

MicroRNAs, long noncoding RNAs, and circular RNAs: potential tumor biomarkers and targets for colorectal cancer

Shuaixi Yang^{1,*}
 Zhenqiang Sun^{1,*}
 Quanbo Zhou^{1,*}
 Weiwei Wang^{2,3}
 Guixian Wang¹
 Junmin Song¹
 Zhen Li¹
 Zhiyong Zhang¹
 Yuan Chang¹
 Kunkun Xia¹
 Jinbo Liu¹
 Weitang Yuan¹

¹Department of Colorectal Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, People's Republic of China; ²Department of Pathology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450001, People's Republic of China; ³Department of Pathology, School of Basic Medicine, Zhengzhou University, Zhengzhou, Henan 450002, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhenqiang Sun; Weitang Yuan
 Department of Colorectal Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, People's Republic of China
 Email zqsun82@csu.edu.cn; yuanweitang@zzu.edu.cn

Abstract: Noncoding RNAs (ncRNAs) can be divided into microRNAs (miRNAs), long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), pRNAs, and tRNAs. Traditionally, miRNAs exert their biological function mainly through the inhibition of translation via the induction of target RNA transcript degradation. lncRNAs and circRNAs were once considered to have no potential to code proteins. Here, we will review the current knowledge on ncRNAs in relation to their origins, characteristics, and functions. We will also review how ncRNAs work as competitive endogenous RNA, gene transcription and expression regulators, and RNA-binding protein sponges in colorectal cancer (CRC). Notably, except for the abovementioned mechanisms, recent advances revealed that lncRNAs can also act as the precursor of miRNAs, and a small portion of lncRNAs and circRNAs was verified to have the potential to code proteins, providing new evidence for the significance of ncRNAs in CRC tumorigenesis and development.

Keywords: biomarker, competitive endogenous RNA, tumorigenesis, epithelial-to-mesenchymal transition, invasion, metastasis, chemoresistance

Introduction

Noncoding RNAs (ncRNAs) are major components of the human transcriptome.¹ Recently, ncRNAs were demonstrated to play important roles in multiple biological processes by directly or indirectly interfering with gene expression in various cancers. The regulatory role of ncRNAs in multiple cancers has been summarized, such as lncRNAs and microRNAs (miRNAs) in endocrine-related cancers,² lncRNAs in hepatocarcinogenesis,³ and circRNAs in multiple types of cancer.⁴ However, a comprehensive and in-depth analysis of ncRNAs in CRC has not been reported to date.

ncRNAs account for the majority of RNA transcribed by human genes, including miRNA, long noncoding RNA (lncRNA), circular RNA (circRNA), pRNA, and tRNA. With the development of RNA sequencing technologies and bioinformatics, numerous ncRNAs have been discovered that influence gene expression levels via chromatin modification, transcription, and posttranscriptional processing.⁵ Moreover, the abnormal expression of ncRNAs is associated with invasion, metastasis, chemoresistance, and radioresistance of colorectal cancer (CRC).⁶ For instance, TUG1 regulates the expression of growth-related genes, activates the expression of epithelial-to-mesenchymal transition (EMT)-associated genes, and plays important roles in signal transduction, cell morphology, migration, proliferation, and apoptosis in CRC. Overexpression of TUG1 is thought to be an independent poor prognostic factor for CRC patients.^{7,8} The circRNA circ_001569 is upregulated in CRC tissues

and promotes CRC proliferation and invasion. This circRNA acts as a sponge to directly inhibit miR-145 transcription, which subsequently affects the functions of miR-145 targets E2F5, BAG4, and FMNL2 in CRC cells.⁹

Herein, we performed a systematic literature review analysis of ncRNAs in CRC and the dysregulation of ncRNAs in CRC tissues or cells. Then, we discussed how these ncRNAs work as miRNA sponges, gene transcription and expression regulators, and RNA-binding protein (RBP) sponges in CRC, providing evidence for the significance of ncRNAs in CRC.

