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Review

Advanced strategies of targeting circular RNAs as therapeutic approaches in colorectal cancer drug resistance

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ABSTRACT

Colorectal cancer (CRC) stands second in terms of mortality and third among the highest prevalent kinds of cancer globally. CRC prevalence is rising in moderately and poorly developed regions and is greater in economically advanced regions. Despite breakthroughs in targeted therapy, resistance to chemotherapeutics remains a significant challenge in the long-term management of CRC. Circular RNAs (circRNAs) have been involved in growing cancer therapy resistance, particularly in CRC, according to an increasing number of studies in recent years. CircRNAs are one of the novel subclasses of non-coding RNAs, previously thought of as viroid. According to studies, circRNAs have been recommended as biological markers for therapeutic targets and diagnostic and prognostic purposes. That is particularly notable given that the expression of circRNAs has been linked to the hallmarks of CRC since they are responsible for drug resistance in CRC patients; thereby, circRNAs are significant for chemotherapy failure. Moreover, knowledge concerning circRNAs remains relatively unclear despite using all these advanced techniques. Here, in this study, we will go over the most recent published work to highlight the critical roles of circRNAs in CRC development and drug resistance and highlight the main strategies to overcome drug resistance to improve clinical outcomes.

1. Introduction

The 3rd most prevalent kind of cancer in the whole world is colorectal cancer (CRC), which ranks among the most popular types of digestive cancer and is responsible for about 10 % of all diagnosed cases of cancer [1]. CRC ranks second in mortality compared with all other cancer forms and is more prevalent in areas of high economic growth [2]. In 2023, there will be a suspected 153,020 new cases of CRC

Abbreviation: BAG4, BCL2-associated athanogene 4; Bcl-2, B-cell lymphoma 2; BMI1, B cell-specific moloney murine leukemia virus integration site 1; CC, Colon cancer; CSE1L, Chromosome segregation 1 like; CXCR4, C-X-C chemokine receptor type 4; EGFR, Epidermal growth factor receptor; FMNL2, Formin-like protein 2; FOXM1, Forkhead box protein M1; FZD7, Frizzled-7; HELLS, Helicase- lymphoid specific; HMGA1, High mobility group AT-hook 1; HOXA9, Homeobox A9; HTERT, Human telomerase reverse transcriptase; KLF12, Krüppel-like factor 12; LASP1, LIM and SH3 protein 1; LAST1, Large tumor suppressor kinase 1; MMP14, Matrix metalloproteinase 14; MMP3, Matrix metalloproteinase 3; MMP9, Matrix metalloproteinase 9; MST1, Macrophage stimulating 1; MYO6, Myosin VI; NFIB, Nuclear factor 1 B-type; RAF1, Rapidly accelerated fibrosarcoma 1; TMED10, Transmembrane P24 trafficking protein 10; TNF-α, Tumor necrosis factor-alpha; TRIP6, Thyroid hormone receptor interactor 6; TYRO3, Tyrosine-protein kinase receptor 3; VEGF-A, Vascular endothelial growth factor A; VEGFC, Vascular endothelial growth factor C; YAP, Yes-associated protein 1.

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diagnosed and 52,550 deaths due to the disease. This includes 19,550 new cases and 3750 fatalities in those under 50 years old [3]. By 2030, it is assumed that the international CRC incidence rate will have increased by approximately 60 % [4]. In the US, around 60 % of CRC cases identified annually may establish hepatic metastases [5]. The exact mechanism of CRC development remains unclear, but interestingly, the main factors that are significantly associated with CRC are being determined, including genetics, epigenetics, age, inactive lifestyle, diet, family history, obesity, and inflammatory bowel disease (IBD) [6,7]. The classical therapeutic choices for CRC are endoscopy, surgery, down-staging preoperative radiotherapy, systemic therapy, target therapy, immunotherapy, and chemotherapy [8]. