The effective function of circular RNA in colorectal cancer

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Abstract
Colorectal cancer (CRC) is the 3rd most common type of cancer worldwide. Late detection plays role in one-third of annual mortality due to CRC. Therefore, it is essential to find a precise and optimal diagnostic and prognostic biomarker for the identification and treatment of colorectal tumorigenesis. Covalently closed, circular RNAs (circRNAs) are a class of non-coding RNAs, which can have the same function as microRNA (miRNA) sponges, as regulators of splicing and transcription, and as interactors with RNA-binding proteins (RBPs). Therefore, circRNAs have been investigated as specific targets for diagnostic and prognostic detection of CRC. These non-coding RNAs are also linked to metastasis, proliferation, differentiation, migration, angiogenesis, apoptosis, and drug resistance, illustrating the importance of understanding their involvement in the molecular mechanisms of development and progression of CRC. In this review, we present a detailed summary of recent findings relating to the dysregulation of circRNAs and their potential role in CRC.

Keywords: Circular RNA, Colorectal cancer, Long non-coding RNA, Noncoding RNA

Background
Colorectal cancer (CRC) is one of the most common malignancies ranking third in the incidence and second in mortality among other cancers in the world. The global incidence of CRC is increasing, with approximately 3640 deaths and 17,930 new cases in 2020 [1, 2]. The exact mechanisms underlying CRC development remain unknown, however, risk factors that are strongly related to CRC include genetics, diet, tobacco smoking, heavy alcohol consumption, inactive lifestyle and age, where > 50 is a significant risk factor for CRC. However, recent evidence has also detected an increased risk for young adults [3]. Clearly the disorder is multifactorial in nature, with no common identifiable predictor of pre-disposition [4]. Here, we will review the molecular evidence to date.

Genetic and epigenetic alterations have both been found in CRC patients; changes in chromosomal copy number, aberrant gene methylation, and dysregulated gene expression, including tumor suppressor genes such as APC, BRAF, DCC, TP53, SMAD4, SMAD2, oncogenes such as KRAS and NRAS, and DNA repair genes including MLH1 and MSH6 [5, 6].

Dividing these mutation types into functional pathways broadly identifies three separate mechanisms: Chromosomal instability, which is the most common cause of genomic instability in CRC, significantly linked to alterations in APC and KRAS genes [7, 8]. In hereditary and sporadic colorectal cancer, microsatellite instability (MSI) is another key pathway. Germline mutation in one of the DNA mismatch repair genes, MLH1, MSH2, MSH6, or PMS2 leads to hereditary nonpolyposis colorectal cancer.
The majority of the human genome (~90%) is transcribed as ncRNAs, which contain multiple classes of RNAs with various lengths [17]. Many studies have identified functional roles for ncRNAs, in various physiological and pathological processes, such as diabetes, cardiovascular disease, and cancer [18–20]. Classes of short ncRNAs include microRNAs (miRNAs), small interfering RNAs (siRNAs) and short piwi-interacting RNAs (piRNAs), meanwhile, linear IncRNAs (long non-coding RNAs) and circular RNAs are both classified as long noncoding RNAs [21]. circRNAs, however, are a new class of long ncRNAs, Processing largely from exotic or intronic sequences, and are remarkably unstable in structure and show tissue-specific expression, also displaying developmental stage regulation, with evolutionary conservation among species [25].

The non-coding RNAs

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Functions of circRNAs

circRNAs have regulatory roles in gene expression by sponging miRNAs, competing with other RNAs for binding to miRNAs and RNA binding proteins (RBPs) to modulate the local concentration of RBPs and RNAs as part of the competing endogenous RNA (ceRNA) network [26]. circRNAcircRNACDR1as (ciRS-5-7), for example, which has more than 70 conserved binding sites for miR-7, and is highly expressed in human and mouse brains [27, 28]. SRY, which encodes both linear and circular RNAs, is involved in sex determination in testis development. circRNA SRY can control metastasis and invasion of tumor cells via sponging miR-138 [29, 30]. Another circRNA, known as CircITCH, plays similar roles as a miRNA sponge, via miR-7, miR-17, and miR214, to inhibit proliferation through the Wnt/β-catenin signaling pathway [31], which is illustrated in Fig. 1A.

Although circRNAs are considered to be non-coding RNAs due to lack of 5′-cap structure and 3′-polyadenylation tail, circRNAs have been shown to generate protein products in a cap-independent manner [32]. Interestingly, many circRNAs are sometimes translated, indeed using high-content genomic screening, Legnini et al. found Circ-ZNF609 can translate into a protein in a splicing-dependent and cap-independent manner [33]. Yang Y et al. discovered CircFBXW7, produced from the FBXW7 gene, encoding a novel 21-kDa protein FBXW7-185aa, which reduced the half-life of c-Myc by antagonizing USP28-induced c-Myc stabilization [34].

