cells in the former are significantly higher than that in the latter. Mechanically, SNHG6 can target the regulation of up-frameshift protein 1 (UPF1) to activate the TGF-β/Smad signaling pathway, promote the proliferation, invasion, and migration of CRC cells by regulating ZEB1 to induce EMT [88].

It is worth mentioning that SNHG6 can act as a molecular sponge for some miRNAs. The interaction between them can benefit to form SNHG6-miRNA molecular networks and regulate the occurrence and development of CRC. For example, it is reported that SNHG6 can be utilized as a ceRNA

Table 3 LncRNA SNHGs and CRC

LncRNA SNHGs	Expression[1]	Genes and pathways	Functions[2]	References
SNHG6	↑	hnRNPA1/PKMmRNA	Aerobic glycolysis (+), tumorigenesis (+), tumor growth (+), metastasis (+)	[84]
		miR-26a/EZH2/P21	Migration (+), invasion (+), EMT (+)	[85]
		miR-26b/EZH2/P21	Migration (+), invasion (+), EMT (+)	[86]
		miR-214/EZH2/P21	Migration (+), invasion (+), EMT (+)	[86]
		UPF1/TGF-β/Smad/ZEB1	EMT (+), proliferation (+), invasion (+), migration (+)	[88]
		miR-181a-5p/E2F5	Tumor growth (+), migration (+), invasion (+)	[89]
		miR-760/FOXC1	Proliferation (+), tumor growth (+)	[90]
		miR-181/JAK2	Proliferation (+), tumorigenesis (+)	[94]
		miR-26a-5p/ULK1	Autophagy (+), drug resistance (+)	[95]
SNHG1	↑	miR-137/RICTOR	Tumorigenesis (+), metastasis (+), unfavourable prognosis (+)	[96]
		miR-497-5p	EMT (+), tumor growth (+)	[97]
		miR-195-5p	EMT (+), tumor growth (+)	[97]
SNHG3	↑	miR-539/RUNX2	Tumor growth (+), metastasis (+)	[98]
SNHG12	↑	KLF5	Tumorigenesis (+), proliferation (+)	[99]
SNHG17	↑	miR -339-5p/FOSL2	Proliferation (+), metastasis (+)	[100]
SNHG16	↑	miRNAs/SCD	Lipometabolism (+), tumorigenesis (+), proliferation (+)	[101]

[1]lncRNA SNHGs either up-regulated (↑) or down-regulated (↓) in CRC cells

[2]lncRNAs either promote (+) or inhibit (−) various physiological processes of CRC

of miR-181a-5p. When SNHG6 is highly expressed, it can inhibit the expression level of miR-181a-5p, attenuate the repressive effect of miR-181a-5p on a critical transcription factor E2F5, and promote tumor growth, cancer cell migration and invasion [89]. In addition, SNHG6 can also target the regulation of miR-760 and activate forkhead box C1 (FOXC1) to promote the occurrence and development of CRC [90].

Janus kinase 2 (JAK2) is a non-receptor tyrosine kinase, which can regulate the processes of apoptosis and proliferation [91]. It has been confirmed that its expression is significantly increased in various tumor cells, including CRC cells [92, 93]. Lai et al. have found that SNHG6 inhibits the expression of miR-181, up-regulates the expression level of JAK2, and plays an active role in the proliferation and development of CRC tissues and cell lines [94]. Interestingly, SNHG6 not only interacts with the above miRNAs to regulate the development process of CRC, but also induces chemoresistance. For example, SNHG6 can bind and inhibit miR-26a-5p, improve ULK1 expression, enhance autophagy, and induce CRC cells to produce chemotherapy resistance [95].

In conclusion, SNHG6 can participate in and regulate the physiological processes, such as proliferation, differentiation and migration of CRC, which is closely related to the degree of tumor malignancy. Meanwhile, SNHG6 can also induce chemoresistance in CRC tissues and cell lines. SNHG6 may become a fresh biomarker in the diagnosis, treatment and prognosis of CRC.

Other SNHGs and CRC

In addition to the SNHG6 as mentioned above, many SNHGs family members can regulate the development of CRC. For example, the expression level of SNHG1 is significantly up-regulated in CRC tissues and cell lines, which may be related to lymph node metastasis, advanced tumor node metastasis (TNM) stage and poor prognosis. In this process, SNHG1 can target and regulate miR-137, promote the expression of the rapamycin-insensitive companion of mTOR (RICTOR), and then induce the further deterioration of CRC [96]. Additionally, SNHG1 can also adsorb downstream miR-497-5p and miR-195-5p and accelerate the EMT process and tumor deterioration by regulating miR-497-5p and miR-195-5p [97]. Similarly, it is confirmed that SNHG3 is higher in CRC than in adjacent normal tissues. When SNHG3 is highly expressed, the expression of miR-539 is drastically inhibited, the expression level of runt-related transcription factor 2 (RUNX2) is significantly increased, and the growth and metastasis of CRC cells are enhanced [98]. In addition, SNHG12 targets kruppel-like factor 5 (KLF5) and plays an active role in the occurrence and development of CRC [99]. A recent study by Bian et al. has shown that SNHG17, which is highly expressed in CRC cells, can adsorb and regulate miR-339-5p and promote the expression of FOSL2. When FOSL2 is highly expressed, it can positively regulate SNHG17. The formed positive and negative feedback loop of SNHG17-miR-339-5p-FOSL2-SNHG17 can further promote the proliferation and metastasis of cancer cells [100]. SNHG16 is a carcinogenic lncRNA, which can target and regulate multiple miRNAs in CRC, up-regulate the expression level of stearoyl-CoA desaturase (SCD), participate in the regulation of lipid metabolism, and exert oncogenic effects [101]. More interestingly, single nucleotide polymorphisms in rs7353, rs8038, and rs15278 of SNHG16 affect the binding sites of SNHG16 and its target genes (such as miRNAs), which regulate susceptibility to CRC [102]. However, the gene polymorphism on SNHG16 and related targeting molecules are largely unclear. Likewise, the correlation mechanism between single nucleotide polymorphisms of rs7353, rs8038 and rs15278, and the expression level of SNHG16 remains to be elucidated.

LncRNAs related to radiotherapy of CRC

Currently, the methods widely used in the clinical treatment of CRC mainly include surgical resection, chemotherapy, radiotherapy and immunotherapy [5]. Among them, radiotherapy is regarded as an essential treatment for CRC, especially for patients with locally advanced CRC [103]. Unfortunately, with the increasing number of radiotherapy, the increased resistance of CRC cells to radiotherapy has become a main obstacle to the treatment of cancer, which can lead not only to tumor recurrence, but also to poor prognosis. Its molecular mechanism has not meant fully appreciated [6]. Therefore, to inhibit radiotherapy resistance and improve its effect, it is of urgent necessity to study the molecular mechanism of radiotherapy resistance in CRC. Surprisingly, recent study shows the disorders in the expression of lncRNAs play an indispensable role in malignant tumors (including CRC), which can lead to the variation of biological behavior of tumor cells and even the alteration of tumor radiosensitivity [104]. In this regard, an increasing number of studies have attached immense importance to the molecular mechanisms of lncRNAs and radiation resistance (Table 4).

Some lncRNAs are highly expressed in CRC cells, which can narrow the sensitivity of cancer cells to radiation and improve the resistance to radiotherapy. For example, the expression of LINC00152 is significantly up-regulated in some CRC cells that survived after radiotherapy, and the invasion and metastasis of cancer cells are significantly enhanced as the effect of late radiotherapy decreases [105]. Likewise, LINC00958 is a member of the lncRNAs family.

