Roles of circular RNAs in colorectal cancer (Review)

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Abstract. Colorectal cancer (CRC) is one of the most common types of malignant cancer worldwide and poses a significant burden on both the individual and healthcare systems. Despite advances in treatment options, advanced-stage CRC has a high mortality rate due to its heterogeneity, metastatic potential and/or delay in diagnosis. In recent years, an increasing number of studies have indicated that circular RNAs (circRNAs) serve important roles in several types of cancer, including CRC. Recent studies have revealed that circRNAs are aberrantly expressed in CRC tissues and function as oncogenic or tumor suppressive regulators of CRC carcinogenesis and development. Numerous circRNAs have been associated with the clinicopathological features of patients with CRC and have been considered as potential biomarkers for the diagnosis and prognosis of CRC, as well as targets for treatment. However, a deeper understanding of their potential function is required. In the present review, the current body of knowledge on the biogenesis and functions of CRC-associated circRNAs, and their potential value in clinical applications, such as in CRC diagnosis, prognosis and treatment, is discussed and summarized.

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1. Introduction

Colorectal cancer (CRC) is responsible for ~10% of all diagnosed cases of cancer and cancer-associated deaths worldwide, with ~900,000 deaths annually (1,2). The incidence and death rate of CRC has increased amongst individuals aged <50 years old between 2000 and 2013 in the United States, where the incidence rate has increased by 22% (3). Although the development of traditional or novel treatment options, including endoscopy, surgery, downstaging preoperative radiotherapy, systemic therapy, targeted therapy and immunotherapy, has extended the overall survival of patients with advanced stage disease to ~3 years, the cure rate of patients with metastases remains low (2,4). Thus, understanding the underlying biology of CRC progression may highlight novel potential biomarkers and therapeutic targets for assistance in the early diagnosis of CRC, or as treatment targets.

In 1976, circular RNAs (circRNAs/circs) were first identified in plant-based RNA viruses under an electron microscope (5). However, for decades, circRNAs were considered as functionless junk-RNA or by-products developed from mRNA splicing (6). In 2013, Hansen *et al* (7) revealed that circRNAs can competitively bind to microRNAs (miRNAs/miRs) and inhibit their expression, functioning as a miRNA 'sponge', and in-turn increasing expression of the downstream miRNA target genes. Since then, functional analysis of circRNAs has increased the current understanding of several physiological and pathophysiological processes. In recent years, due to the rapid development of bioinformatics algorithms and experimental techniques, such as high-throughput RNA sequencing and circRNA microarray screening, thousands of circRNAs have been identified and found to be involved in various disease processes. In cardiovascular diseases, circRNAs regulate the activation of endothelial cells, vascular smooth

muscle cells and macrophages, and thus function in the initiation and development of atherosclerosis (8). Additionally, emerging evidence from *in vitro* and *in vivo* experimental studies have indicated that circRNAs can regulate adipogenesis and obesity (9,10). Cerebellar degeneration-related protein 1 antisense RNA (CDR1as, also known as CiRs-7), was the first circRNA found to act as a sponge of a miRNA, miR-7 (7), serving important roles in Alzheimer's disease and Parkinson's disease, amongst other neurodegenerative diseases (11). In 2015, Bachmayr-Heyda *et al* (12) first reported a global reduction of circRNA abundance in CRC cell lines and cancer tissues compared with in normal cells and tissues. These results suggest that cells with high proliferative rates, particularly tumors, universally trend towards exhibiting low levels of circRNA expression. This may suggest that circRNAs are not likely to be involved in cancer (13). However, the roles of several circRNAs in different types of cancer have emerged in recent years. In the present review, the association between circRNAs and CRC is discussed. The biogenesis and functions of circRNAs are first discussed, followed by a comprehensive summary of the role of circRNAs in CRC biological processes, their association with clinicopathological features, as well as their involvement in the therapeutic response, highlighting their potential as CRC biomarkers in diagnosis, prognosis and treatment of CRC (Fig. 1).

2. circRNAs: Biogenesis and characteristics

circRNAs are a major type of non-coding RNA that are produced by back-splicing of exons from pre-mRNA (14). During back-splicing, a downstream splice-donor site is covalently linked to an upstream splice-acceptor site (15), through which a covalently closed RNA molecule is formed. Typically, mRNA maturation consists of transcription, splicing, capping, polyadenylation, export and final surveillance (16); however, in circRNA production, no polyadenylation or capping is required (14). Notably, different circRNAs can be produced from the same sequence through alternative back-splicing events (17). Generally, according to the different structures and cycling mechanisms, circRNA are divided into four subtypes: Exonic circRNA, intronic circRNA, exon-intron circRNA and intergenic circRNA, with exonic circRNAs being the most common type (15). Although back-splicing of exons takes place in the nucleus, most circRNAs are localized to the cytoplasm by RNA helicase in a length-dependent manner (18). Compared with the linear mRNA counterpart, due to the presence of a covalent bond joining the 3' and 5' end, circRNAs form a continuous loop structure and are thus resistant to the degradation by RNA exonucleases, as well as being highly stable, with a longer median half-life ranging from 18.8-23.7 h (15,17). How circRNAs are degraded remains poorly understood. Park *et al* (19) demonstrated that N^6-methyladenosine (m6A)-containing circRNAs are selectively cleaved by RNase P/MRP, which are essential ribonucleoprotein complexes that function as endoribonucleases, and engage in tRNA maturation and the cleavage of ribosomal RNAs, long non-coding RNAs and mRNAs. Other possible mechanisms have been reviewed elsewhere (17). The characteristics of circRNAs can be summarized as universality, diversity, stability and conservatism of evolution (20).