Classification of ncRNAs

Generally, according to their product size, ncRNAs can be divided into two groups: small ncRNAs and long ncRNAs.¹⁰ The size of small ncRNAs, such as miRNA, is typically less than 200 nucleotides (nt).^{11,12} By contrast, long ncRNAs are typically greater than 200 nt, including long intergenic ncRNAs, long intronic ncRNAs, and pseudogene RNAs.¹³

Except for these linear ncRNAs, circRNAs, which are formed through the ligation of the 5' and 3' ends of linear RNA, have been investigated recently.^{14,15} Accumulating evidence has revealed that aberrant ncRNA expression is correlated with various cancers, especially CRC.

Mechanisms of ncRNAs in regulating CRC progression

ncRNAs control individual genes and gene expression programs through changing the fundamental transcriptional mechanism or via epigenetic regulation at multiple levels, such as transcription, translation, and protein function (Figure 1).

As a competitive endogenous RNA (ceRNA) or miRNA sponge

miRNA is a small ncRNA that is 19–24 nt in length. miRNA binds to miRNA response elements (MREs) in

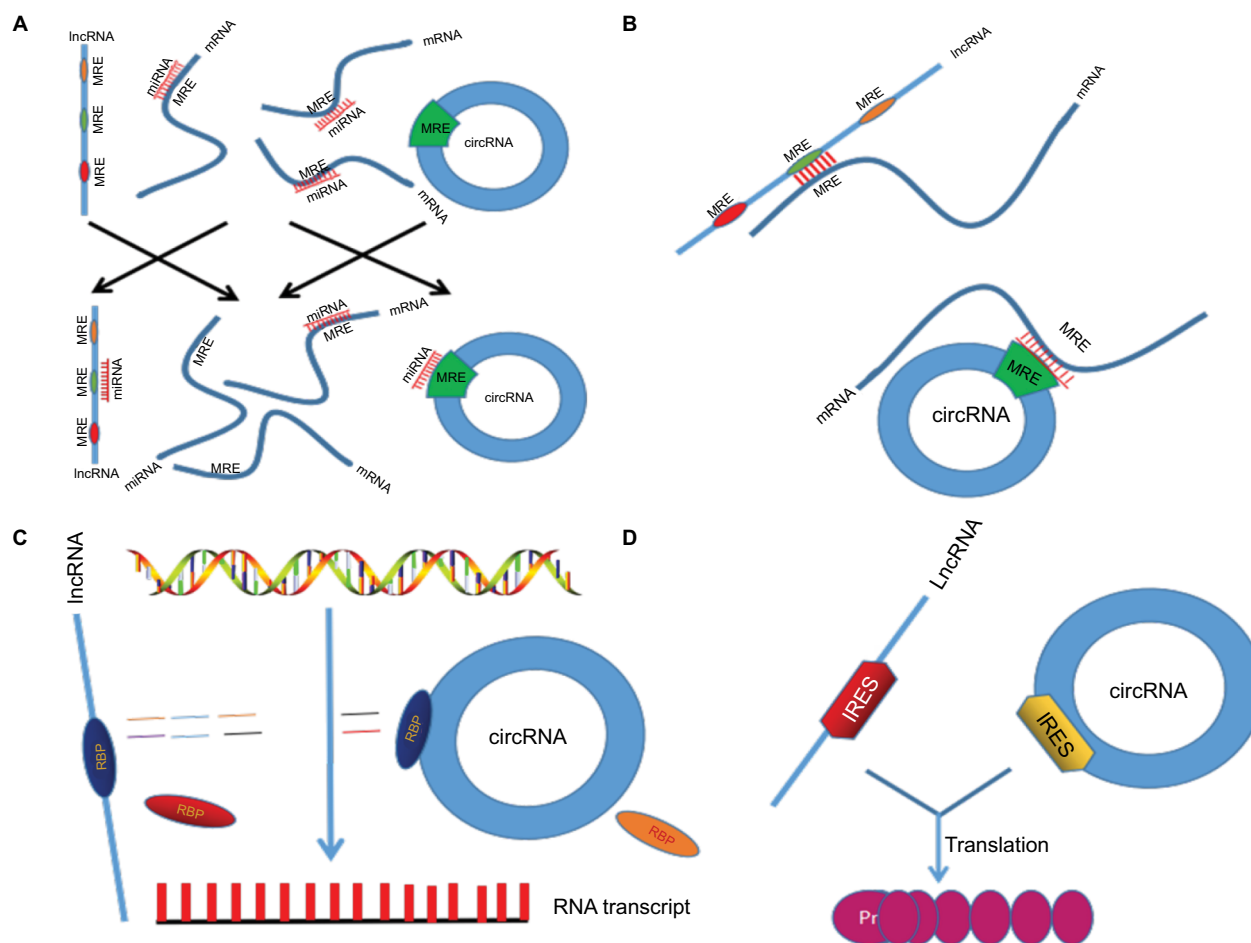


Figure 1 Mechanism of lncRNAs/circRNAs regulating CRC biological activities. **(A)** lncRNAs and circRNAs act as miRNA sponge or ceRNA. **(B)** Directly targeting mRNA by partial base pairing. **(C)** Binding RBP to regulate protein expression. **(D)** A small portion of lncRNAs/circRNAs can be translated to proteins.

Abbreviations: lncRNAs, long noncoding RNAs; circRNAs, circular RNAs; CRC, colorectal cancer; miRNA, microRNA; ceRNA, competitive endogenous RNA; IRES, internal ribosome entry site; RBP, RNA-binding protein.

RNA sequences and negatively regulates gene expression through the inhibition of translation via the induction of target RNA transcript degradation.^{16,17} ceRNA contains an MRE, which competitively binds to miRNA. Therefore, ceRNA affects the regulatory functions of miRNAs in gene expression and reduces the inhibitory effect of miRNAs on target molecules^{18–21} (Figure 1A). For instance, UCC may act as an endogenous sponge by competing for miR-143, thereby regulating the targets of this miRNA. UCC and miR-143 may be promising molecular targets for CRC therapy.