The overall activities of circRNAs are intricately intertwined with RNA binding proteins, modulating the stability of mRNAs, regulating gene transcription, and translating proteins [35] and are involved in the regulation of cell proliferation, pluripotency and early lineage differentiation, epithelial-mesenchymal transition (EMT), cancer progression and chemoradiotherapy resistance, as shown in Fig. 2.

Upregulation of circRNAs in CRC

Among all the validated aberrantly expressed circRNAs in colorectal cancer, upregulation of circRNAs more often associates with oncogenesis. Xia et al. found abnormally expressed circRNAs through CircRNA high-throughput
sequencing, identifying Circ-0053277 as having the ability to sponge miR-2467-3p, and as being significantly upregulated in CRC tissues, where it facilitated CRC cell migration, proliferation, and epithelial-mesenchymal transition [36]. Similarly, Li et al. identified CircVAPA as being upregulated in tissues and plasma, serving as a sponge for miR-101. Furthermore, they showed that the expression level of miR-125a was decreased in CRC cells, and CircVAPA knockdown repressed CRC cells cycle progression, invasion, and migration [37]. Knockdown of CircVAPA can also suppress CRC cell cycle progression, invasion, and migration by sponging miR-125a [38].

Yahang et al. found that Hsa_Circ_0026416 which was upregulated in CRC tissues and plasma, and has a key role in promoting the progression of CRC both in vitro and in vivo, may function as a ceRNA to sponge miR-346 [39].

Knockdown of another upregulated circRNA, CircACAP2 (hsa_circ_0007331), which was reported to be significantly upregulated in CRC tissues and colon cancer cells lines, suppressed proliferation and invasion by downregulating T lymphoma invasion and metastasis protein 1 (Tiam1) expression, through upregulated miR-21-5p expression (40). Another highly overexpressed circRNA in CRC is Hsa_circ_0136666, derived from the PRKDC gene, which can regulate proliferation and migration of CRC cells by sponging miR-136 [41].
**Downregulated circRNAs in CRC**

As well as being overexpressed, other circRNAs are downregulated in CRC. Wang X et al. showed hsa_Circ_001988 was significantly downregulated in 31 matched colorectal cancer tissue samples, proposing this circRNA as a novel diagnosis potential biomarker in the CRC [42]. Geng Y reported hsa_Circ_0009361 to be significantly downregulated in both CRC tissues and derived cells. circRNA promoting the proliferation, epithelial-mesenchymal transition, migration, and invasion of CRC cells by sponging of miR-582. Conversely, overexpression of hsa_Circ_0009361 caused upregulation in the expression of adenomatous polyposis coli 2 (APC2) and blocked the activity of the Wnt/β-catenin pathway [43]. Circ-ITGA7, which sponges’ miR-370-3p to increase ITGA7 transcription, through inhibition of RREB1 via oncogenic Ras has been shown to be down-regulated in CRC tissue samples [44]. Indeed, Circ-ITGA7 has also been shown to directly act as a tumor suppressor in CRC, with clinical features including cancer differentiation, lymph node metastasis, distant metastasis, and alterations in the TNM stage [45]. circRNA Circ-FBXW7 silencing was previously reported to enhance the proliferation, cell migration, and invasion of CRC cells in culture. In contrast, overexpression of Circ-FBXW7 significantly suppressed CRC cell proliferation, migration, and invasion. Similarly, Circ-FBXW7 silencing was also shown to stimulate tumor growth in SW480 and SW620 tumor models, whereas Circ-FBXW7 overexpression repressed tumor progression in the same system. This suggests that Circ-FBXW7 could serve as a target biomarker of CRC. Potential mechanisms have been proposed, including upregulated mRNA and protein expressions of NEK2 and mTOR, and diminished the PTEN expression (46). circRNA Circ_021977 is another circRNA found to be down-regulated in CRC. Circ_021977 was shown to sponge miR-10b-5p, with a regulatory axis inhibiting proliferation, migration, and invasion in CRC via p21 and p53 [47]. Dysregulated circRNA expression in CRC is summarized in Table 1.