3. circRNA function

Numerous studies have shown that circRNAs function as miRNA sponges, protein sponges, decoys, scaffolds, recruiters and translation templates, and can promote transcription in multiple biological processes.

circRNAs as miRNA sponges. In 2013, Hansen *et al* (7) revealed that circRNAs can competitively bind to a miRNA, inhibit their expression and thus increase the expression of the downstream miRNA target genes. Specifically, Hansen *et al* (7) found that CDR1as is universally co-expressed with miR-7 in the brain, contains >70 binding sites complementary to miR-7 and acts as a potent sponge of miR-7. Since then, an increasing number of circRNAs have been identified to interact with miRNAs with the development of RNA-sequencing techniques and bioinformatics algorithms. Several circRNAs contain miRNA response elements and binding sites, and weaken miRNA activity through sequestration, thus upregulating the expression levels of the miRNA target genes (21). This has been termed 'miRNA sponging' and is the most significant mechanism involved in regulation of the initiation and progression of human cancer and several other diseases.

circRNAs regulate protein expression. RNA binding proteins (RBPs) participate in gene transcription and translation, and interaction with RBPs is regarded as a central role of circRNAs (22). circRNAs can interact with regulatory RBPs, through which they act as protein sponges, decoys, scaffolds or recruiters, and further affect their target mRNAs (23). For example, circular antisense non-coding RNA in the INK4 locus (circANRIL) impairs pre-ribosomal RNA processing and ribosome biogenesis by binding to pescadillo homologue 1, an essential 60S pre-ribosomal assembly factor, in human vascular smooth muscle cells and macrophages (24). As a result, circANRIL increases nucleolar stress and p53 activation, which may improve the atheroprotective effect by promoting the removal of hyperproliferative cells from atherosclerotic plaques (24). circFOXO3 functions as a protein scaffold and promotes MDM2-induced mutant p53 ubiquitination and subsequent degradation, causing an overall reduction in p53 levels (25). Another nuclear circRNA, circ-potassium sodium-activated channel subfamily T member 2, functions as a protein recruiter, and inhibits basic leucine zipper ATF-like transcription factor (Batf) expression by recruiting the nucleosome remodeling deacetylase complex onto the Batf promoter, which then represses IL-17 expression, and thereby inactivates group 3 innate lymphoid cells (ILC3), to promote resolution of innate colitis (26). Certain circRNAs possess dual roles in the regulation of protein expression. For example, circ-mitochondrial ribosomal protein S35 (circMRPS35) functions as a protein scaffold to recruit the histone acetyltransferase lysine acetyltransferase 7 to the promoters of FOXO1 and FOXO3a genes, which leads to acetylation of H4K5 in their promoters. circMRPS35 specifically and directly binds to the FOXO1/3a promoter regions, significantly increasing their transcription, and thus triggering activation of their downstream target genes, including p21, p27, Twist1 and E-cadherin (27). Thus, circMRPS35 contributes to a suppressive effect on cell proliferation and invasion.

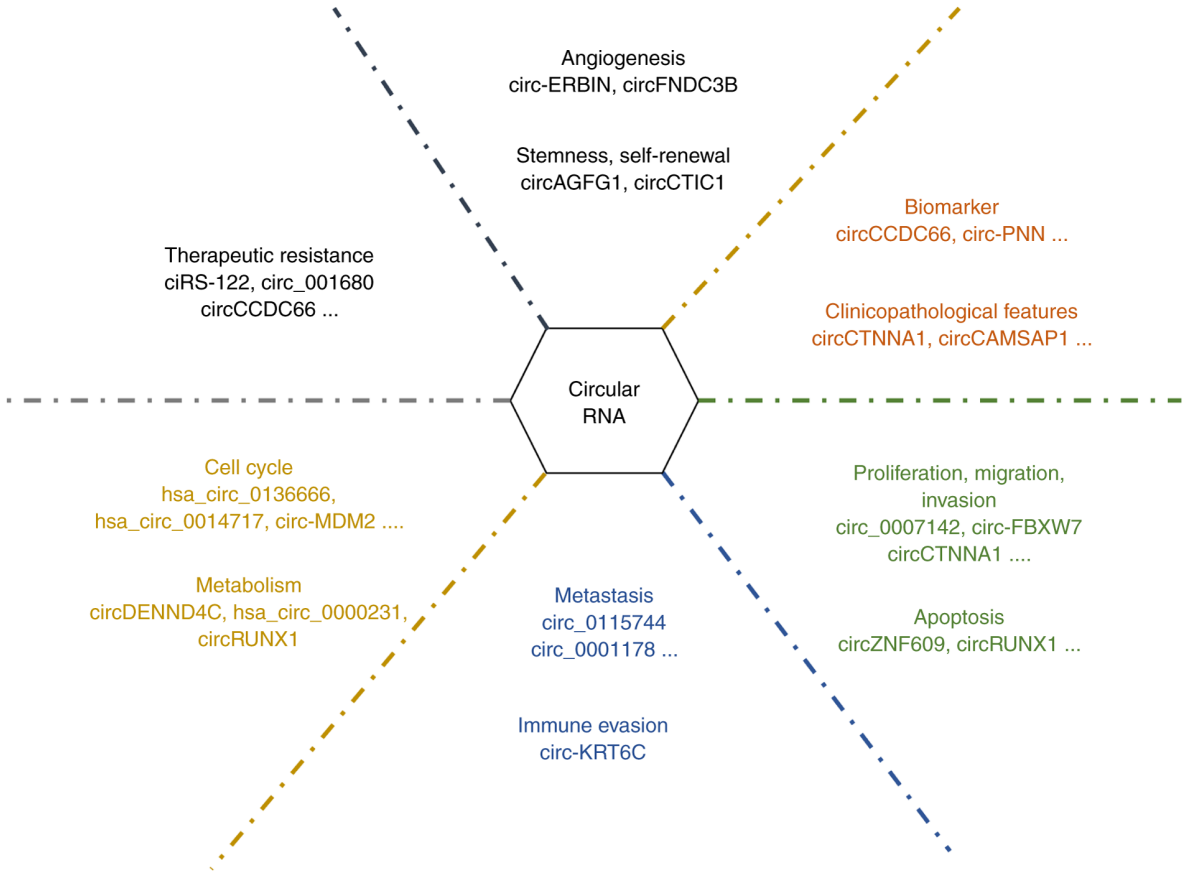

Figure 1. Roles of circRNAs in colorectal cancer. circRNA/circ, circular RNA; ERBIN, ERBB2 interacting protein; FNDC3B, fibronectin type III domain containing 3B; AGFG1, ArfGAP with FG repeats 1; CTIC1, colon tumor initiating cells 1; PNN, pinin demosome associated protein; CCDC66, coiled-coil domain containing 66; KRT6C, keratin 6C; ZNF609, zinc finger protein 609.

circRNAs as templates for translation. Previously, circRNAs have been regarded as non-coding RNAs due to their circular structure, which lacks 5' and 3' untranslated regions that are crucial for the initiation of translation in eukaryotic cells (28). However, more recently, circRNAs have been found to encode peptides, where an Internal Ribosome Entry site and N^6-methyladenosines mediated cap-independent translation initiation were suggested as potential mechanisms involved in the translation of circRNAs. Detailed mechanisms of circRNA translation are reviewed elsewhere (28-30). Legnini *et al* (31) provided an example of translatable circRNAs in eukaryotes, suggesting that circ-zinc finger protein 609 (circZNF609) was translated into protein in a splicing-dependent and cap-independent manner, and this was shown to be involved in regulating myogenesis. Translation of circβ-catenin, another translatable circRNA, produces a novel β-catenin isoform that can antagonize GSK3β-induced β-catenin phosphorylation and degradation, and thus stabilize full-length β-catenin, resulting in the activation of the Wnt signaling pathway and promoting liver cancer cell proliferation (32).

circRNAs regulate transcription. In addition to the aforementioned functions, nucleolar circRNAs promote transcription. Li *et al* (33) showed circRNAs that contain introns that regulate gene transcription in cis by specifically interacting with the U1 small nuclear ribonucleoprotein RNA (snRNA). The intercommunication between U1 snRNA and the U1-binding sites of exon-intron circRNAs, EIciEIF3J and EIciPAIP2, enhance eukaryotic translation initiation factor 3 subunit J and poly(A) binding protein interacting protein 2 transcription, respectively (33).

4. circRNAs as potential invasive/non-invasive diagnostic or prognostic biomarkers, and their association with CRC clinicopathological features

Using RNA-sequencing, microarray or other sequencing techniques combined with reverse transcription-quantitative (RT-q)PCR, differential expression levels of circRNAs in cancerous vs. non-cancerous tissues have been previously detected (34,35). With their special circular structure making them resistant to the degradation of RNase (15), circRNAs are considered as promising candidates for liquid biopsy, which is a non-invasive tool to reflect the disease state using body fluids, such as plasma or urine (36). Studies have demonstrated that the variations in the expression levels of circRNAs are significantly associated with several clinicopathological features of patients with CRC, including overall survival, prognosis, TNM stage, lymphovascular invasion and lymph node metastasis (37-39). Thus, these circRNAs are likely to serve as novels target genes for screening, diagnosis and monitoring of CRC.

Three circRNAs (hsa_circ_0082182, hsa_circ_0000370 and hsa_circ_0035445) have been validated to be

differentially expressed (increased for hsa_circ_0082182 and hsa_circ_0000370, and decreased for hsa_circ_0035445) in CRC plasma compared with in normal plasma by microarray analysis, with area under the curves (AUCs) of 0.815, 0.737, and 0.703, respectively (40). Moreover, the expression levels of hsa_circ_0082182 and hsa_circ_0035445 were significantly different between preoperative and postoperative stages (40). Lin *et al* (41) investigated the plasma levels of circ-coiled-coil domain containing 66 (CCDC66), circ-ATP binding cassette subfamily C member 1 and circ-STIL centriolar assembly protein (STIL) by RT-qPCR, revealing that their plasma expression levels were significantly decreased in patients with CRC (n=45) compared with those in healthy controls (HC; n=61) (41). Receiver operating characteristic (ROC) curve analysis demonstrated that the AUC of the three-circRNA panel was 0.780, exceeding that of carcinoembryonic antigen (CEA; AUC, 0.695) and carbohydrate antigen 19-9 (CA19-9; AUC, 0.678) (41). Combining the circRNA panel with CEA and CA19-9 further improved the accuracy of CRC diagnosis (AUC, 0.855) (41). It has been also found that circ-CCDC66 and circ-STIL may be used for the diagnosis of early-stage CRC, and the three-circRNA panel may be useful in diagnosing CEA-negative and CA19-9-negative CRC (41). However, using the same techniques, Hsiao *et al* (42) verified increased expression levels of circCCDC66 in polyps and colon cancer using RT-qPCR (n=48) and demonstrated its association with a poor prognosis. This controversy may be explained by the heterogeneity of CRC; thus, large cohorts of patients of various ethnicities, possibly through multicenter studies, are required for further confirmation.

Xie *et al* (37) revealed that exosomal levels of circ-pinin demosome associated protein (PNN; hsa_circ_0101802) were significantly upregulated in CRC cases compared with those in the HC group. ROC curve analysis indicated that circ-PNN was significantly valuable for diagnosing CRC, with an AUC of 0.855 and 0.826 in the training and validation sets, respectively (37). Additionally, the AUC of serum exosomal circ-PNN for early-stage CRC was 0.854 (43). Another circulating exosomal circRNA, hsa-circ-0004771, has been found to be upregulated in the serum of patients with CRC compared with HCs and those with benign intestinal diseases (BIDs) by RT-qPCR (44). The AUCs of circulating exosomal hsa-circ-0004771 were 0.59, 0.86 and 0.88 when used to differentiate between BIDs, stage I/II CRC cases and patients with CRC from the HCs, respectively (44). The AUC was 0.816 when differentiating stage I/II CRC cases from patients with BIDs (44). Overall, the aforementioned results suggest that serum exosomal circRNAs may serve as promising non-invasive biomarkers for early detection of CRC.

Using microarrays, Chen *et al* (45) found that circ-catenin α1 expression was significantly upregulated in colon cancer (CC), and its aberrant expression was associated with advanced TNM stages and a poor prognosis in patients with CC. Using next-generation RNA sequencing from eight CRC and paired matching non-cancerous tissues. Zhou *et al* (46) found that circ-calmodulin regulated spectrin associated protein 1 expression was significantly upregulated in CRC tissues compared with in matched non-cancerous tissues, and its high expression was significantly associated with advanced TNM stages and shortened overall survival.

Overall, the aforementioned studies indicate the potential value of circRNAs as diagnostic and prognostic biomarkers, as well as therapeutic targets for CRC. Other circRNAs with similar potential functions are presented in Table I (34,37-39,41-61).

5. circRNAs regulate CRC cell proliferation, migration, invasion and apoptosis

Understanding the underlying mechanisms by which CRC cells progress is key to the identification of novel therapeutic targets. Emerging studies have shown the role of circRNAs in numerous biological processes associated with the development and/or progression of CRC. circRNAs exert their oncogenic or suppressive roles by promoting or inhibiting CRC cell proliferation, migration, invasion and apoptosis.

hsa_circ_0007142 is significantly upregulated in CRC tissues compared with in neighboring para-cancerous tissues (62). Bioinformatics analysis and luciferase reporter assays have revealed that hsa_circ_0007142 sponges miR-103a-2-5p, and silencing of hsa_circ_0007142 using small interfering (si)RNAs decreases the proliferation, migration and invasion of HT-29 and HCT-116 cells (62). Yin *et al* (63) showed that knockdown of circ_0007142 decreased cell division cycle 25A expression by sponging miR-122-5p, and repressed CRC cell proliferation, colony formation, migration and invasion.

Wu *et al* (64) demonstrated that circZNF609 expression was upregulated in CRC tissues compared with in mucosal tissues using RT-qPCR. Moreover, circZNF609 expression has been positively correlated with glioma-associated oncogene 1 expression, knockdown of circZNF609 or overexpression of miR-150 has resulted in inhibition of migration of HCT116 cells by sponging miR-150, and co-transfection with circZNF609 siRNA and miR-150 inhibitor promoted HCT116 cell migration (64). However, another study performed by Zhang *et al* (65) obtained contrasting results. Zhang *et al* (65) found significantly downregulated expression levels of circZNF609 in CRC tissues compared with in matched normal tissues, as well as in the serum of patients suffering CRC compared with the HC group. Mechanistically, it was revealed that circZNF609 increased apoptosis and upregulated the expression levels of p53 and the pro-apoptotic protein, Bax, while downregulating the expression of the anti-apoptotic protein, Bcl-2 (65).

Thus, distinct mechanisms exerted by the same circRNA and the effects of expression levels of the same circRNA highlight the heterogeneity and complexity of circRNAs. A deeper understanding of the biological behaviors of circRNAs is required to reconcile these differences and other contrasting results.

6. circRNAs regulate epithelial-mesenchymal transition (EMT) and metastasis

EMT is a process in which dynamic changes occur in the cellular organization transforming cells from an epithelial phenotype to a mesenchymal phenotype, and this facilitates the development of migratory and invasive cells (66). Metastasis or advanced CRC are the major causes of cancer morbidity,

Table I. circRNAs, their associated clinicopathological features in colorectal cancer and their potential functions.

First author, year	circRNAs	Expression[a]	AUC	Potential functions				Associated clinicopathological features	(Ref.)
				P	D	T	B		
Lin *et al*, 2019	circ-CCDC66, Circ-ABCC1, Circ-STIL	↓	0.780		✓		✓		(41)
Hsiao *et al*, 2017	circ-CCDC66	↑		✓				Prognosis	(42)
Xie *et al*, 2020	circ-PNN	↑	0.854				✓		(43)
Pan *et al*, 2019	hsa-circ-0004771	↑	0.816		✓				(44)
Chen *et al*, 2020	circCTNNA1	↑			✓	✓		TNM stage, prognosis	(45)
Zhou *et al*, 2020	circCAMSAP1	↑		✓	✓	✓	✓	TNM stage, OS	(46)
Chen *et al*, 2020	circHUWE1	↑	0.732		✓	✓	✓	Lymphovascular invasion, lymph node and distant metastasis, TNM stage	(37)
Li *et al*, 2019	circVAPA	↑	0.724			✓	✓	Tumor stage, lymph node and distant metastasis,TNM stage, lymphovascular invasion	(38)
Wang *et al*, 2018	hsa_circ_0000567	↓	0.865		✓		✓	Tumor size, lymph node and distal metastasis, TNM stage	(39)
Zhang *et al*, 2018	hsa_circ_0007534	↑	0.780	✓			✓	Tumor and node stage, distant metastasis, differentiation	(47)
Zhang *et al*, 2018	hsa_circ_0007534	↑				✓		Tumor stage, lymph node metastasis	(48)
Ji *et al*, 2018	circ_0001649	↓	0.857				✓	Pathological differentiation	(49)
Wang *et al*, 2020	circITGA7	↓	0.879		✓				(50)
Zhuo *et al*, 2017	circ_0003906	↓	0.818		✓	✓		Lymphatic metastasis, differentiation	(51)
Ruan *et al*, 2019	circ_0002138	↓	0.725		✓	✓	✓		(52)
Wang *et al*, 2015	circ_001988	↓	0.788		✓	✓	✓	Differentiation, perineural invasion	(53)
Li *et al*, 2018	circ_0000711	↓	0.810	✓	✓		✓	OS	(54)
Yuan *et al*, 2018	circ_0026344	↓		✓				Tumor stage, lymphoid node metastasis, prognosis	(55)
Wang *et al*, 2019	circPVT1	↑				✓		Prognosis, TNM stage, liver metastasis	(56)
Ge *et al*, 2018	circMTO1	↓				✓	✓	TNM stage, lymph node metastasis, OS	(57)
Ren *et al*, 2020	hsa_circ_0001178	↑				✓		Metastasis, TNM stage, prognosis	(58)
Chen *et al*, 2019	hsa_circ_101555	↑		✓		✓		Prognosis	(59)
Ge *et al*, 2019	hsa_circ_0142527	↓			✓		✓	Age, CEA, invasion, differentiation, distal metastasis, TNM stage	(34)
Li and Zhou, 2019	hsa_circ_102209	↑				✓		Histology grade, liver metastasis	(60)
Li *et al*, 2018	circDDX17	↓				✓	✓	Lymphovascular invasion, tumor stage, lymph node and distant metastasis, TNM stage	(61)