²² The lncRNA CRNDE regulates the progression and chemoresistance of CRC via modulating the expression levels of miR-181a-5p and the activity of Wnt/ β -catenin signaling.²³ HOXA11-AS promotes liver metastasis in CRC by functioning as a miR-125a-5p sponge, and the novel HOXA11-AS-miR-125a-5p-PADI2 regulatory network is involved in CRC liver metastasis.²⁴ At present, the main function of some lncRNAs and circRNAs involves acting as a miRNA sponge.

Regulating gene transcription

In addition to the abovementioned mechanisms, ncRNAs, as the product of transcription, are major regulators of the transcriptional process.²⁵ Researchers reported that ncRNAs can function as positive regulators of their parental gene transcription, targeting mRNA by partially base pairing²⁶ (Figure 1B). Accumulating evidence indicates that ncRNAs play a pivotal role in posttranscriptional and gene expression regulation. For example, the circRNAs circ-EIF3J and circ-PAIP2 combine with the U1 snRNP to further interact with RNA Pol II and enhance the expression of their parental genes in HeLa and HEK293 cells.²⁷

Regulating RBPs

miRNA biogenesis is modulated by a variety of RBPs²⁸ (Figure 1C), and the adsorption of protein factors by linear lncRNA has been reported.^{29–31} For example, sno-lncRNAs regulate alternative splicing of downstream genes by adsorbing the alternative splicing factor Fox2.³² NEAT1 also has a profound effect on global pri-miRNA processing. Mechanistic dissection reveals that NEAT1 broadly interacts with the NONO-PSF heterodimer and numerous other RBPs. In addition, multiple RNA segments in NEAT1, including a pseudo pri-miRNA near its 3' end, help attract the microprocessor.³³

Protein translation

A small portion of ncRNAs can also be translated to proteins similar to mRNAs. circRNA is efficiently translated in living

human cells to produce abundant protein product via the RCA mechanism.³⁴ Long-repeating polypeptide chains were synthesized from RNA circles with continuous open reading frames, and an internal ribosome entry site and the initiation codon ATG in a specific circRNA allow the circRNA translation template to function as mRNA (Figure 1D).³⁵