Table 4 LncRNAs and radiotherapy resistance in CRC

LncRNAs	Expression[1]	Genes and pathways	Functions[2]	References
LINC00152	↑	——	Radiation resistance (+), invasion (+), metastasis (+)	[105]
LINC00958	↑	miR-422a/MAPK1	Radiation resistance (+), apoptosis (−)	[106]
LINC00630	↑	EZH2/BEX1	Radiation resistance (+), apoptosis (−)	[107]
LincRNA ROR	↑	P53/miR-145	Radiation resistance (+), apoptosis (−)	[108]
HOTAIR	↑	miR-93/ATG12	Radiation resistance (+), gene translation (+)	[109]
MALAT1	↑	miR-101-3p	Radiation resistance (+), tumorigenesis (+)	[110]
EGOT	↑	miR-211-5p/ErbB4	Radiation resistance (+), tumor growth (+)	[111]
lnc-RI	↑	miR-4727-5p/LIG4	Radiation resistance (+), unfavorable prognosis (+), apoptosis (−)	[112]
UCA1	↑	MMP2/MMP9/ZEB1/vimentin	Radiation resistance (+), EMT (+), migration (+), apoptosis (−)	[113]
lnc-TLCD2-1	↑	hsa-miR-193a-5p/YY1/NF-κB-P65	Radiation resistance (+), OS (−)	[114]
TTN-AS1	↑	miR-134-5p/PAK3/P21	Radiation resistance (+), autophagy (+), apoptosis (−)	[115]
OIP5-AS1	↓	miR-369-3p/DYRK1A	Radiation resistance (−), migration (−), apoptosis (+)	[116]
lincRNA-p21	↓	P53/Noxa/Wnt/β-catenin pathway	Radiation resistance (−), OS (+), unfavorable prognosis (−)	[117, 118]

[1]lncRNAs either up-regulated (↑) or down-regulated (↓) in CRC cells with radiotherapy resistance

[2]lncRNAs either promote (+) or inhibit (−) various physiological processes of CRC

It can precisely regulate the expression of miR-422a and is involved in the direct binding of miR-422a to the 3'- UTR of mitogen-activated protein kinase 1 (MAPK1), thereby increasing the expression of MAPK1, reducing apoptosis and improving radiation resistance in cancer cells [106]. Additionally, aberrant expression of LINC00630 in CRC tissues and cell lines is also a factor affecting radiation resistance. It can form a complex with EZH2, negatively regulate BEX1 through promoter DNA methylation, induce the BEX1 silencing, significantly increase the vitality of cancer cells, inhibit cancer cell apoptosis, and promote radiation resistance [107].

It is worthwhile noting that the long intergenic non-coding RNA (lincRNA) is in the category of lncRNAs, and its expression level is also closely related to radiotherapy resistance. For example, lincRNA ROR is up-regulated in CRC cell lines and tissues, inhibits the p53/miR-145 pathway and improves radiotherapy resistance in CRC cells [108]. Liu et al. have found lincRNA in plasma and CRC cells from CRC patients treated with radiotherapy. The expression of homeobox transcript antisense intergenic RNA (HOTAIR) is significantly up-regulated. LincRNA HOTAIR inhibits the expression of miR-93, up-regulates the expression level of autophagy-related 12 (ATG12) protein, and significantly decreases the radiosensitivity of cancer cells [109].

Of course, in addition to the above lncRNAs, many lncRNAs can enhance the radiation resistance of cancer cells and reduce the survival time of patients by regulating some molecular pathways. It has been demonstrated that MALAT1, a ceRNA for miR-101-3p, inhibits the expression of miR-101-3p and enhances radiation tolerance of CRC cells [110]. Eosinophil granule ontogeny transcript (EGOT) acts as a sponge for miR-211-5p and inhibits the expression of miR-211-5p, thereby enhancing the expression of ErbB4, a downstream target of miR-211-5p, and decreasing the radiotherapy sensitivity of cancer cells [111]. Similarly, lnc-RI/miR-4727-5p/ligase 4 (LIG4) axis, urothelial carcinoma-associated 1 (UCA1)/MMP2/MMP9/ZEB1/vimentin pathway, and lnc-TLCD2-1/hsa-miR-193a-5p/Yin Yang 1 (YY1)/NF-κB-p65 regulatory cascade can affect radiation resistance of CRC cells and the OS of patients [112–114]. Furthermore, Zuo et al. have found that TTN antisense RNA 1 (TTN-AS1) is highly expressed in CRC cells after simulating radiotherapy in vitro, which could negatively regulate the expression of miR-134-5p and significantly increase the expression of PAK3 and P21 proteins. On the one hand, when PAK3 is highly expressed, it can promote AKT and GSK-3β phosphorylation and, in regulating the β-catenin pathway, can improve the radiation resistance of cancer cells. On the other hand, when P21 protein is highly expressed, it can reduce the radiosensitivity of cancer cells and inhibit X-ray-induced apoptosis [115].

It is worthwhile mentioning that some lncRNAs can enhance the sensitivity of CRC cells to radiation and inhibit tumor proliferation. As an example, OIP5 antisense RNA 1(OIP5-AS1) inhibits miR-369-3p expression. Subsequently, the downstream gene of miR-369-3p is up-regulated to express dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A), which inhibits the viability of CRC cells and enhances apoptosis of cancer cells after radiation exposure [116]. Compared with normal tissue cells, lincRNA-p21 is low expressed in CRC cells. When highly

expressed, it improves radiotherapy sensitivity and predicts higher OS, which may be related to P53, Noxa and the Wnt/β-catenin signaling pathway [117, 118].

In summary, with the gradual deepening of research, an increasing number of lncRNAs have been verified to play a significant role in radiotherapy resistance in CRC cells and provide a promising strategy for treating patients with radiotherapy resistance. However, before these schemes are implemented in clinical first-line treatment, further research on the mechanisms of lncRNAs involvement in signaling pathways and many clinical experimental samples are needed. Supplementary research should take these issues into account.

LncRNAs related to chemotherapy of CRC

With the progressive research of the gene-level research of CRC cells, a considerable number of lncRNAs are found to be dysregulated in tumor cells, which is closely linked to cancer progression and chemoresistance. At the same time, more and more studies have shown that lncRNAs may affect the drug resistance of CRC cells to chemotherapeutic drugs by regulating some genes and signaling pathways (Table 5). For example, MIR22HG and PCBP1 antisense RNA 1 (PCBP1-AS1) can regulate the expression of hsa-miR-1827 and hsa-miR-582-5p, respectively, and thus inhibit the proliferation, invasion and chemoresistance of CRC cells. In contrast, urothelial carcinoma associated 1 (UCA1) and SNHG16 can regulate the expression of hsa-miR-198 and improve chemoresistance [119].

LncRNAs and 5-fluorouracil resistance

5-Fluorouracil (5-FU) is the standard pyrimidine analog for CRC, which can block thymidylate synthase and further inhibit the synthesis of DNA and RNA. It often serves as a first-line drug in CRC chemotherapy [120]. However, with the accumulation of medication time, CRC cells are prone to develop 5-FU resistance, which reduces the efficacy and is accompanied by poor prognosis [121]. It is worth mentioning that after studying 5-FU-resistant CRC cells and 5-FU-sensitive CRC cells, significant differences were found in the expression levels of lncRNAs between them. For example, some studies have found that nuclear paraspeckle assembly transcript 1 (NEAT1) is highly expressed in 5-FU-resistant CRC cells, which can inhibit the expression of miR-34a and regulate the binding sites involved in autophagy activation in the 3'-UTR of high mobility group box 1 (HMGB1), autophagy-related proteins ATG9A and ATG4B, to enhance autophagy and reduce the sensitivity of cancer cells to 5-FU, to improve the 5-FU resistance in CRC [122]. At the same time, NEAT1 can act as a ceRNA for miR-150-5p, induce the down-regulation of miR-150-5p expression, up-regulate the expression of cleavage and polyadenylation specific factor 4 (CPSF4), and then reduce the sensitivity of CRC cells to 5-FU [123]. In addition, NEAT1 can affect chromatin remodeling in tumor stem cells, increase the acetylation level of histone, increase its enrichment on ALDH1 and c-Myc promoters, promote the expression of ALDH1 and c-Myc, and thus enhance the resistance of CRC cells to 5-FU [124].