[a]Relative circRNA expression in cancerous tissues/cell lines compared with in non-cancerous tissues/cell lines. P, prognostic; D, diagnostic; T, therapeutic; B, biomarker; TNM, Tumor-Node-Metastasis; circRNA/circ, circular RNA; OS, overall survival; CEA, carcinoembryonic antigen; AUC, area under the curve.

mortality and tumor burden. Several studies have shown that circRNAs regulate EMT and metastasis in CRC.

Using secondary sequencing, Xu *et al* (67) identified 66,855 differentially expressed circRNAs in the cancer tissue

samples from patients with CRC liver metastasis (CRLM) and three matched tissue samples from patients with CRC, of which 92 circRNAs were significantly upregulated and 21 circRNAs were significantly downregulated in CRLM tissues. Aiming at screening promising biomarkers for CRLM, Ma *et al* (68) used a high-throughput microarray to screen circRNAs; circ_0115744 was detected significantly elevated in patients with CRLM and mechanistic experiments revealed that circ_0115744 functioned as a competing endogenous RNA (ceRNA) of miR-144, thus removing the suppressive effect of miR-144 on its target enhancer of zeste homolog 2. Ren *et al* (58) demonstrated that high hsa_circ_0001178 expression was associated with metastatic clinical features, a higher TNM stage and an adverse prognosis of patients. Stable knockdown of hsa_circ_0001178 using short hairpin RNAs largely impaired CRC cell migration and invasion *in vitro*, as well as in lung and liver metastases *in vivo* (58). Mechanistically, hsa_circ_0001178 acted as a ceRNA or as a sponge of miR-382/587/616 to upregulate zinc finger E-box binding homeobox 1, which is a crucial initiator of EMT, and thus promoted CRC metastasis (58). The aforementioned study suggests that circRNAs are crucial in EMT of CRC, as well as in metastasis, and also highlights a promising target for patients with end-stage CRC. Similar mechanisms have been elaborated in another study by Xiao and Liu (69), in which it was revealed that knockdown of hsa_circ_0053277 suppressed CRC cell proliferation, migration and EMT by upregulating expression of matrix metalloproteinase 14, another key molecule involved in the process of EMT, and that hsa_circ_0053277 possessed a binding site for miR-2467-3p and acted as a sponge of it.

Although the field of EMT research has seen increased interest over the past two decades, particularly in the past 5 years, there remain several unknowns (64). It is necessary to explore the various roles of numerous circRNAs, either as oncogenic or suppressive agents, to delay the progression of EMT and metastasis. Other circRNAs involved in EMT and metastasis are summarized in Table II.

7. circRNAs are involved in the cell cycle

In addition to the aforementioned biological functions, circRNAs can regulate other processes. circ-MDM2 (hsa_circ_0027492) is coded by the MDM2 gene, which is regarded as a transcriptional target of p53 (70). Based on a previous study, which revealed that MDM2 is crucial in suppressing p53 activity and p53 protein expression (71), Chaudhary *et al* (72) knocked down circ-MDM2 using siRNAs, resulting in an increase in basal p53 levels and growth defects, both *in vitro* and *in vivo*. Further transcriptome profiling following knockdown of circMDM2 showed upregulation of several direct p53 targets, decreased expression of retinoblastoma protein phosphorylation and G_1-S progression defects (72). Overall, a new role for the circRNA derived from the MDM2 locus was identified in cell cycle progression, which preceded the suppression of p53 levels (72). High expression levels of hsa_circ_0136666 and hsa_circ_0014717 result in arrest of CRC cells in the G_0/G_1 phase (73). Mechanistically, hsa_circ_0136666 increases SH2B adaptor protein 1 expression by sponging miR-136 (73), whereas hsa_circ_0014717 induces cell cycle G_0/G_1 phase arrest *in vitro* partly by upregulating p16 expression, a cell cycle inhibitory protein (74).

8. circRNAs regulate cellular metabolism

circRNAs can exert their roles in the complex processes of cellular metabolism. circRNA differentially expressed in normal cells and neoplasia domain containing 4C has been found to accelerate proliferation and migration, as well as glycolysis, in CRC cells by increasing glucose transporter 1 expression by sponging miR-760 (75). Knockdown of hsa_circ_0000231 blocks CRC glycolysis and progression via Myosin VI downregulation by sponging miR-502-5p (76). During serum deprivation, circ-ACC1, which derives from preACC1 mRNA, increases glycolysis and fatty acid oxidation to adapt the metabolic change of HCT116 cells (77). Another novel circRNA, circRUNX1, has been found to promote glutamine metabolism and to repress apoptosis by upregulating solute carrier family 38 member 1 SLC38A1 through miR-485-5p (78).

9. circRNAs are involved in angiogenesis

circ-001971 functions as an oncogenic ceRNA, which aggravates the proliferation, invasion and angiogenesis of CRC by relieving miR-29c-3p-induced inhibition of vascular endothelial growth factor A (79). circ-ERBB2 interacting protein (ERBIN), which derives from exons 2 to 4 of the ERBIN gene, promotes angiogenesis, proliferation, invasion and migration of CRC cells by targeting miR-125a-5p and miR-138-5p; this sponging effect increases eIF4E-binding protein 1 expression, which then increases hypoxia inducible factor-1α (HIF-1α) translation and activates the HIF-1α signaling pathway (80). Zeng *et al* (81) revealed significantly decreased expression levels of circ-fibronectin type III domain containing 3B (FNDC3B) in CRC tissues, cell lines and exosomes. Functional experiments indicated that overexpression of circFNDC3B suppressed CRC angiogenesis, which could be reversed by overexpression of miR-937-5p (81). Furthermore, it was demonstrated that tumor growth, angiogenesis and liver metastasis were suppressed by overexpression of circFNDC3B or circFNDC3B-exosome treatment (81).