Biological functions of miRNAs in CRC

miRNAs are 19–24 nt in length that regulate gene expression at the posttranscriptional level by binding to the 3'-untranslated regions or the open reading frames of target genes, leading to the degradation of target mRNAs or repression of mRNA translation.³⁶ Numerous investigations have been performed to analyze the biological functions of miRNAs in CRC.^{37,38}

miRNAs promote CRC cell proliferation and invasion

miRNAs exhibit a close relationship with the initiation and development of various human malignancies.³⁹ Abundant miRNAs play oncogenic roles in CRC tumorigenesis via diverse mechanisms.^{40,41} On one hand, miRNAs exert their tumor oncogenic functions primarily by binding to the 3'-untranslated region of the mRNA of target genes. For instance, miR19b-3p is overexpressed in CRC tissues compared with normal tissues. Furthermore, miR19b-3p plays an oncogenic role in CRC via directly targeting ITGB8.⁴² Similarly, TIA1 is an important tumor suppressor in CRC. In addition, miR-19a is highly expressed in tumor tissues compared with normal tissues and exerts its oncomiR function by targeting TIA1.⁴³ On the other hand, miRNAs promote CRC cell proliferation and invasion via other multiple mechanisms. For example, the EMT plays important roles in tumor metastasis. For example, miR-19a is upregulated in CRC tissues, and high expression of miR-19a is significantly associated with lymph node metastasis. Interestingly, miR-19a is upregulated by TNF- α and is required for TNF- α -induced EMT and metastasis in CRC cells.⁴⁴

miRNAs suppress CRC cell proliferation and invasion

By contrast, miRNA may function as a tumor-repressive gene to inhibit cell proliferation in CRC. Some miRNAs suppress CRC cell proliferation and invasion by regulating tumor angiogenesis, tumor metabolism, and cancer stemness features.^{45,46} For instance, miR-590-5p overexpression inhibits CRC angiogenesis and metastasis by targeting nuclear factor

90, which acts as a positive regulator of vascular endothelial growth factor mRNA stability and protein synthesis. Notably, knockdown of miR-590-5p promotes the progression of CRC in vitro.⁴⁷ AEG-1 is a key oncogenic factor in various tumors.⁴⁸ In addition, miR-217 suppresses CRC cell proliferation and invasiveness by inhibiting AEG-1 expression with modulation of MMP2 or AMPK signaling.^{49,50}

Biological functions of lncRNAs in CRC

lncRNA is defined as an RNA transcript of greater than 200 nt located in nuclear or cytosolic fractions.⁵¹ The overexpression, deficiency, or mutation of lncRNAs could be involved in CRC progression via a variety of mechanisms.^{52,53} Abundantly expressed lncRNAs play crucial roles in CRC, such as HOTAIR, CCAT1, and MALAT1 (Table 1).

lncRNAs interact with miRNAs in CRC

The ceRNA hypothesis demonstrated that lncRNAs with shared miRNA binding sites compete for posttranscriptional control.⁵⁴ In early studies, it was found that PTENP1 shares conserved miRNA seed target sites with PTEN for the miR-17, miR-21, miR-214, miR-19, and miR-26 miRNA families. The role of lncRNAs as a miRNA sponge is the main mechanism of lncRNAs in cancer. For example, H19 is overexpressed in colon cancer tissues and cell lines, whereas miR-138 expression in tumor tissues is reduced compared

with normal tissues. Interestingly, the silencing of H19 strongly increases the expression of miR-138 and suppresses the expression of high-mobility group A (HMGA1) protein, indicating that H19 promotes the migration and invasion of colon cancer by sponging miR-138 to upregulate HMGA1 expression.⁵⁵

Notably, lncRNAs act as the precursor of miRNAs. For example, the lncRNA MIR100HG is the precursor of miR-100 and miR-125b, which coordinately represses five Wnt/ β -catenin negative regulators, leading to cetuximab resistance. Furthermore, the transcription factor GATA6 represses MIR100HG. By contrast, the repression is relieved by miR-125b targeting of GATA6, revealing a double-negative feedback loop between MIR100HG and the transcription factor GATA6 (Figure 2). In addition, miR-17-5p expression is increased in tumors compared with paired non-tumorous tissues, and high miR-17-5p expression is significantly associated with TNM staging and lymph node metastasis. Furthermore, miR-17-5p expression is upregulated by CCAT2 through TCF7 L2-mediated transcriptional regulation, enhancing WNT activity.⁵⁶

lncRNAs function through other mechanisms in CRC

Tumor metabolism is responsible for rapid recurrence and poor survival of CRC. The relationship between ncRNAs and