**circRNAs as biomarkers for colorectal cancer**

Through improvements in high-throughput sequencing, circRNA microarray, and chip analysis we now know circRNAs are differentially expressed in CRC, and certain circRNAs are involved in various biological processes such as proliferation, migration, invasion, and apoptosis. Due to the unique structure of circRNAs, which confers resistance to RNase and longer half-lives, they can therefore be potential candidates for diagnostic biomarkers. However, the underlying biological function of circRNAs requires further investigation [138, 139].

Several circRNAs have been proposed as useful therapeutic targets for CRC. For instance, hsa_circ_022382 which is derived from the human FADS2 gene is overexpressed in 200 CRC tissues, where CircFADS2 overexpression was positively associated with clinicopathological features. CircFADS2 expression may therefore be a promising biomarker for prognostic investigation in CRC patients [95]. In another study, hsa_circ_0026344 was shown to be significantly downregulated in 32 CRC patients compared to paired adjacent non-tumorous tissues. The expression of hsa_circ_0026344 was correlated with tumor size and lymph metastasis. Functionally, circRNA-0026344 overexpression significantly suppressed CRC cell proliferation and colony formation as well as promoted apoptosis by...
| CircRNA | GENE Related miRNA | Expression | Targeted molecules/ pathways | Function | References (DOI) |
|---------|------------------|------------|-------------------------------|----------|-----------------|
| circ_0007142 | miR-455-5p | Up | SGK1 | Regulates cell proliferation, apoptosis, migration, and invasion | [48] 2021 |
| hsa_circ_102049 | miR-761, miR-192-3p | Up | FRAS1 | Promoting liver metastasis | [49] 2021 |
| LONP2 | Mir-17 | Up | DGCR8 | Prognostic predictor for anti-metastasis target | [50] 2020 |
| CircPTK2 (hsa_circ_0005273) | | Up | binding to vimentin protein | Metastasis and may serve as a potential therapeutic target for CRC metastasis, Promote EMT | [51] 2020 |
| circPACRGL | miR142-39,506-3p | Up | TGF-β1 | Promoted CRC cell proliferation, migration, and invasion, as well as differentiation | [52] 2020 |
| hsa_circ_0053277 | miR-2467-3p | Up | MMP14 | Facilitated the development of CRC accelerated cell proliferation | [37] 2020 |
| Hsa_circ_001680 | miR-340 | Up | BMI1 | Enhance the proliferation and migration capacity of CRC cells | [53] 2020 |
| circSAMRCC1 | miR-140-3p | Up | MMP-2, MMP-9, VEGF | Cell viability, migration, and invasion | [54] 2020 |
| CircHIPK3 | miR-1207-5p | Up | FMNL2 | Promote Cell Progression, migration, and invasion in CRC | [55] 2020 |
| circ-HIPK3 | Mir-7 | Up | FAK/IGF1R/EGFR/YY1 | Promotes CRC growth and metastasis Prognostic | [56] 2020 |
| circHUWE1 | miR-486 | Up | | Promotes Cell Proliferation, Migration, and Invasion | [57] 2020 |
| circVAPA | miR-101 | Up | CREB5 | Promotes CRC cell proliferation, migration, invasion, and inhibit apoptosis | [38] 2020 |
| CircAPLP2 | miR-101-3p | Up | Notch Signaling Notch1 | Promotes proliferation and metastasis | [58] 2020 |
| circ-FARSA | miR-330-5p | Up | LASP1 | Proliferation, migration, and invasion of CRC cells in vitro | [59] 2020 |
| CircAGFG1 | miR-4262 and miR-185-5p | Up | WNT/β-catenin CTNNB1 | Promote metastases | [60] 2020 |
| circ5615 | miR-149-5p | Up | WNT/β-catenin pathway | Exerted oncogenic function | [61] 2020 |
| circular RNA 001,971 | miR-29c-3p | Up | VEGFA | CRC cell proliferation, Invasion and angiogenesis | [62] 2020 |
| CircPRMT5 | miR-377 | Up | E2F3 | Cell proliferation and migration | [63] 2020 |
| Circular RNA NOX4 | microRNA-485-5p | Up | CKS1B | Promotes the development of colorectal cancer | [64] 2020 |
| circRAE1 | miR-338-3p | Up | TYRO3 | Promotes colorectal cancer cell migration and invasion | [65] 2020 |
| CircRNA            | GENE Related miRNA | Expression | Targeted molecules/pathways                  | Function                                                                 | References (DOI) |
|-------------------|--------------------|------------|---------------------------------------------|---------------------------------------------------------------------------|------------------|
| Hsa_circ_0079662  |                    | Up         | TNF-α HOXA9                                 | Induces the resistance mechanism of the chemotherapy drug oxaliplatin through the TNF-α pathway | [66] 2020        |
| Hsa_circ_0026416  | miR-346            | Up         | NFIB                                        | Promotes proliferation and migration                                       | [39] 2020        |
| circ_0136666      | miR-383            | Up         | CREB1 proteins (HK2 and LDHA)               | Accumulation on the proliferation and glycolysis and the promoting impact on the apoptosis of CRC | [67] 2020        |
| hsa_circRNA_102209| miR-761            | Up         |                                             | Promotes the growth and metastasis                                         | [68] 2020        |
| Hsa_circ_0005963  | miR-122            | Up         | PKM2                                        | Chemoresistance. In vitro and in vivo studies                              | [69] 2020        |
| Circ TUBB         |                    |            |                                             | Interacting with smoking can enhance colorectal cancer risk                     | [70] 2020        |
| CircRNA_101951    | miR-6833, miR-1301-3P | Up       | KIF3A                                       | Promote migration and invasion                                               | [71] 2020        |
| Circ-PNN, hsa_circ_0101802 | miR-937-5p | Up         | circFNDC3B-enriched exosomes can inhibit angio genesis and CRC progression |                                                                                       | [74] 2020        |
| CircFNDC3B        |                   |            |                                             | Promotes Colorectal Cancer Cell Proliferation and Metastasis                |                  |
| circ_0060745      | miR-473,6          | Up         | CSE1L                                       | Promotes Colorectal Cancer Cell Proliferation and Metastasis                | [75] 2020        |
| circRUNX1         | miR-145-5p         | Up         | IGF1 signaling                              | Promote Cell Growth Metastasis/Proliferation/migration                       | [76] 2020        |
| circHOMER1        | miR-138-5p         | Up         | HEY1                                        | A decrease in glucose consumption Treated with lidocaine, indicating the inhibition of CRC cell viability mediated by lidocaine through suppressing aerobic glycolysis | [77] 2020        |
| Hsa_circ_0001806  | miR-193a-5p        | Up         | COL1A1                                      | Correlated with TNM stage, depth of invasion, lymphatic metastasis, and distant metastasis | [78] 2020        |
| circMAT2B         | miR-610            | Up         | E2F1                                        | Induces Colorectal Cancer Proliferation                                     | [79] 2020        |
| circ_0000512      | miR-296-5p/        | Up         | RUNX1                                       | Cell Proliferation cell viability and colony formation                      | [80] 2020        |
| Circ_0056618      | miR-206            | Up         | CXCR4 VEGF-A                                | Promoted cell proliferation, migration, and angiogenesis                    | [81] 2020        |
| CircRNA_0001946   | MicroRNA-135a-5p   | Up         | EMT                                         | A tumor promoter by activating the miR-135a                                  | [82] 2020        |
| CircRNA          | GENE Related miRNA | Expression | Targeted molecules/ pathways | Function                                                                 | References (DOI) |
|------------------|--------------------|------------|-----------------------------|---------------------------------------------------------------------------|-----------------|
| Hsa_circ_0038646 | miR-331-3p         | Up         | GRIK3                        | Promotes cell proliferation and migration                                  | [83] 2020       |
| Circ_circ_000731 | miR-760            | Up         | DCP1A                        | Regulate the Growth and Chemoradiotherapy Resistance might play a positive role | [84] 2020       |
| Circ-PRKDC       | miR-375/           | Up         | FOXM1 Axis and Wnt/β-Catenin | Circ-PRKDC enhanced 5-FU resistance in CRC                                 | [85] 2020       |
| CircRNA UBAP2    | Mir-199a           | Up         | VEGFA                        | Regulate the Growth and Chemoradiotherapy Resistance might play a positive role | [86] 2020       |
| Hsa_circ_0000231 | miR-502-5p         | Up         | MYO6                         | CRC progression                                                            | [87] 2020       |
| circGLIS2        | miR-671            | Up         | NF-κB                        | Promotes colorectal cancer cell motility                                   | [88] 2020       |
| Circular RNA CCDC66 | miR-3140        | Up         | PI3KK                        | Apoptosis                                                                 | [89] 2020       |
| circCCDC66       | miR-33b/miR-93/    | Up         | autophagy                    | Promotes the tumorigenesis                                                  | [90] 2020       |
| Hsa_circ_0128846 | hsa-miR-1184       | Up         | YAP signaling                | Promotes CRC growth and metastasis                                         | [91] 2020       |
| Hsa_circ_0007534 | miR613 SLC25A22    | Up         | SLC25A22                     | Promote proliferation was correlated with tumor stage and lymph node metastasis | [93] 2020       |
| CircFAT1         | miR-520b miR-302c-3p | Up         | UHRF1                        | CRC cell proliferation, apoptosis, and glycolysis                          | [94] 2020       |
| CircFADS2        |                    |            |                              | Biomarkers of CRC                                                          | [95] 2020       |
| Circ-000166      | miR-326            | Up         | LASP1                        | Cell growth and apoptosis in CRC cell lines                                | [96] 2020       |
| circ-ACAP2       | Mir21-5p           | Up         | Tiam1                        | Promotes CRC cell proliferation, migration, and invasion                   | [49] 2020       |
| circ-ZNF609      | miR-150            | Up         | Gli1                         | Promotes CRC cell migration                                                | [33] 2020       |
| circ-NSD2        | miR-199b           | Up         | Sp/DDR1/JAG1                 | Promotes CRC metastasis                                                    | [97] 2020       |
| Circ-DENND4C     | miR-760            | Up         | SLC2A1                       | Promote Migration and glycolysis                                           | [98] 2020       |
| circ-Lgr4        |                    | Up         | circLgr4-peptide/Lgr4/ Wnt/β-catenin | Promotes CRC stem cell self-renewal, tumorigenesis and invasion             | [99] 2020       |
| hsa_circ_000984  | miR-106b           | Up         | CDK6                         | Promotes CRC growth and metastasis                                         | [100] 2020      |
| Has _circ -140,388 | Mir486 -Sp        | Up         | PLAGL2 IGF2 WNT- β-CATENIN    | Metastasis                                                                 | [57] 2020       |
| Has-circ-0004680 | Mir- 613           | Up         | CCT3 WNT3/EGFR               | Metastasis                                                                 | [101] 2020      |
| Has _circ-001,900 | Mir328-Sp Mir7    | Up         | E2F1 IGF1 CAMSAP1            | Promotes CRC progression                                                    | [102] 2020      |
| hsa_circ_0007534 |                    | Up         | ARHGAP32                     | Migration, invasion                                                        | [93] 2021       |
| Has-circ- 0,007,843 | Mir- 518-Sp       | Up         |                              | Promotes proliferation and inhibits apoptosis                               | [103] 2020      |
| CircRNA       | GENE Related miRNA | Expression | Targeted molecules/pathways                  | Function                              | References (DOI) |
|--------------|--------------------|------------|----------------------------------------------|---------------------------------------|-----------------|
| circRNA_100876 | miR-516b           | Up         |                                              | Inhibit proliferation and metastasis  | [104] 2020      |
| CircRNA_0000392 | miR-193a-5p       | Up         | PIK3R3/AKT                                   | Promoter proliferation of CRC         | [105] 2020      |
| circRNA_002144 | miR-615-5p         | Up         | LARP1                                        | Promotes growth and metastasis        | [106] 2020      |
| Circ-Erbin    | miR-125a-5p and miR-138-5p | Up       | 4EBP-1                                      | Promotes growth and metastasis of CRC | [107] 2020      |
| CircRNA 100,146 | miR-149           | Up         | HMGA2                                        | Promotes Colorectal Cancer Progression | [108] 2020      |
| circ-NSUN2    | miR-125a-5p and miR-138-5p | Up       | IGF2BP2/HMG A2                               | Promotes CRC liver metastasis         | [109] 2019      |
| circCCT3      | Mir613             | Up         | VEGFA, WNT signaling                        | Contributes to metastases             | [101] 2019      |
| Circ_0000218  | miR-139-3p         | Up         | RAB1A                                        | Promoted CRC proliferation and metastasis | [110] 2019      |
| circFMN2      | miR-1182           | Up         | hTERT                                        | Cell proliferation and migration       | [111] 2019      |
| Circ 32,883   | Mir501-5p          | Up         | EML5                                         | Promote resistance to folfox          | [112] 2019      |
| Circ ACC1     | Up                 |            | c-Jun/AMPK                                   | Promotes CRC cell fatty acid β-oxidation, glycolysis and growth | [113] 2019      |
| hsa_circ_102958 | miR-585           | Up         | CDC25B                                       | Promotes CRC tumorigenesis            | [114] 2019      |
| Has- circ-101555 | Mir 597-5p        | Up         | CDK6/RPA3                                   | Promote progression                   | [115] 2019      |
| Has-circ-0079993 | Mir 139-3p        | Up         | CREB1                                        | Promotes CRC cell proliferation       | [116] 2019      |
| Has-circ-PIP5K1A | Mir 1273           | Up         | Irf4/cdx2/ZIC1                              | Promote progression CRC               | [117] 2019      |
| hsa_circ_0055625 | ITG88             | Up         | miR-106b                                     | Increases colon cancer cell growth was associated with pathological TNM stage and metastasis | [118] 2019      |
| hsa_circ_0136666 | PRKDC             | SH2B1      | Mir136                                       | Promote proliferation and invasion    | [41] 2019       |
| hsa_circ_0073195 | miR-199-b         | Up         | Ddr1 and Jag1 signaling                      | Promotes metastasis                   | [97] 2019       |
| hsa_circ_0071589 | MIR-600           | Up         | Fat1/EZH2                                    | Promotes carcinogenesis tumor growth, invasion, and migration | [119] 2018      |
| circRNA_100290 | FZD4/SCL30A7      | Up         | Mir516b                                      | Promotes colorectal cancer            | [120] 2018      |
| Cirs7         | miR-7              | Up         | EGFR and IGF1R                               | Promotes progression                  | [27, 121] 2017  |
| Circ00000504  | Mir485-5p          | Up         | Tubgpc3/Stat3                                | Promote resistance to 5fu              | [122] 2017      |
| hsa_circ_000984 | CDK6              | Up         | Mir 106b                                     | Promotes cells proliferation and metastasis | [100] 2017      |
| hsa_circ_0020397 (circBNAP) | DOCK1/FD3/1 | Up         | Mir138                                       | Can regulate CRC cell viability, apoptosis, and invasion | [123] 2017      |
| Circ-0001313  | Mir-3383p/33b5p/935p | Up         | Cc066                                        | Promote resistance to radiotherapy and 5fu | [124] 2017      |
| CircRNA         | GENE Related miRNA | Expression | Targeted molecules/pathways | Function                                                                 | References (DOI) |
|----------------|--------------------|------------|------------------------------|--------------------------------------------------------------------------|-----------------|
| Has-circ-001569 miR145 | Up    | ABC1       | E2F5            | The regulator in cell proliferation and invasion                       | [125] 2016      |
| circ_0007142 miR-122-5p | Down  | CDC25A     |                | Proliferation, colony formation, migration, and invasion               | [48] 2020       |
| CircCSNK1G1 miR-455-3p | Down  | MYO6       |                | Proliferation, migration and invasion cell growth and metastasis       | [126] 2020      |
| CircTADA2A miR-374a-3p | Down  | KLF14      |                | Tumor suppressor in CRC                                                | [127] 2020      |
| circ-SMAD7 miR‑374a‑3p, miR‑31‑5p | Down  | eIF4A3     | PCNA            | circ-SMAD7 could inhibit cell migration and invasion of CRC by suppressing the EMT process, | [128] 2020      |
| circ_cse1l           | Down  | eIF4A3     | PCNA            | circ_cse1l inhibited the proliferation of CRC                          | [129] 2020      |
| ITGA5 circRNA      | miR-107, | Down  | FOXJ3           | Act as a tumor suppressor in CRC                                       | [130] 2020      |
| CircDDX17 miR‑31‑5p/ | Down  | KANK1      |                | Tumor suppressor blocked CRC progression                               | [131] 2020      |
| Hsa_circ_0137008 microRNA-338-5p | Down  | eIF4A3     | PCNA            | Inhibited the progression of CRC                                       | [132] 2020      |
| CircNOL10 miR-135a-Sp; miR-135b-Sp | Down  | KLF9       |                | Mediating proliferation, cell cycle, migration, and invasion           | [133] 2020      |
| circ_0021977 miR-10b-5p | Down  | P21; P53   |                | Suppresses proliferation, migration, and invasion by CRC cells         | [47] 2020       |
| circRNACBL11 YWHAE | Up    | Mir6778-5p |                | Suppress cell proliferation                                            | [134] 2019      |
| Circ CDYL c-Myc cyclin D1 | Down  | miR-150-5p/ |                | Inhibits CRC cell growth and migration                               | [135] 2019      |
| circITGA7 ITGA7 Reb1 Ras’s pathway ASXL1 | Down  | miR-370-3p, miR-3187-3p | | Inhibits colorectal cancer growth and metastasis | [44] 2019, [45] 2018 |
| hsa_circ_0009361 Mir582-3p | Down  | APC2/Wnt/β-catenin |                | Inhibits CRC progression                                              | [43] 2019      |
| hsa_circ_0000523 METTL3 dKK1 WNT/β-catenin | Down  | Mir-31 |                | Correlated to the tumorigenesis-Proliferation                         | [136] 2018      |
| circTCH DDX17 WNT/β-catenin | Down  | miR-7, miR-17, miR-214 | | Proliferation (−)                                                      | [31] 2015
regulating miR-21 and miR-31 levels [45]. Other circRNAs with biomarker potential are summarized in Table 3.

**circRNAs as therapeutic targets in colorectal cancer**

Targeted therapy has been widely used in the clinic due to its excellent efficacy, and it can work on cancerous cells by directly inhibiting cell proliferation, differentiation, and migration [50]. Indeed, monoclonal antibodies, for instance, are currently an important player in targeted therapies [51]. circRNAs moderate drug resistance by sponging microRNAs both in traditional chemotherapeutic drugs, advanced targeted drugs, and immunotherapeutic drugs. For example, therapeutic targeting of ciRS-7 may become a promising strategy for colorectal cancer patients, since higher expression of ciRS-7 correlated with multiple clinicopathologic factors, such as advanced T-stage, lymph node, and distant metastasis, and ciRS-7 overexpression promotes the EGFR/RAF1/MAPK pathway by inhibiting miR-7 activity [121, 155]. Yang et al. indicated that high expression of circPTK2 positively correlated with poorer survival, showing CircPTK2 can bind to vimentin and promote EMT growth and metastasis in CRC cells, therefore ciRS-7 may become a therapeutic target for CRC metastasis [51]. The relation between circPTK2 in CRC is shown in Fig. 3.

Another highly expressed circRNA in CRC tissue is Circ_001680 which was observed to enhance the proliferation and migration capacity of CRC cells. Fluorescence reporter assays confirmed that circ_001680 alters the expression of BMI1 by targeting miR-340. More importantly, Circ_001680 was found to promote the propagation of cancer stem cells in CRC and induce resistance against Irinote by modifying the miR-340 target gene BMI1 n [53]. Safe and effective delivery of ncRNAs is a significant therapeutic paradigm for all cancers. Since unmodified oligonucleotides are not stable in circulation, modifications of oligonucleotides are essential to increasing efficacy and stability. Most current oligonucleotide therapies need an additional delivery system to achieve these desired biological effects. Several options need to be considered in selecting a delivery system, including stability, evasion of the innate immune system, avoidance of non-specific interactions with serum proteins, and non-target cells. One of the common strategies to increase the circulation time for therapeutic oligonucleotides is shielding the exterior of delivery vehicles with polyethylene glycol (PEG). This strategy may prevent the non-specific function of particles with immune cells and other non-target tissues. Although a variety of delivery systems has been developed in the laboratory, challenges remain in bringing the full potential of RNAi to clinical approaches [156].

### Table 2 The characteristics of circRNAs in CRC as a chemotherapy resistance

| CircRNA          | GENE related miRNA | Expression | Targeted molecules/ pathways | Function                                                                                           | References (DOI) | Year |
|------------------|--------------------|------------|------------------------------|---------------------------------------------------------------------------------------------------|------------------|------|
| Hsa_circ_0079662 | Up                 | TNF-α, HOXA9 | Induces the resistance mechanism of the chemotherapy drug oxaliplatin through the TNF-α pathway | [66] 2020                                                   |                  |      |
| Hsa_circ_0005963 | miR-122            | Up         | PKM2                         | Chemo-resistance: In vitro and in vivo                                                              | [69] 2020        |      |
| Circ_0007031     | miR-760            | Up         | DCP1A                        | Regulate the Growth and Chemoradiotherapy Resistance                                                  | [84] 2020        |      |
| CircDDX17        | miR-31-5p          | Down       | KANK1                        | Tumor suppressor, Strengthened chemosensitivity of CRC to 5-Fu                                      | [131] 2020       |      |
| Circ-PRKDC       | miR-375            | Up         | FOXM1, Axis and WBT/β-Catenin | Enhanced 5-FU resistance in CRC                                                                     | [85] 2020        |      |
| Circ-0001313     | mir-3383p          | Up         | Ccdec66                       | Promote resistance to radiotherapy and 5fu                                                             | [124] 2019       |      |
| Circ 32,883      | Mir501-5p          | Up         | EmL5                         | Promote resistance to folfox                                                                         | [122] 2019       |      |
| Circ0007006      | Mir300, 653-5p, 628-5p | Up     | Promote resistance to 5fu                      |                                                                                                       | [122] 2017       |      |
| Circ0000504      | Mir485-5p          | Up         | Tubgcp3, Stat3                | Promote resistance to 5fu                                                                            | [122] 2017       |      |
circRNAs however, offer significant increases in stability over current strategies.

### Conclusions and perspectives
Following advancements in high-throughput sequencing, the field of circRNAs has attracted more attention and is currently an area of intense interest in the field of cancer research. circRNAs are an ideal biomarker in cancer, and are stably expressed in exosomes, blood, and saliva, where specific circRNAs have been indicated as promising prognostic or diagnostic biomarkers already.

Abnormal expression of circRNAs has been observed in a wide range of human malignancies and their dysregulation can alter gene expression networks, leading to dramatic changes in cell fates, including cancer initiation and progression. circRNAs can be both oncogenic

| CircRNA                  | GENE related miRNA | Expression | Targeted molecules/pathways | Function                                                                 | References (DOI) |
|-------------------------|--------------------|------------|-----------------------------|--------------------------------------------------------------------------|-----------------|
| Hsa_circ_0002320        | miR-519d-3p        | Down       | Noninvasive diagnostic blood biomarker for CRC prognosis                | [140] 2020       |
| circMBOAT2              | miR-33b/miR-93/    | Up tissues serum | A novel tumor marker and regulates proliferation/migration               | [141] 2020       |
| hsa_circ_0060927        |                   | Up DNMT3B/EZH2/MYC/YAP1 | Potential diagnostic markers                                               | [142] 2020       |
| circ-CCDC66             |                   | Up Wnt/β-catenin pathway | Promoting CRC growth and metastasis                                        | [91] 2020        |
| circ_0005075            |                   | Up TROAP | Potential target for the prognosis biomarker                              | [143] 2020       |
| Hsa_circ_0004831        |                   | Up WNT and p53 signaling pathway | Prognostic biomarker                                                      | [144] 2020       |
| hsa_circ_104916         |                   | Down       | Prognosis biomarker Inhibiting CRC cell proliferation, migration, invasion, and inducing apoptosis | [145] 2019       |
| hsa_circ_0004585        |                   | Up tissues serum | Potential diagnostic biomarker for CRC                                   | [146] 2019       |
| hsa-circ-0004771        |                   | Up tissues serum | Novel potential diagnostic biomarker                                      | [147] 2019       |
| circ-PPP1R12A Has-circ-000,423 | Up tissues serum | Hippo/YAP Prognosis | Prognostic biomarker Promoting pathogenesis and metastasis                | [148] 2019       |
| circ-MTO1               |                   | Down WNT/β-catenin | Prognostic biomarker, Inhibiting cell proliferation and invasion          | [149] 2018       |
| hsa_circ_0001649        | SHARE             | Down       | Novel diagnostic biomarker Expression level is closely associated with pathological differentiation | [150] 2018       |
| Has_circ_14,717         |                   | Down P16  | Prognostic biomarker Inhibiting CRC cell proliferation, colony formation, and growth | [151] 2018       |
| hsa_circ_0026344        | miR-21/miR-31      | Down       | Prognostic biomarker Inhibiting CRC cell growth and invasion and induces apoptosis | [45] 2018        |
| Has-circ-0000711        |                   | Down       | Diagnostic Prognostic biomarker                                          | [152] 2018       |
| Cir-7 CDR1 EGFR/RAF1/MAPK pathway | Up tissues serum | Mir-7 | Prognostic biomarker                                                    | [27] 2018        |
| hsa_circ_0000567        | SETD3             | Down       | Potential diagnostic biomarker                                           | [153] 2018       |
| hsa_circ_001988         | FBXW7             | Down       | Diagnostic biomarker                                                    | [42] 2015        |
| hsa_circ_0003906        |                   | Down       | Diagnostic biomarker                                                    | [154] 2015       |
and anti-oncogenic, so could potentially be utilized in the treatment and prognosis of colorectal cancer. Although recent advances on circRNAs have highlighted some interesting insights, much work remains to be done to translate circRNAs into clinical application for clinical patient benefit. Major hurdles include the development of an efficient siRNAs delivery system, and the assessment of safety and side effects, yet, clearly circRNAs have significant potential for the treatment and diagnosis of CRC.

**Abbreviations**
cRNA: Competing endogenous RNA; circRNAs: Circular RNAs; siRNA: Small interfering RNA; ncRNA: Noncoding RNA; HNPCC: Hereditary nonpolyposis colorectal cancer; ciRNAs: Intronic circRNAs; ecircRNA: Exonic circRNAs; ELciRNA: Exon–intron-circRNAs; miRNA: MicroRNA; RBP: RNA-binding protein; PEG: Polyethylene glycol; CRC: Colorectal cancer.

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**Fig. 3** CircPTK2 is overexpressed in CRC tissues and is associated with tumor metastasis

**Declarations**

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no conflict of interest, All authors approved the final version for submission.

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