10. circRNAs regulate cancer stem cells (CSCs) or tumor initiating cells (TICs)

Recent findings have indicated the role of circRNAs in the self-renewal of CSCs and the maintenance of stemness in CRC. Silencing of circRNA ArfGAP with FG repeats 1 (circAGFG1) markedly suppresses CRC cell stemness and promotes apoptosis (82). Further experiments have revealed that circAGFG 1 sponges miR-4262 and miR-185-5p, and promotes CTNNB1 gene (also known as β-catenin) transcription in CRC cells (82). Circular colon tumor initiating cells 1 (circCTIC1) is upregulated in colon TICs compared with in non-TICs; depletion of this circRNA impairs the self-renewal capacity of colon TICs, while its overexpression promotes colon TIC self-renewal (83). Mechanistically, circCTIC1 recruits the nuclear remodeling factor complex to the c-Myc promotor and drives the initiation of c-Myc transcription (83).

Table II. Biological processes regulated by circRNAs and targets of circRNAs.

First author, year	circRNA	Expression[a]	Targets	Biological processes									(Ref.)
				P	Mi	I	M	C	A	Me	S	An	
Zhu *et al*, 2019	hsa_circ_0007142	↑	miR-103a-2-5p	✓	✓	✓							(62)
Yin *et al*, 2020	hsa_circ_0007142	↑	miR-122-5p/CDC25A	✓	✓	✓							(63)
Zhang *et al*, 2019	circZNF609	↓	Bax, Bcl-2, p53	✓					✓				(65)
Wu *et al*, 2018	circZNF609	↑	miRNA-150		✓				✓				(64)
Ren *et al*, 2020	hsa_circ_0001178	↑	miR-382/587/616/ZEB1		✓	✓	✓						(58)
Xiao *et al*, 2020	hsa_circ_0053277	↑	miR-2467-3p/MMP14	✓	✓								(69)
Chaudhary *et al*, 2020	circ-MDM2	↑	p53					✓					(72)
Jin *et al*, 2019	hsa_circ_0136666	↑	miR-136/SH2B1	✓	✓	✓		✓					(73)
Wang *et al*, 2018	hsa_circ_0014717	↓	p16	✓				✓					(74)
Zhang *et al*, 2020	circDENND4C	↑	miR-760/GLUT1	✓	✓					✓			(75)
Chen *et al*, 2020	circ-001971	↑	miR-29c-3p	✓		✓							(79)
Lu *et al*, 2020	circ-FARSA	↑	miR-330-5pLASP1	✓	✓	✓	✓						(87)
Li and Zhou, 2020	hsa_circ_102209	↑	miR-761/RIN1	✓	✓	✓		✓	✓				(60)
Lu *et al*, 2019	circ-FBXW7	↓	NEK2/mTOR/PTEN	✓	✓	✓							(88)
Chen *et al*, 2019	circ-NSD2	↑	miR-199b-5p/DDR1, JAG1		✓		✓						(89)
Chen *et al*, 2020	circCTNNA1	↑	miR-149-5p/FOXM1	✓	✓	✓							(45)
Chen *et al*, 2019	circ101555	↑	miR-597-5p/CDK6 & RPA3	✓					✓				(59)
Chen *et al*, 2020	circRUNX1	↑	miR-145-5p/IGF1	✓	✓				✓				(90)
Cui *et al*, 2019	circCDYL	↑	miR-105-5p		✓	✓			✓				(91)
Du *et al*, 2020	hsa_circ_0038646	↑	miR-331-3p/GRIK3	✓	✓								(92)
Ge *et al*, 2018	circMTO1	↓	Wnt/β-catenin signaling pathway	✓		✓							(57)
Geng *et al*, 2019	hsa_circ_0009361	↓	miR-582/APC2	✓	✓	✓	✓						(93)
Han *et al*, 2020	circLONP2	↑	miR-17			✓	✓						(94)
He *et al*, 2018	circRNA-ACAP2	↑	miR-21-5p	✓	✓	✓							(95)
Jian *et al*, 2020	circ_001680	↑	miR-340/BMI1	✓	✓								(96)
Jin *et al*, 2018	hsa_circ_0000523	↓	miR-31/Wnt/β-catenin signaling	✓					✓				(97)
Li *et al*, 2019	circRNA CBL.11	↑	miR-6778-5p/YWHAE	✓									(98)
Li *et al*, 2019	hsa_circ_102958	↑	miR-585/CDC25B	✓	✓	✓							(99)
Li *et al*, 2020	circCCT3		miR-613/VEGFA			✓			✓				(100)
Zheng *et al*, 2019	circPPP1R12A	↑	Hippo-YAP signaling pathway	✓	✓	✓							(101)
Zhao *et al*, 2020	circ-ABCC1	↑	Wnt/β-catenin signaling				✓						(102)
Zhang *et al*, 2020	circNOL10	↓	miR-135a-5p, miR-135b-5p	✓	✓	✓		✓					(103)
Zhang *et al*, 2017	hsa_circ_0020397	↑	miR-138			✓			✓				(104)
Zhang *et al*, 2020	circVAPA	↑	miR-125a/CREB5		✓	✓		✓		✓			(105)
Li *et al*, 2018	circVAPA	↑	miR-101	✓	✓	✓			✓				(38)
Zhang *et al*, 2019	circPIP5K1A	↑	miR-1273a/AP-1, IRF-4, CDX-2, Zic-1		✓	✓							(106)
Zhang *et al*, 2020	circAGFG1	↑	miR-4262, miR-185-5p/CTNNB1, Wnt/β-catenin pathway	✓	✓	✓	✓		✓				(82)
Zeng *et al*, 2018	circHIPK3	↑	c-Myb	✓	✓	✓	✓		✓				(107)
Yuan *et al*, 2018	circ_0026344	↓	miR-21, miR-31			✓			✓				(55)
Shen *et al*, 2019	circ_0026344		miR-183/Wnt/β-catenin pathway		✓	✓							(108)
Yong *et al*, 2018	hsa_circ_0071589	↑	miR-600/EZH2		✓	✓							(109)
Yang *et al*, 2020	hsa_circ_0137008	↓	miR-338-5p	✓	✓	✓							(110)
Yang *et al*, 2020	hsa_circ_0004277	↑	miR-512-5p/PTMA	✓					✓				(111)

Table II. Continued.

First author, year	circRNA	Expression[a]	Targets	Biological processes									(Ref.)
				P	Mi	I	M	C	A	Me	S	An	
Li *et al*, 2018	circ-ITGA7	↓	miR-3187-3p/ITGA7	✓	✓		✓						(112)
Yang *et al*, 2019	circ-ITGA7	↓	miR-3187-3p/ASXL1	✓			✓						(113)
Yang *et al*, 2020	circPRMT5	↑	miR-377/E2F3	✓									(114)
Xu *et al*, 2017	hsa_circ_000984	↑	miR-106b/CDK6	✓	✓	✓							(115)
Xian *et al*, 2020	circABCB10	↑	miR-326/CCL5						✓				(116)
Wang *et al*, 2019	circRNA PVT1	↑	miR-145				✓						(56)
Wang *et al*, 2020	circRNA 0060745	↑	miR-4736/CSE1L	✓			✓						(117)
Wang *et al*, 2020	circ_0008285	↓	miR-382-5p/PTEN	✓	✓								(118)
Wang *et al*, 2020	circ-SMAD7	↓	EMT-related proteins		✓	✓							(119)
Pei *et al*, 2020	circ_0000218	↑	miR-139-3p/RAB1A	✓			✓						(120)
Ma *et al*, 2020	circ5615	↑	miR-149-5p/TNKS, Wnt/β-catenin pathway	✓					✓				(121)
Lu *et al*, 2019	hsa_circ_0079993	↑	miR-203a-3p/CREB1	✓									(122)
Li *et al*, 2020	circRNA_101951	↑	KIF3A	✓	✓	✓							(123)
Li *et al*, 2019	circFMN2	↑	miR-1182/hTERT	✓	✓								(124)
Li *et al*, 2020	circCCT3	↑	miR-613/WNT3, VEGFA			✓			✓				(100)
Liu *et al*, 2020	hsa_circ_0000231	↑	miR-502-5p/MYO6	✓	✓	✓			✓	✓			(76)
Chen *et al*, 2020	circ-ERBIN	↑	miR-125a-5p-5p/miR-138-5p/4EBP-1, HIF-1α activation	✓	✓		✓					✓	(80)
Zeng *et al*, 2020	circFNDC3B	↓	miR-937-5p/TIMP3	✓	✓	✓	✓				✓	✓	(81)
Zhang *et al*, 2020	circAGFG1	↑	miR-4262□miR-185-5p/CTNNB1	✓	✓	✓	✓		✓		✓		(82)
Yu *et al*, 2021	circRUNX1	↑	miR-485-5p/SLC38A1		✓	✓	✓		✓	✓			(78)
Chen *et al*, 2021	circ1662	↑	YAP1, SMAD3 pathway		✓	✓	✓						(125)
Liu *et al*, 2021	circ_0000372	↑	miR-495 and IL6	✓	✓	✓							(126)

[a]Relative circRNA expression in cancerous tissues/cell lines compared with in non-cancerous tissues/cell lines. miR, microRNA; P, proliferation; Mi, migration; I, invasion; M, metastasis; C, cell cycle; A, apoptosis; Me, metabolism; S, stemness; An, angiogenesis; circRNA/circ, circular RNA.

11. circRNAs are possibly involved in immune evasion

Immune evasion is a crucial problem in effective anticancer therapeutic strategies (84). Emerging evidence has shown that utilization of immune checkpoints by cancer cells is important for immune evasion (85). Recently, Jiang *et al* (86) revealed the association between circRNAs and immune evasion in CRC. It was demonstrated that circ-keratin 6C (KRT6C), which is encoded from the KRT6C gene, functioned as a miR-485-3p sponge and promoted immune evasion by upregulating programmed cell death receptor ligand 1, which is the ligand for the immune check point programmed cell death protein 1 (86). This suggests the possible role of circRNAs in immune regulation and immune evasion.

Additional potential biological functions of circRNAs are now under exploration to provide a deeper understanding of the roles of circRNAs in CRC progression. Additionally, as a clearer picture of the complex network of non-coding RNA regulation is built, the clinical value of circRNAs has become more evident. The roles of other circRNAs in biological processes in CRC are listed in Table II (38,45,55-60,62-65,69,72-76,78-82,87-126).

12. circRNAs can mediate resistance to cancer therapy

In addition to surgical resection, chemotherapy and radiotherapy constitute some of the primary therapeutic options utilized for the treatment of CRC. However, escaping from chemotherapy- or radiotherapy-induced cell death is one of the characteristics of cancer cells, and numerous mechanisms contribute to therapeutic resistance (127). Although limited in number, some studies have investigated the role of certain circRNAs in CRC therapeutic resistance, highlighting potential targeted strategies to overcome or inhibit the acquisition of resistance.

Recently, Wang *et al* (128) reported on an M2 isoform of pyruvate kinase (PKM2)-mediated transition from chemo-sensitive to chemo-resistant cells. Wang *et al* (128) confirmed that oxaliplatin resistance can be acquired through exosomal delivery of ciRS-122, which acts as a sponge for miR-122, and finally upregulates PKM2, a key molecule that mediates glycolysis. The underlying mechanism of action includes the promotion of glycolysis through a ciRS-122/miR-122/PKM2 pathway, which provides ATP for

Table III. circRNAs in the therapeutic response in colorectal cancer.

First author, year	circRNA	Expression	Targets	Therapy	(Ref.)
Chen *et al*, 2020	circ-PRKDC	↑[b]	miR-375/FOXM1, Wnt/β-catenin pathway	5-FU	(131)
He *et al*, 2020	circ_0007031	↑[a]	miR-133b/ABCC5	5-FU	(132)
Wang *et al*, 2020	circ_0007031	↑[a]	miR-760/DCP1A	5-FU, radiotherapy	(133)
Xiong *et al*, 2017	circ_0007031	↑[b]	miR-885-3p	5-FU-based chemoradiation	(134)
Xiong *et al*, 2017	circ-0000504	↑[b]	miR-485-5p	5-FU-based chemoradiation	(134)
Xu *et al*, 2020	circ-FBXW7	↓[b]	miR-18b-5p	Oxaliplatin	(135)
Wang *et al*, 2019	circ_0001313	↑[b]	miR-338-3p	Radiotherapy	(129)
Wang *et al*, 2020	ciRS-122	↑[b]	miR-122/PKM2	Oxaliplatin	(128)
Jian *et al*, 2020	circ_001680	↑[a]	miR-340/BMI1	Irinotecan	(96)
Wang *et al*, 2019	circCCDC66	↑[b]	miR-338-3p	Radiotherapy	(129)
Lin *et al*, 2020	circCCDC66	↑[b]		Oxaliplatin	(130)
Abu *et al*, 2019	has_circ_103306	↑[b]	miR-370-3p	5-FU, oxaliplatin	(136)
Abu *et al*, 2019	has_circ_32883	↑[a]	miR-130b/PI3K/AKT pathway	5-FU, oxaliplatin	(136)
Ren *et al*, 2020	circ-DDX17	↓[a]	miR-31-5p/KANK1	5-FU	(137)
Zhang *et al*, 2021	circ_0071589	↑[b]	miR-526b-3p/KLF12	oxaliplatin	(138)
Zhao *et al*, 2021	circ_0000338	↑[b]	miR-217, miR-485-3p	5-FU	(139)
Xi *et al*, 2021	circCSPP1	↑[b]	miR-944/FZD7	Doxorubicin	(140)

[a]Relative circRNA expression in cancerous tissues/cell lines compared with in non-cancerous tissues/cell lines; [b]relative circRNA expression in resistant tissues/cell lines compared with in sensitive tissues/cell lines. miR, microRNA; circRNA/circ, circular RNA; 5-FU, 5-fluorouracil.

the oxaliplatin-chemo-resistant cells (128). Another circRNA, circ_001680, which sponges miR-340, affects the expression levels of the downstream target gene B cell-specific Moloney murine leukemia virus integration site 1, which is an important cancer stem cell self-renewal factor, and is involved in gene silencing (96). circ_001680 may serve as a novel molecule to determine the success of irinotecan-based chemotherapy (96).

circCCDC66 (hsa_circ_0001313) has recently been identified to be aberrantly upregulated in CC tissues (42). Wang *et al* (129) found that circCCDC66 was significantly increased in CRC cells following radiation treatment, whereas knockdown of circCCDC66 decreased cell viability and colony formation rate, and increased caspase-3 activity. Another circCCDC66 study conducted by Lin *et al* (130) indicated increased circCCDC66 expression in oxaliplatin-resistant CRC cells, and knockdown of circCCDC66 decreased oxaliplatin-resistance. Notably, it was found that phosphatidylinositol 3-kinase-related kinases-mediated DExH-box helicase 9 phosphorylation, which favors oncogenic circCCDC66 expression, was involved in the development of oxaliplatin resistance (130). The discovery of the roles of circRNAs in acquisition of therapeutic resistance is an important avenue for future research. Other circRNAs associated with acquisition of therapeutic resistance are summarized in Table III (96,131-140).

13. Conclusions and future perspective

In the present review, the role of circRNAs in CRC was summarized, from their involvement in cellular processes to their association with clinicopathological features and therapeutic resistance. Additionally, their potential value as diagnostic, prognostic and therapeutic targets in patients with CRC was highlighted.

However, there are still significant challenges that remain to be addressed before circRNAs can be considered in clinical applications. First, despite the notable progress in the field of circRNA research, relatively few circRNAs with biological functions have been discovered, and the exact underlying molecular mechanisms of circRNA generation, localization, degradation and turnover process remain unclear. Further understanding of their biology may demonstrate why circRNAs are dysregulated in tumors, and thus accelerate their clinical utility. Second, there are controversies amongst different studies on the same circRNA, such as the expression levels of the same circRNA in different studies. Large cohorts from multicenter studies are required for further confirmation. Third, the biological functions of circRNAs are complex. One circRNA can exert its function through multiple pathways and targets. Thus, the roles of circRNAs and their crosstalk with the tumor microenvironment requires further study. Roles of circRNAs and their crosstalk with the tumor microenvironment, cancer cell metabolism and therapeutic resistance need further investigations. Finally, although certain circRNAs have been suggested as promising diagnostic and prognostic biomarkers, especially as non-invasive biomarkers, increasing their sensitivity and specificity for clinical use is challenging. Utilization of circRNAs in clinical practice has several hurdles to overcome. Understanding how to block those with oncogenic properties and magnify those with tumor suppressive effects

may be helpful. Notably, an artificial synthesized circRNA from linear RNA molecule containing miR-21 binding sites using simple enzymatic ligation steps has been proven to function as a miR-21 sponge and to suppress the downstream cancer protein death domain-associated tumor suppressor protein (141). The artificial synthesis of circRNAs may be another effective tool in clinical application. With the development of new technologies, the crosstalk between circRNAs and tumor biogenesis will be further explored, and this may lead to the development of promising clinical approaches for the treatment of CRC.

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Authors' contributions

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Competing interests

The authors declare that they have no competing interests

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