Table 1 lncRNAs reported in CRC

lncRNA	Expression	Biofunctions in tumor	Potential mechanisms	PMID
H19	Up	Oncogene	Modifies the EMT pathway; acts as a ceRNA for miR-138 and miR-200a; mediates methotrexate resistance by activating the WNT/ β -catenin pathway	26989025; 26068968; 19926638
HOTAIR	Up	Oncogene	Acts as a miR-197 sponge; suppresses miR-218; activates NF- κ B/TS signaling; modifies the EMT pathway	29137688; 28918035; 27069543
CCAT1	Up	Oncogene	Activated by the super-enhancer cMYC	25185650; 24662484
MALAT1	Up	Oncogene	Increases AKAP-9 expression by promoting SRPK1-catalyzed SRSF1 phosphorylation; regulating PRKA kinase anchor protein 9	26887056; 25446987
XIST	Upregulated in 5FU-resistant patients	Promote 5FU resistance	Promotes the expression of thymidylate synthase	29137332
HEIH	Up	Oncogene	Counteracting miR-939-mediated transcriptional repression of Bcl-xL	29081216
lncRNA-422	Down	Tumor suppressor	By PI3K/AKT/mTOR pathway in CRC	29050940
MIR100HG	Overexpressed in cetuximab-resistant patients	Cetuximab resistance	Host gene of cetuximab resistance, which mediates cetuximab resistance via Wnt/ β -catenin signaling	29035371
CPS1-IT1	Down	Tumor suppressor	Suppresses metastasis and EMT by inhibiting hypoxia-induced autophagy through inactivation of HIF-1 α	29017924
NONHSAT062994	Down	Tumor suppressor	By inactivating Akt signaling	28978149

Abbreviations: lncRNAs, long noncoding RNAs; CRC, colorectal cancer; EMT, epithelial-to-mesenchymal transition; ceRNA, competitive endogenous RNA.

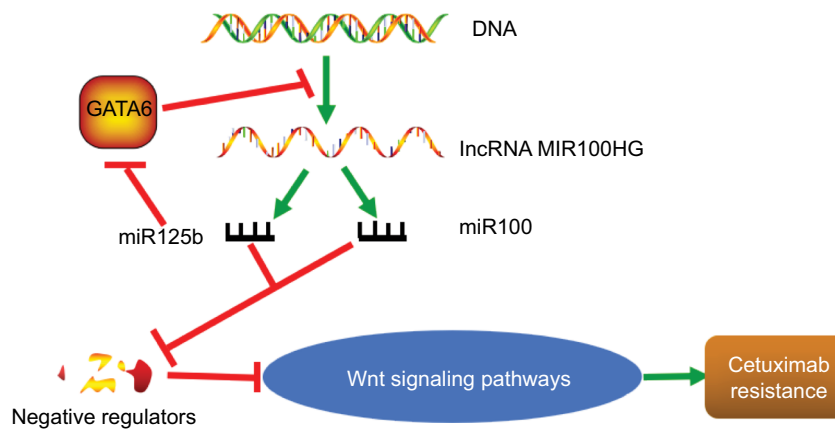


Figure 2 lncRNAs function as precursors of miRNAs in CRC.

Note: Red lines represent inhibition effect; green arrows indicate promotion effect.

Abbreviations: lncRNAs, long noncoding RNAs; miRNA, microRNA; CRC, colorectal cancer.

tumor metabolism was investigated recently. For instance, lncRNA NONHSAT062994 expression was negatively correlated with the Akt downstream targets c-Myc and cyclin D1 in clinical CRC samples, indicating that NONHSAT062994 functioned as a tumor suppressor to inhibit CRC cell growth by inactivating Akt signaling.⁵⁷ Autophagy is a crucial intracellular process associated with CRC tumorigenesis and progression. lncRNAs play crucial roles in CRC by regulating tumor autophagy by targeting various proteins, such as CPS1-IT1, AC023115.3, and MALAT1.^{58,59} For example, the lncRNA CPS1-IT suppresses metastasis and EMT by inhibiting hypoxia-induced autophagy through inactivation of HIF-1 α in CRC.⁶⁰

Biological functions of circRNAs in CRC

circRNAs are a special type of endogenous ncRNA molecule. We have witnessed an explosion in published studies on all aspects of circRNA biology leading to the common understanding that these molecules are important players in cancers, especially in CRC. As previously mentioned, circRNAs differ structurally from other lncRNAs given that their 3' and 5' ends are covalently joined. Certain circRNAs act as highly stable sponges for specific miRNAs, such as CiRS-7 and SRY for miR-7 and miR-138, respectively, and are involved in competing endogenous RNA networks.⁶¹ Thousands of circRNAs have been identified and annotated in the circRNA repository (circBase). However, the biogenesis of circRNAs remains elusive.⁶²

miRNAs are extremely well studied as tumor suppressors or oncogenes. It has been hypothesized that circRNAs form a class of posttranscriptional regulators, acting as epigenetic,

highly stable miRNA sponges to compete with the endogenous RNA network and directly affecting the expression of any related gene.⁶³ circRNAs sequester specific miRNA complexes and release them after cleavage.⁶⁴ Circ_001569 was upregulated in CRC tissues compared with adjacent normal tissues, and high circ_001569 expression was closely correlated with differentiation and TNM classification. Interestingly, circ_001569 is negatively correlated with miR-145, and miR-145 is negatively correlated with E2F5, BAG4, and FMNL2 expression. These data indicate that circ_001569 promotes CRC cell proliferation and invasion by regulating miR-145 and its targets E2F5, BAG4, and FMNL2.⁶⁵ In addition, circ_0020397 promotes CRC cell viability and invasion and inhibits their apoptosis by promoting the expression of the miR-138 target genes TERT and PD-L1.⁶⁶ circCCDC66 possesses an oncogenic capacity through protecting multiple oncogenes from being attacked by a group of miRNAs, and overexpression of circCCDC66 potentiates multiple tumor characteristics, including proliferation, migration, and invasion (Figure 3).⁶⁷

In addition to the abovementioned circRNAs, numerous other circRNAs govern fundamental biological process and cancer progression through multiple mechanisms instead of acting as a special class of endogenous RNAs. circ-Foxo3 functions as a tumor suppressor in CRC by forming circ-Foxo3-p21-CDK2 ternary complexes.⁶⁸ CDK2 interacts with cyclin A and cyclin E to facilitate cell cycle entry, whereas p21 inhibits these interactions and arrests cell cycle progression.⁶⁹

Therefore, circRNAs can also exert biological function in CRC by binding to partners.