Xian et al. have discovered that UCA1 is highly expressed in CRC cells. When its expression is down-regulated, it can target to regulate miR-23b-3p and up-regulate the expression

Table 5 LncRNAs and chemoresistance in CRC

LncRNAs	Expression[1]	Genes and pathways	Chemotherapy-resistant drugs	Drug resistance	References
MIR22HG	↓	hsa-miR-1827	——	Down	[119]
PCBP1-AS1	↓	hsa-miR-582-5p	——	Down	[119]
SNHG16	↑	hsa-miR-198	——	Up	[119]
UCA1	↑	hsa-miR-198	——	Up	[119]
		miR-23b-3p/ZNF281	5-Fluorouracil	Up	[125]
NEAT1	↑	miR-34a/HMGB1/ATG9A/ATG4B	5-Fluorouracil	Up	[122]
		miR-150-5p/CPSF4	5-Fluorouracil	Up	[123]
		ALDH1/c-Myc	5-Fluorouracil	Up	[124]
ANRIL	↑	let-7a/TGF-β1/ Smad	5-Fluorouracil	Up	[126]
cCSC1	↑	SMO/GLI1/Hedgehog pathway	5-Fluorouracil	Up	[127]
HAND2-AS1	↓	miR-20a/PDCD4	5-Fluorouracil	Down	[128]
BORG	↑	P53	Carboplatin	Up	[129]
AGAP2-AS1	↑	miR-497/FGFR1	Gemcitabine	Up	[130]

[1]lncRNAs either up-regulated (↑) or down-regulated (↓) in chemotherapy-resistant CRC cells

of zinc finger protein 281 (ZNF281), promote the process of apoptosis, and inhibit the drug resistance of CRC cells to 5-FU [125]. Similarly, antisense non-coding RNA in the INK4 locus (ANRIL) is also an lncRNA molecule. As a molecular sponge of serum let-7a, it negatively regulates the expression of let-7a and then regulates the TGF-β1/Smad signaling pathway inducing 5-FU resistance and tumor metastasis in CRC cells [126]. In CRC cells and tissues, overexpression of lncRNA cCSC1 activates the Hedgehog pathway and alters the expression of smoothened (SMO) and GLI family zinc finger 1 (GLI1) in the Hedgehog pathway, thereby enhancing the self-renewal ability and 5-FU resistance of tumor stem cells [127].

Nevertheless, not all lncRNAs can improve 5-FU resistance. Some lncRNAs can reduce chemotherapy resistance. For example, compared with 5-FU-tolerant CRC cells, HAND2 antisense RNA 1 (HAND2-AS1) is highly expressed in 5-FU-sensitive CRC cells. It has been observed that HAND2-AS1 can up-regulate the secretion of programmed cell death factor 4 (PDCD4) by inhibiting the expression of miR-20a, inhibiting the resistance of CRC cells to 5-FU, and inducing apoptosis in cancer cells [128]. Thus, HAND2-AS1 may be a promising therapeutic target for reversing 5-FU resistance in CRC patients.

LncRNAs and other drug resistance

In addition to lncRNAs regulating 5-FU resistance in CRC tissues and cell lines, lncRNAs are also involved in regulating resistance to many other chemotherapeutic drugs, such as carboplatin, gemcitabine and many other drugs in the chemotherapy of CRC. Recently, it has been reported that lncRNA BMP/OP-responsive gene (BORG) is involved in the drug resistance of CRC cells to carboplatin and induces CRC cells to develop drug resistance to carboplatin inhibiting the expression of tumor-suppressor P53 from reducing the effect of chemotherapy [129]. Additionally, Hong et al. have found that AGAP2 antisense RNA 1 (AGAP2-AS1) is highly expressed in gemcitabine-resistant CRC cells, targets miR-497, increases the expression of fibroblast growth factor receptor 1 (FGFR1), enhances the vitality and mobility of cancer cells, and endows CRC cells with gemcitabine resistance [130].

However, little is recognized about how lncRNAs participate and regulate the process and mechanism of chemoresistance. In the clinical treatment of CRC, some CRC cells are highly resistant to some chemotherapeutic drugs, which also dramatically improve the malignancy of CRC and seriously affect the survival time of patients. It is necessary to explore further the distinctive action pathways of lncRNAs in drug resistance and combine traditional chemotherapy with drugs targeting lncRNAs to treat CRC patients who are resistant to some chemotherapeutic drugs.

LncRNAs as prognostic factors of CRC

Currently, the most common treatments for CRC are surgery, postoperative radiotherapy and chemotherapy [5]. Nevertheless, about 25–40% of CRC patients will have tumor recurrence [131]. Regardless of the fact that the classical staging system commonly used in clinical practice is widely used, it is not yet sufficient to predict the prognosis due to inter- and intra-tumor heterogeneity [132]. Therefore, the search for highly sensitive and accurate molecular biomarkers is crucial to improve prognosis. With the deepening of genetic research, more and more experimental results have revealed that the expression levels of lncRNAs are related to the prognosis of CRC patients (Table 6) [133, 134]. On the one hand, lncRNAs can serve as critical regulatory factors for regulating the development process of CRC in the Toll-like receptor (TLR) signaling networks [135]. On the other hand, lncRNAs can participate in and regulate signaling pathways associated with the occurrence and development of CRC, such as cell cycle, DNA replication, mismatch repair, oxidative phosphorylation, autophagy regulation, and insulin signaling pathway, and predict the prognosis of patients with CRC [136].

Generally, the expression level of lncRNAs, which can be invoked as tumor prognosis indicators, is positively correlated with the degree of poor prognosis. For example, increased expression of lncRNA differentiation antagonizing non-protein coding RNA (DANCR) in CRC cells indicates a shorter survival time for patients with CRC [137]. Additionally, high expression of LINC01116 in CRC tissues and cell lines also indicates poor prognosis. Recent studies by Bi et al. have shown that LINC01116 can negatively regulate miR-9-5p, promote up-regulation of STMN1 expression, and promote distant tumor migration and lymph node metastasis [138]. In addition, overall survival (OS), disease-free survival (DFS) and release-free survival (RFS) are significantly shorter when MAFG antisense RNA 1 (MAFG-AS1) and HOTAIR are highly expressed in patients with CRC. Further studies have revealed that high expression of HOTAIR is also related to venous invasion, advanced tumor invasion and distant metastasis [139, 140]. Chen et al. have found that the highly expressed lncRNA ADAMTS9-AS1 can regulate and promote physiological processes in CRC tissues and cell lines, such as TNM stage, lymph node infiltration, G1/S infiltration, migration, invasion and EMT [141]. In addition, LUNAR1, a molecular sponge for miR-495-3p, inhibits the expression of miR-495-3p, induces the up-regulation of Myc binding protein (MYCBP), promotes proliferation, migration, and invasion of CRC cells, and predicts lower OS of

Table 6 LncRNAs and prognosis of CRC

LncRNAs	Expression[1]	Genes and pathways	Functions[2]	References
DANCR	↑	——	Unfavorable prognosis (+), tumor growth (+)	[137]
LINC01116	↑	miR-9-5p/STMN1	Unfavorable prognosis (+), migration (+), metastasis (+)	[138]
MAFG-AS1	↑	——	Unfavorable prognosis (+), OS (−), DFS (−), RFS (−)	[139]
HOTAIR	↑	——	Unfavorable prognosis (+), OS(−), DFS (−), RFS (−), invasion (+), tumor growth (+), metastasis (+)	[140]
ADAMTS9-AS1	↑	——	Unfavorable prognosis (+), TNM (+), migration (+), invasion (+), EMT (+)	[141]
LUNAR1	↑	miR-495-3p/MYCBP	Unfavorable prognosis (+), proliferation (+), migration (+), invasion (+), OS (−)	[142]
NEAT1	↑	——	Unfavorable prognosis (+), migration (+)	[143]
XIST	↑	——	Unfavorable prognosis (+), invasion (+), cellular differentiation (+), metastasis (+), migration (+)	[144]
GACAT3	↑	LINC00152/miR-103	Unfavorable prognosis (+), lymphatic metastasis (+), TNM (+)	[146]
LINC00152	↑	GACAT3/miR-103	Unfavorable prognosis (+), lymphatic metastasis (+), TNM (+)	[146]
SNHG11	↑	Hippo pathway	Unfavorable prognosis (+), proliferation (+), metastasis (+)	[147]
ZFAS1	↑	——	Unfavorable prognosis (+), proliferation (+), metastasis (+)	[147]
LINC00909	↑	——	Unfavorable prognosis (+), proliferation (+), metastasis (+)	[147]
LINC00654	↑	——	Unfavorable prognosis (+), proliferation (+), metastasis (+)	[147]
MALAT1	↑	hsa-miR-194-5p	Unfavorable prognosis (+), OS (−), DFS (−)	[148]
MFI2-AS1	↑	mRNA/TFs	Unfavorable prognosis (+), tumorigenesis (+), OS (−)	[149]

[1]lncRNAs either up-regulated (↑) or down-regulated (↓) in CRC cells

[2]lncRNAs either promote (+) or inhibit (−) various physiological processes of CRC

patients [142]. Nuclear paraspeckle assembly transcript 1 (NEAT1) is a particular class of lncRNAs. Interestingly, its level is higher in the serum of patients with CRC than in CRC cells and adjacent normal tissues. Therefore, metastatic CRC and non-metastatic CRC can be well distinguished according to the expression of serum NEAT1. NEAT1 is considered as a biomarker and potential prognostic indicator to distinguish the types of CRC [143]. It has been verified that CRC cell-derived extracellular vesicles (EVS) can promote tumor growth. Yu et al. have found that X inactive-specific transcript (XIST) derived from EVs can be used as a biological indicator to diagnose and predict CRC. CRC patients with high expression of XIST have lower 5-year survival rates, shorter life cycles, less differentiation, and a higher probability of lymph node metastasis and tumor metastasis [144].

It is worth noticing that the performance of a single biomarker in predicting patient survival and prognosis is inconsistent across different data sets. In contrast, the combination of multiple biomarkers can improve the accuracy of the results [145]. For example, gastric cancer-associated transcript 3 (GACAT3) and LINC00152 are highly expressed and associated with each other in patients with colorectal cancer. At the same time, they can regulate miR-103. The expression levels of the two lncRNAs are positively correlated with the depth of invasion, lymph node metastasis and TNM stage. By identifying and comparing any lncRNA in GACAT3 and LINC00152, it is found that the combination of GACAT3 and LINC00152 shows more vital diagnostic and prognostic abilities [146]. Additionally, Xu et al. have found that lncRNA SNHG11 can target the Hippo pathway to promote the proliferation and metastasis of CRC. Although the specific mechanism and regulatory pathway of SNHG11 are not clear, it is found that the combined detection of the expression levels of four lncRNAs (SNHG11, ZFAS1, LINC00909 and LINC00654) is more prominent in the diagnosis and pre- and post-treatment effects of early colorectal cancer compared with the detection of single SNHG11 levels, which has important clinical implications [147]. More interestingly, binding site polymorphism of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) gene is also associated with CRC risk and prognosis. MALAT1 is negatively correlated with the expression of hsa-miR-194-5p. MALAT1 can inhibit the expression of hsa-miR-194-5p. Meanwhile, carriers of the G allele of the MALAT1 gene rs664589 have a relatively higher risk of developing CRC [148]. However, the mechanism of the role of hsa-miR-194-5p in the development of colorectal cancer is unclear and needs to be further investigated. In addition, studies have shown that MFI2 antisense RNA 1 (MFI2-AS1) is negatively correlated with OS in patients with stage III/IV CRC. Its potential target mRNA is mainly involved in the cell cycle and cytokine-cytokine receptor interaction. At the same time, it has 17 potential transcriptional factors (TFs),

which can form lncRNA-TF-mRNA interaction networks. Through this molecular network, one can perform molecular targeting therapy and predict the prognosis of CRC patients [149].

Therefore, the above lncRNAs may become valuable biomarkers and potential prognostic indicators, providing new directions for the diagnosis and prognosis of CRC patients. However, although the prognosis of a variety of abnormally expressed lncRNAs in CRC is more accurate than that of a single lncRNA, the interaction and interaction mechanisms of different lncRNAs in combination and the signaling pathways of lncRNA-TF-mRNA networks are still unclear and need further investigation.

Conclusion

At present, the clinical treatment effect of CRC is still far from satisfactory. How to carry out correct early screening, early diagnosis, effective intervention, and treatment of CRC is a crucial issue in the current treatment of CRC. The intimate relationship between lncRNAs and the development of CRC has attracted extensive attention from the field of the academy. Also, it provides a pleasant prospect for the early diagnosis and effective treatment of CRC. In this review, the authors describe the potential application value of lncRNAs as biomarkers for diagnosis, radiotherapy resistance, chemotherapy resistance, prognosis and treatment, and describe the critical significance of lncRNA SNHGs family and lncRNA–miRNA networks in regulating the occurrence and development of CRC. Growing investigations are helpful to decipher novel CRC-related lncRNAs, unravel their structures and potential capabilities in CRC screening, diagnosis, radiotherapy, chemotherapy and prognosis, contributing to the developing of clinically targeted drugs and improving the accuracy of CRC diagnosis and prognosis. Unfortunately, up to now, despite the fact that lncRNAs are hopeful biomarkers and potential targets for diagnosing and treating CRC, the detailed functional mechanism of lncRNAs is deeply unclear and lacks clinical verification. Importantly, current preclinical and clinical studies using human body as sampling are greatly insufficient. Additionally, the targets and signaling pathways of lncRNAs in CRC need to be further explored. Nevertheless, it is believed that intensive experimental and clinical studies related to lncRNAs will soon become diagnostic targets and therapeutic strategies for CRC.

Acknowledgements We sincerely thank the help from Dr. Caowen Wang and Prof. Xuelin Yang of Analysis and Testing Center, China Three Gorges University for their suggestions.

Author contributions YL wrote and revised the manuscript. YW reviewed the literature and approved the version to be published. ZZ, JB and HS participated in the revision and polishing of the manuscript.

Funding This work was supported by the National Natural Science Foundation of China (grant no. 81602559), sponsored by Research Fund for Excellent Dissertation of China Three Gorges University (2019SSPY107) and by Youth Science Fund Program of China Three Gorges University (grant no. 1115064).

Availability of data and materials Not applicable.

Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

Research involving human participants or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication Informed consent was obtained from all individual participants included in the study.

References

1. Kang L, Chen YG, Zhang H, et al. Transanal total mesorectal excision for rectal cancer: a multicentric cohort study. Gastroenterol Rep (Oxf). 2019;8(1):36–41.
2. Rejhová A, Opattová A, Čumová A, Slíva D, Vodička P. Natural compounds and combination therapy in colorectal cancer treatment. Eur J Med Chem. 2018;144:582–94.
3. Modest DP, Pant S, Sartore-Bianchi A. Treatment sequencing in metastatic colorectal cancer. Eur J Cancer. 2019;109:70–83.
4. Loree JM, Kopetz S. Recent developments in the treatment of metastatic colorectal cancer. Ther Adv Med Oncol. 2017;9(8):551–64.
5. Lee GC, Bordeianou LG, Francone TD, et al. Superior pathologic and clinical outcomes after minimally invasive rectal cancer resection, compared to open resection. Surg Endosc. 2020;34(8):3435–48.
6. Li CC, Liang JA, Chen WT, Chien CR. Effectiveness of image-guided radiotherapy for rectal cancer patients treated with neoadjuvant concurrent chemoradiotherapy: a population-based propensity score-matched analysis. Asia Pac J Clin Oncol. 2019;15(5):e197–203.
7. Van der Jeught K, Xu HC, Li YJ, Lu XB, Ji G. Drug resistance and new therapies in colorectal cancer. World J Gastroenterol. 2018;24(34):3834–48.
8. Compton C, Fenoglio-Preiser CM, Pettigrew N, Fielding LP. American joint committee on cancer prognostic factors consensus conference: colorectal working group. Cancer. 2000;88(7):1739–57.
9. Duffy MJ, van Dalen A, Haglund C, et al. Tumour markers in colorectal cancer: European group on tumour markers (EGTM) guidelines for clinical use. Eur J Cancer. 2007;43(9):1348–60.
10. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol. 2006;24(33):5313–27.
11. Primrose JN, Perera R, Gray A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. JAMA. 2014;311(3):263–70.
12. Tsai MC, Spitale RC, Chang HY. Long intergenic noncoding RNAs: new links in cancer progression. Cancer Res. 2011;71(1):3–7.

13. Chen Y, Zhou J. LncRNAs: macromolecules with big roles in neurobiology and neurological diseases. Metab Brain Dis. 2017;32(2):281–91.
14. Kapranov P, Cheng J, Dike S, et al. RNA maps reveal new RNA classes and a possible function for pervasive transcription. Science. 2007;316(5830):1484–8.
15. Hung J, Miscianinov V, Sluimer JC, Newby DE, Baker AH. Targeting non-coding RNA in vascular biology and disease. Front Physiol. 2018;9:1655.
16. Wang X, Arai S, Song X, et al. Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription. Nature. 2008;454(7200):126–30.
17. Lee JT. Epigenetic regulation by long noncoding RNAs. Science. 2012;338(6113):1435–9.
18. Maruyama R, Suzuki H. Long noncoding RNA involvement in cancer. BMB Rep. 2012;5(11):604–11.
19. Kung JT, Colognori D, Lee JT. Long noncoding RNAs: past, present, and future. Genetics. 2013;193(3):651–69.
20. Mercer TR, Mattick JS. Structure and function of long noncoding RNAs in epigenetic regulation. Nat Struct Mol Biol. 2013;20(3):300–7.
21. Gutschner T, Diederichs S. The hallmarks of cancer: a long noncoding RNA point of view. RNA Biol. 2012;9(6):703–19.
22. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? Cell. 2011;146(3):353–8.
23. Zhang Y, Tang L. The application of lncRNAs in cancer treatment and diagnosis. Recent Pat Anticancer Drug Discov. 2018;13(3):292–301.
24. Wu P, Mo Y, Peng M, et al. Emerging role of tumor-related functional peptides encoded by lncRNA and circRNA. Mol Cancer. 2020;19(1):22.
25. Ghafouri-Fard S, Hussen BM, Gharebaghi A, Eghtedarian R, Taheri M. LncRNA signature in colorectal cancer. Pathol Res Pract. 2021;222: 153432.
26. Bykov VJ, Zhang Q, Zhang M, Ceder S, Abrahmsen L, Wiman KG. Targeting of mutant p53 and the cellular redox balance by APR-246 as a strategy for efficient cancer therapy. Front Oncol. 2016;6:21.
27. Schuler M, Green DR. Mechanisms of p53-dependent apoptosis. Biochem Soc Trans. 2001;29(Pt 6):684–8.
28. Prokocimer M, Molchadsky A, Rotter V. Dysfunctional diversity of p53 proteins in adult acute myeloid leukemia: projections on diagnostic workup and therapy. Blood. 2017;130(6):699–712.
29. Wei LJ, Bai DM, Wang ZY, Liu BC. Up-regulated lncRNA CACNA1G-AS1 aggravates the progression of colorectal cancer by downregulating p53. Eur Rev Med Pharmacol Sci. 2020;24(1):130–6.
30. Xue W, Wang F, Han P, et al. The oncogenic role of LncRNA FAM83C-AS1 in colorectal cancer development by epigenetically inhibits SEMA3F via stabilizing EZH2. Aging (Albany NY). 2020;12(20):20396–412.
31. Niwa Y, Kanda H, Shikauchi Y, et al. Methylation silencing of SOCS-3 promotes cell growth and migration by enhancing JAK/STAT and FAK signalings in human hepatocellular carcinoma. Oncogene. 2005;24(42):6406–17.
32. Li D, Wen S. Silencing of lncRNA LINC00346 inhibits the proliferation and promotes the apoptosis of colorectal cancer cells through inhibiting JAK1/STAT3 signaling. Cancer Manag Res. 2020;12:4605–14.
33. Xue J, Liao L, Yin F, Kuang H, Zhou X, Wang Y. LncRNA AB073614 induces epithelial- mesenchymal transition of colorectal cancer cells via regulating the JAK/STAT3 pathway. Cancer Biomark. 2018;21(4):849–58.
34. Duan Q, Cai L, Zheng K, et al. lncRNA KCNQ1OT1 knockdown inhibits colorectal cancer cell proliferation, migration and invasiveness via the PI3K/AKT pathway. Oncol Lett. 2020;20(1):601–10.
35. Chen C, Wei M, Wang C, et al. Long noncoding RNA KCNQ1OT1 promotes colorectal carcinogenesis by enhancing aerobic glycolysis via hexokinase-2. Aging (Albany NY). 2020;12(12):11685–97.
36. Liu J, Qian J, Mo Q, Tang L, Xu Q. LncRNA NR2F2-AS1 silencing induces cell cycle arrest in G0/G1 phase via downregulating cyclin D1 in colorectal cancer. Cancer Manag Res. 2020;12:1835–43.
37. Meng N, Chen M, Chen D, et al. Small protein hidden in lncRNA LOC90024 promotes "cancerous" RNA splicing and tumorigenesis. Adv Sci (Weinh). 2020;7(10):1903233.
38. Tang GH, Chen X, Ding JC, et al. LncRNA LUCRC regulates colorectal cancer cell growth and tumorigenesis by targeting endoplasmic reticulum stress response. Front Genet. 2020;10:1409.
39. Yang X, Tao H, Wang C, Chen W, Hua F, Qian H. lncRNA-ATB promotes stemness maintenance in colorectal cancer by regulating transcriptional activity of the β-catenin pathway. Exp Ther Med. 2020;19(4):3097–103.
40. Yang X, Wu S, Li X, Yin Y, Chen R. MAGI2-AS3 rs7783388 polymorphism contributes to colorectal cancer risk through altering the binding affinity of the transcription factor GR to the MAGI2-AS3 promoter. J Clin Lab Anal. 2020;34(10): e23431.
41. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009;136(2):215–33.
42. Friedman RC, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res. 2009;19(1):92–105.
43. Wu X, He X, Li S, Xu X, Chen X, Zhu H. Long non-coding RNA ucoo2kmd.1 regulates CD44-dependent cell growth by competing for miR-211–3p in colorectal cancer. PLoS One. 2016;11(3):e0151287.
44. Huang G, Wu X, Li S, Xu X, Zhu H, Chen X. The long noncoding RNA CASC2 functions as a competing endogenous RNA by sponging miR-18a in colorectal cancer. Sci Rep. 2016;6:26524.
45. Zhu Y, Qiao L, Zhou Y, Ma N, Wang C, Zhou J. Long noncoding RNA FOXD2-AS1 contributes to colorectal cancer proliferation through its interaction with microRNA-185-5p. Cancer Sci. 2018;109(7):2235–42.
46. Vu T, Datta PK. Regulation of EMT in colorectal cancer: a culprit in metastasis. Cancers (Basel). 2017;9(12):171.
47. Huarte M. The emerging role of lncRNAs in cancer. Nat Med. 2015;21(11):1253–61.
48. Tao Y, Han T, Zhang T, Ma C, Sun C. LncRNA CHRF-induced miR-489 loss promotes metastasis of colorectal cancer via TWIST1/EMT signaling pathway. Oncotarget. 2017;8(22):36410–22.
49. Li J, Zhao LM, Zhang C, et al. The lncRNA FEZF1-AS1 promotes the progression of colorectal cancer through regulating OTX1 and targeting miR-30a-5p. Oncol Res. 2020;28(1):51–63.
50. Yan Z, Bi M, Zhang Q, Song Y, Hong S. LncRNA TUG1 promotes the progression of colorectal cancer via the miR-138-5p/ZEB2 axis. Biosci Rep. 2020;40(6):BSR20201025.
51. Lou T, Ke K, Zhang L, Miao C, Liu Y. LncRNA PART1 facilitates the malignant progression of colorectal cancer via miR-150-5p/LRG1 axis. J Cell Biochem. 2020;121(10):4271–81.
52. Kono M, Fujii T, Lim B, Karuturi MS, Tripathy D, Ueno NT. Androgen receptor function and androgen receptor-targeted therapies in breast cancer: a review. JAMA Oncol. 2017;3(9):1266–73.
53. LoRusso PM. Inhibition of the PI3K/AKT/mTOR pathway in solid tumors. J Clin Oncol. 2016;34(31):3803–15.
54. Liu B, Pan S, Xiao Y, Liu Q, Xu J, Jia L. LINC01296/miR-26a/GALNT3 axis contributes to colorectal cancer progression by

regulating O-glycosylated MUC1 via PI3K/AKT pathway. J Exp Clin Cancer Res. 2018;37(1):316.
55. Wu H, Wei M, Jiang X, et al. lncRNA PVT1 promotes tumorigenesis of colorectal cancer by stabilizing miR-16-5p and interacting with the VEGFA/VEGFR1/AKT Axis. Mol Ther Nucleic Acids. 2020;20:438–50.
56. Bai N, Ma Y, Zhao J, Li B. Knockdown of lncRNA HCP5 suppresses the progression of colorectal cancer by miR-299-3p/PFN1/AKT Axis. Cancer Manag Res. 2020;12:4747–58.
57. Li B, Sun H, Zhang J. LncRNA DSCAM-AS1 promotes colorectal cancer progression by acting as a molecular sponge of miR-384 to modulate AKT3 expression. Aging (Albany NY). 2020;12(10):9781–92.
58. Lin H, Hong YG, Zhou JD, et al. LncRNA INHBA-AS1 promotes colorectal cancer cell proliferation by sponging miR-422a to increase AKT1 axis. Eur Rev Med Pharmacol Sci. 2020;24(19):9940–8.
59. Xu G, Wang H, Yuan D, et al. RUNX1-activated upregulation of lncRNA RNCR3 promotes cell proliferation, invasion, and suppresses apoptosis in colorectal cancer via miR-1301-3p/AKT1 axis in vitro and in vivo. Clin Transl Oncol. 2020;22(10):1762–77.
60. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.
61. Deshpande A, Sicinski P, Hinds PW. Cyclins and cdks in development and cancer: a perspective. Oncogene. 2005;24(17):2909–15.
62. Malumbres M, Barbacid M. Cell cycle, CDKs and cancer: a changing paradigm. Nat Rev Cancer. 2009;9(3):153–66.
63. Gao Z, Zhou H, Wang Y, Chen J, Ou Y. Regulatory effects of lncRNA ATB targeting miR-200c on proliferation and apoptosis of colorectal cancer cells. J Cell Biochem. 2020;121(1):332–43.
64. Gong T, Li Y, Feng L, et al. CASC21, a FOXP1 induced long non-coding RNA, promotes colorectal cancer growth by regulating CDK6. Aging (Albany NY). 2020;12(12):12086–106.
65. Li F, Jiang Z, Shao X, Zou N. Downregulation of lncRNA NR2F2 antisense RNA 1 induces G1 arrest of colorectal cancer cells by downregulating cyclin-dependent kinase 6. Dig Dis Sci. 2020;65(2):464–9.
66. Ma X, Luo J, Zhang Y, Sun D, Lin Y. LncRNA MCM3AP-AS1 upregulates CDK4 by sponging miR-545 to suppress G1 arrest in colorectal cancer. Cancer Manag Res. 2020;12:8117–24.
67. Zhang Q, Chen Z. lncRNA UASR1 sponges miR-107 in colorectal cancer to upregulate oncogenic CDK8 and promote cell proliferation. Oncol Lett. 2020;20(6):305.
68. Li W, Yu W, Jiang X, et al. The construction and comprehensive prognostic analysis of the LncRNA-associated competitive endogenous RNAs network in colorectal cancer. Front Genet. 2020;11:583.
69. Danielsen SA, Eide PW, Nesbakken A, Guren T, Leithe E, Lothe RA. Portrait of the PI3K/AKT pathway in colorectal cancer. Biochim Biophys Acta. 2015;1855(1):104–21.
70. Jafarzadeh M, Soltani BM, Soleimani M, Hosseinkhani S. Epigenetically silenced LINC02381 functions as a tumor suppressor by regulating PI3K-Akt signaling pathway. Biochimie. 2020;171–172:63–71.
71. An Y, Zhang S, Zhang J, et al. Overexpression of lncRNA NLIPMT inhibits colorectal cancer cell migration and invasion by downregulating TGF-β1. Cancer Manag Res. 2020;12:6045–52.
72. Li N, Li J, Mi Q, et al. Long non-coding RNA ADAMTS9-AS1 suppresses colorectal cancer by inhibiting the Wnt/β-catenin signalling pathway and is a potential diagnostic biomarker. J Cell Mol Med. 2020;24(19):11318–29.
73. Yu B, Chen J, Hou C, Zhang L, Jia J. LncRNA H19 gene rs2839698 polymorphism is associated with a decreased risk of colorectal cancer in a Chinese Han population: a case-control study. J Clin Lab Anal. 2020;34(8): e23311.
74. Zhang Q, Ding Z, Wan L, et al. Comprehensive analysis of the long noncoding RNA expression profile and construction of the lncRNA-mRNA co-expression network in colorectal cancer. Cancer Biol Ther. 2020;21(2):157–69.
75. Bai J, Xu J, Zhao J, Zhang R. LncRNA NBR2 suppresses migration and invasion of colorectal cancer cells by down-regulating miRNA-21. Hum Cell. 2020;33(1):98–103.
76. Lin M, Li Y, Xian J, et al. Long non-coding RNA AGER-1 inhibits colorectal cancer progression through sponging miR-182. Int J Biol Markers. 2020;35(1):10–8.
77. Wang J, Dong S, Zhang J, et al. LncRNA NR2F1-AS1 regulates miR-371a-3p/TOB1 axis to suppress proliferation of colorectal cancer cells. Cancer Biother Radiopharm. 2020;35(10):760–4.
78. Yin SL, Xiao F, Liu YF, Chen H, Guo GC. Long non-coding RNA FENDRR restrains the aggressiveness of CRC via regulating miR-18a-5p/ING4 axis. J Cell Biochem. 2019. https://doi.org/10.1002/jcb.29555.
79. Zheng Z, Li X, You H, Zheng X, Ruan X. LncRNA SOCS2-AS1 inhibits progression and metastasis of colorectal cancer through stabilizing SOCS2 and sponging miR-1264. Aging (Albany NY). 2020;12(11):10517–26.
80. Williams GT, Farzaneh F. Are snoRNAs and snoRNA host genes new players in cancer? Nat Rev Cancer. 2012;12(2):84–8.
81. Qin Y, Sun W, Wang Z, et al. Long non-coding small nucleolar RNA host genes (SNHGs) in endocrine-related cancers. Onco Targets Ther. 2020;13:7699–717.
82. Li M, Bian Z, Yao S, et al. Up-regulated expression of SNHG6 predicts poor prognosis in colorectal cancer. Pathol Res Pract. 2018;214(5):784–9.
83. Yao X, Lan Z, Lai Q, Li A, Liu S, Wang X. LncRNA SNHG6 plays an oncogenic role in colorectal cancer and can be used as a prognostic biomarker for solid tumors. J Cell Physiol. 2020;235(10):7620–34.
84. Lan Z, Yao X, Sun K, Li A, Liu S, Wang X. The interaction between lncRNA SNHG6 and hnRNPA1 contributes to the growth of colorectal cancer by enhancing aerobic glycolysis through the regulation of alternative splicing of PKM. Front Oncol. 2020;10:363.
85. Zhang M, Duan W, Sun W. LncRNA SNHG6 promotes the migration, invasion, and epithelial-mesenchymal transition of colorectal cancer cells by miR-26a/EZH2 axis. Onco Targets Ther. 2019;12:3349–60.
86. Xu M, Chen X, Lin K, et al. LncRNA SNHG6 regulates EZH2 expression by sponging miR-26a/b and miR-214 in colorectal cancer. J Hematol Oncol. 2019;12(1):3.
87. Li Z, Qiu R, Qiu X, Tian T. SNHG6 promotes tumor growth via repression of P21 in colorectal cancer. Cell Physiol Biochem. 2018;49(2):463–78.
88. Wang X, Lai Q, He J, et al. LncRNA SNHG6 promotes proliferation, invasion and migration in colorectal cancer cells by activating TGF-β/Smad signaling pathway via targeting UPF1 and inducing EMT via regulation of ZEB1. Int J Med Sci. 2019;16(1):51–9.
89. Yu C, Sun J, Leng X, Yang J. Long noncoding RNA SNHG6 functions as a competing endogenous RNA by sponging miR-181a-5p to regulate E2F5 expression in colorectal cancer. Cancer Manag Res. 2019;11:611–24.
90. Zhu Y, Xing Y, Chi F, Sun W, Zhang Z, Piao D. Long non-coding RNA SNHG6 promotes the progression of colorectal cancer through sponging miR-760 and activation of FOXC1. Onco Targets Ther. 2018;11:5743–52.
91. Xu Y, Lv SX. The effect of JAK2 knockout on inhibition of liver tumor growth by inducing apoptosis, autophagy and anti-proliferation via STATs and PI3K/AKT signaling pathways. Biomed Pharmacother. 2016;84:1202–12.

92. He HL, Lee YE, Liang PI, et al. Overexpression of JAK2: a predictor of unfavorable prognosis for nasopharyngeal carcinoma. Future Oncol. 2016;12(16):1887–96.
93. Perner F, Perner C, Ernst T, Heidel FH. Roles of JAK2 in aging, inflammation, hematopoiesis and malignant transformation. cells. Cells. 2019;8(8):854.
94. Lai F, Deng W, Fu C, Wu P, Cao M, Tan S. Long non-coding RNA SNHG6 increases JAK2 expression by targeting the miR-181 family to promote colorectal cancer cell proliferation. J Gene Med. 2020;22(12): e3262.
95. Wang X, Lan Z, He J, et al. LncRNA SNHG6 promotes chemoresistance through ULK1-induced autophagy by sponging miR-26a-5p in colorectal cancer cells. Cancer Cell Int. 2019;19:234.
96. Fu Y, Yin Y, Peng S, et al. Small nucleolar RNA host gene 1 promotes development and progression of colorectal cancer through negative regulation of miR-137. Mol Carcinog. 2019;58(11):2104–17.
97. Bai J, Xu J, Zhao J, Zhang R. LncRNA SNHG1 cooperated with miR-497/miR-195-5p to modify epithelial-mesenchymal transition underlying colorectal cancer exacerbation. J Cell Physiol. 2020;235(2):1453–68.
98. Dacheng W, Songhe L, Weidong J, Shutao Z, Jingjing L, Jiaming Z. LncRNA SNHG3 promotes the growth and metastasis of colorectal cancer by regulating miR-539/RUNX2 axis. Biomed Pharmacother. 2020;125: 110039.
99. Liao Q, Chen L, Zhang N, et al. Network analysis of KLF5 targets showing the potential oncogenic role of SNHG12 in colorectal cancer. Cancer Cell Int. 2020;20:439.
100. Bian Z, Zhou M, Cui K, et al. SNHG17 promotes colorectal tumorigenesis and metastasis via regulating Trim23-PES1 axis and miR-339-5p-FOSL2-SNHG17 positive feedback loop. J Exp Clin Cancer Res. 2021;40(1):360.
101. Christensen LL, True K, Hamilton MP, et al. SNHG16 is regulated by the Wnt pathway in colorectal cancer and affects genes involved in lipid metabolism. Mol Oncol. 2016;10(8):1266–82.
102. Zhou L, Zhang Y, Jin J, Gu X. Correlation between lncRNA SNHG16 gene polymorphism and its interaction with environmental factors and susceptibility to colorectal cancer. Medicine (Baltimore). 2020;99(48): e23372.
103. Parikh K, DeNittis AS, Marks G, Zeger E, Oncology J. Neoadjuvant chemotherapy and high-dose radiation using intensity-modulated radiotherapy followed by rectal sparing TEM for distal rectal cancer. J Radiation Onco. 2019;8(2):217–24.
104. Xue Y, Ni T, Jiang Y, Li Y. Long noncoding RNA GAS5 inhibits tumorigenesis and enhances radiosensitivity by suppressing miR-135b expression in non-small cell lung cancer. Oncol Res. 2017;25(8):1305–16.
105. Chen Z, Cai X, Chang L, et al. LINC00152 is a potential biomarker involved in the modulation of biological characteristics of residual colorectal cancer cells following chemoradiotherapy. Oncol Lett. 2018;15(4):4177–84.
106. Liang H, Zhao Q, Zhu Z, Zhang C, Zhang H. Long noncoding RNA LINC00958 suppresses apoptosis and radiosensitivity of colorectal cancer through targeting miR-422a. Cancer Cell Int. 2021;21(1):477.
107. Liu F, Huang W, Hong J, et al. Long noncoding RNA LINC00630 promotes radio-resistance by regulating BEX1 gene methylation in colorectal cancer cells. IUBMB Life. 2020;72(7):1404–14.
108. Yang P, Yang Y, An W, et al. The long noncoding RNA-ROR promotes the resistance of radiotherapy for human colorectal cancer cells by targeting the p53/miR-145 pathway. J Gastroenterol Hepatol. 2017;32(4):837–45.
109. Liu Y, Chen X, Chen X, et al. Long non-coding RNA HOTAIR knockdown enhances radiosensitivity through regulating microRNA-93/ATG12 axis in colorectal cancer. Cell Death Dis. 2020;11(3):175.
110. Guo J, Ding Y, Yang H, Guo H, Zhou X, Chen X. Aberrant expression of lncRNA MALAT1 modulates radioresistance in colorectal cancer in vitro via miR-101-3p sponging. Exp Mol Pathol. 2020;115: 104448.
111. Li C, Liu H, Wei R, et al. LncRNA EGOT/miR-211-5p affected radiosensitivity of rectal cancer by competitively regulating ErbB4. Onco Targets Ther. 2021;14:2867–78.
112. Liu R, Zhang Q, Shen L, et al. Long noncoding RNA lncRI regulates DNA damage repair and radiation sensitivity of CRC cells through NHEJ pathway. Cell Biol Toxicol. 2020;36(5):493–507.
113. Yang X, Liu W, Xu X, et al. Downregulation of long non-coding RNA UCA1 enhances the radiosensitivity and inhibits migration via suppression of epithelial-mesenchymal transition in colorectal cancer cells. Oncol Rep. 2018;40(3):1554–64.
114. Yu Q, Zhang W, Zhou X, Shen W, Xing C, Yang X. Regulation of lnc-TLCD2-1 on radiation sensitivity of colorectal cancer and comprehensive analysis of its mechanism. Front Oncol. 2021;11: 714159.
115. Zuo Z, Ji S, He L, Zhang Y, Peng Z, Han J. LncRNA TTN-AS1/miR-134-5p/PAK3 axis regulates the radiosensitivity of human large intestine cancer cells through the P21 pathway and AKT/GSK-3β/β-catenin pathway. Cell Biol Int. 2020;44(11):2284–92.
116. Zou Y, Yao S, Chen X, et al. LncRNA OIP5-AS1 regulates radioresistance by targeting DYRK1A through miR-369-3p in colorectal cancer cells. Eur J Cell Biol. 2018;97(5):369–78.
117. Li Y, Castellano JJ, Moreno I, et al. LincRNA-p21 levels relates to survival and post-operative radiotherapy benefit in rectal cancer patients. Life (Basel). 2020;10(9):172.
118. Wang G, Li Z, Zhao Q, et al. LincRNA-p21 enhances the sensitivity of radiotherapy for human colorectal cancer by targeting the Wnt/β-catenin signaling pathway. Oncol Rep. 2014;31(4):1839–45.
119. Ghasemi T, Khalaj-Kondori M, Hosseinpour Feizi MA, Asadi P. LncRNA-miRNA-mRNA interaction network for colorectal cancer; An in silico analysis. Comput Biol Chem. 2020;89: 107370.
120. Joag MG, Sise A, Murillo JC, et al. Topical 5-fluorouracil 1% as primary treatment for ocular surface squamous neoplasia. Ophthalmology. 2016;123:1442–8.
121. Guo Z, Liu Z, Yue H, Wang J. Beta-elemene increases chemosensitivity to 5-fluorouracil through down-regulating microRNA-191 expression in colorectal carcinoma cells. J Cell Biochem. 2018;119(8):7032–9.
122. Liu F, Ai FY, Zhang DC, Tian L, Yang ZY, Liu SJ. LncRNA NEAT1 knockdown attenuates autophagy to elevate 5-FU sensitivity in colorectal cancer via targeting miR-34a. Cancer Med. 2020;9(3):1079–91.
123. Wang X, Jiang G, Ren W, Wang B, Yang C, Li M. LncRNA NEAT1 regulates 5-Fu sensitivity, apoptosis and invasion in colorectal cancer through the MiR-150-5p/CPSF4 Axis. Onco Targets Ther. 2020;13:6373–83.
124. Zhu Y, Hu H, Yuan Z, et al. LncRNA NEAT1 remodels chromatin to promote the 5-Fu resistance by maintaining colorectal cancer stemness. Cell Death Dis. 2020;11(11):962.
125. Xian Z, Hu B, Wang T, et al. lncRNA UCA1 contributes to 5-fluorouracil resistance of colorectal cancer cells through miR-23b-3p/ZNF281 axis. Onco Targets Ther. 2020;13:7571–83.
126. Zhang L, Liu J, Lin S, Tan J, Huang B, Lin J. Qingjie Fuzheng granule inhibited the migration and invasion of colorectal cancer cells by regulating the lncRNA ANRIL/let-7a/TGF-β1/Smad axis. Evid Based Complement Alternat Med. 2020;2020:5264651.
127. Zhou H, Xiong Y, Peng L, Wang R, Zhang H, Fu Z. LncRNA-cCSC1 modulates cancer stem cell properties in colorectal cancer via activation of the Hedgehog signaling pathway. J Cell Biochem. 2020;121(3):2510–24.

128. Jiang Z, Li L, Hou Z, et al. LncRNA HAND2-AS1 inhibits 5-fluorouracil resistance by modulating miR-20a/PDCD4 axis in colorectal cancer. Cell Signal. 2020;66: 109483.
129. Li J, Ma J, Zhang X, Tai X, Liu L, Zhang L. Long non-coding RNA (lncRNA) BMP/OP-responsive gene (BORG) promotes development of chemoresistance of colorectal cancer cells to carboplatin. Med Sci Monit. 2020;26: e919103.
130. Hong S, Yan Z, Song Y, Bi M, Li S. LncRNA AGAP2-AS1 augments cell viability and mobility, and confers gemcitabine resistance by inhibiting miR-497 in colorectal cancer. Aging (Albany NY). 2020;12(6):5183–94.
131. Walker AS, Johnson EK, Maykel JA, et al. Future directions for the early detection of colorectal cancer recurrence. J Cancer. 2014;5(4):272–80.
132. Aziz MA, Yousef Z, Saleh AM, Mohammad S, Al KB. Towards personalized medicine of colorectal cancer. Crit Rev Oncol Hematol. 2017;118:70–8.
133. Huang R, Zhou L, Chi Y, Wu H, Shi L. LncRNA profile study reveals a seven-lncRNA signature predicts the prognosis of patients with colorectal cancer. Biomark Res. 2020;8:8.
134. Sun Y, Peng P, He L, Gao X. Identification of lnc RNAs related to prognosis of patients with colorectal cancer. Technol Cancer Res Treat. 2020;19:1533033820962120.
135. Chu Y, Liu Z, Liu J, Yu L, Zhang D, Pei F. Characterization of lncRNA-perturbed TLR-signaling network identifies novel lncRNA prognostic biomarkers in colorectal cancer. Front Cell Dev Biol. 2020;8:503.
136. Li S, Chen S, Wang B, Zhang L, Su Y, Zhang X. A robust 6-lncRNA prognostic signature for predicting the prognosis of patients with colorectal cancer metastasis. Front Med (Lausanne). 2020;7:56.
137. Shen X, Xue Y, Cong H, et al. Circulating lncRNA DANCR as a potential auxillary biomarker for the diagnosis and prognostic prediction of colorectal cancer. Biosci Rep. 2020;40(3):BSR20191481.
138. Bi C, Cui H, Fan H, Li L. LncRNA LINC01116 promotes the development of colorectal cancer by targeting miR-9-5p/STMN1. Onco Targets Ther. 2020;13:10547–58.
139. Cui W, Wang Y, Shen X, Wu X, Liu H, Xu X. High-expression of LncRNA MAFG-AS1 is associated with the prognostic of patients with colorectal cancer. Rev Assoc Med Bras (1992). 2020;66(11):1530–5.
140. Chen S, Zhang C, Feng M. Prognostic value of LncRNA HOTAIR in colorectal cancer: a meta-analysis. Open Med (Wars). 2020;15:76–83.
141. Chen W, Tu Q, Yu L, et al. LncRNA ADAMTS9-AS1, as prognostic marker, promotes cell proliferation and EMT in colorectal cancer. Hum Cell. 2020;33(4):1133–41.
142. Qian J, Garg A, Li F, Shen Q, Xiao K. lncRNA LUNAR1 accelerates colorectal cancer progression by targeting the miR-495-3p/MYCBP axis. Int J Oncol. 2020;57(5):1157–68.
143. Wang Y, Zhang D, Zhang C, Sun Y. The diagnostic and prognostic value of serum lncRNA NEAT1 in colorectal cancer. Cancer Manag Res. 2020;12:10985–92.
144. Yu J, Dong W, Liang J. Extracellular vesicle-transported long non-coding RNA (LncRNA) X inactive-specific transcript (XIST) in serum is a potential novel biomarker for colorectal cancer diagnosis. Med Sci Monit. 2020;26: e924448.
145. Salomaa V, Havulinna A, Saarela O, et al. Thirty-one novel biomarkers as predictors for clinically incident diabetes. PLoS One. 2010;5(4): e10100.
146. Ye S, Lu Y, Ru Y, et al. LncRNAs GACAT3 and LINC00152 regulate each other through miR-103 and are associated with clinicopathological characteristics in colorectal cancer. J Clin Lab Anal. 2020;34(9): e23378.
147. Xu W, Zhou G, Wang H, et al. Circulating lncRNA SNHG11 as a novel biomarker for early diagnosis and prognosis of colorectal cancer. Int J Cancer. 2020;146(10):2901–12.
148. Yang Q, Zheng W, Shen Z, Huang G, Yang G. MicroRNA binding site polymorphisms of the long-chain noncoding RNA MALAT1 are associated with risk and prognosis of colorectal cancer in Chinese Han population. Genet Test Mol Biomarkers. 2020;24(5):239–48.
149. Luo R, Song J, Zhang W, Ran L. Identification of MFI2-AS1, a novel pivotal lncRNA for prognosis of stage III/IV colorectal cancer. Dig Dis Sci. 2020;65(12):3538–50.