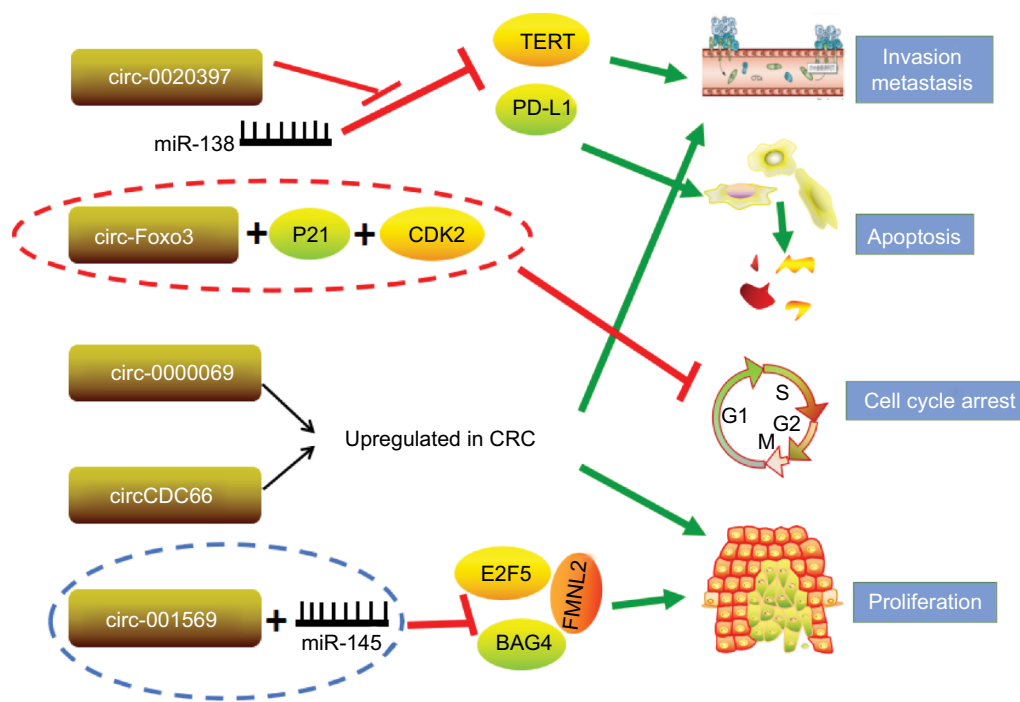


Figure 3 circRNAs investigated in CRC.

Note: Red lines represent inhibition effect; green arrows indicate promotion effect.

Abbreviations: circRNAs, circular RNAs; CRC, colorectal cancer.

ncRNAs as new potential tumor biomarkers and targets

An increasing number of ncRNAs are being reported to be aberrantly expressed in CRC, and differential expression of ncRNAs can be detected in the circulation of CRC patients. Importantly, ncRNAs are abundant and their expression is both step and location specific. The characteristics of ncRNAs afford them the potential to become novel diagnostic and prognostic markers for cancer. For instance, lncRNA SPRY4-IT1 is upregulated in CRC tissues and promotes proliferation and invasion by targeting miR-101-3p. These data indicate that knockdown of SPRY4-IT1 represents a rational therapeutic strategy for colorectal carcinoma.⁷⁰ CircHIPK3 was significantly highly expressed in CRC tissues and positively correlated with metastasis and TNM stage, revealing that circHIPK3 may be a potential prognostic biomarker in CRC.⁷¹ On the basis of the results acquired from latest papers, circulating ncRNA profiles are emerging as potential biomarkers of diagnosis, prognosis, and therapeutic response in CRC.

Conclusion

With the development of high-throughput sequencing technologies and bioinformatics methods, ncRNAs are

increasingly investigated.⁷² Traditionally, ncRNA has been viewed as an unstable molecule because ribonucleases are ubiquitous and extremely stable biomarkers for CRC. Emerging evidence have revealed the biological roles and relevant mechanisms of diverse ncRNAs in CRC tumorigenesis.^{73,74} For example, miR-17 acts as an oncogenic miRNA that promotes CRC development by activating the Wnt/ β -catenin pathway and by targeting P130.⁷⁵ We also found that miR-149 methylation contributes to CRC growth and invasion by targeting the transcription factor Sp1.⁷⁶

Notably, the molecular mechanisms of these dysregulated ncRNAs have been investigated recent years. EMT is an important step in cancer development that involves the cooperation of a variety of signaling pathways, including the transformation growth factor- β , Sonic Hedgehog, and WNT pathways.^{77,78} HOTAIR, H19, AFAP1-AS1, TUG1, BANCR, lncRNA-ATB, SPRY4-IT1, SLC25A25-AS1, LINC01133, PANDAR, lncRNA-ATB, and Sox2ot are involved in the EMT pathways.

circRNAs as a new class of ncRNAs contributing to the regulatory network governing protein coding gene expression by acting as miRNA target decoys, RBP sponges and transcriptional regulators exhibit great biological potential for circRNA-related functionalities. Uncovering these additional functions (if any) and understanding these

functionalities represent key research topics in the circRNA field in the future.

Via a systematic literature review, we have discussed the origins, characteristics, and main functions of ncRNAs in CRC. Continuous exploration and research in this field will provide an important molecular basis for understanding the complex regulation of CRC.

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Disclosure

The authors report no conflicts of interest in this work.

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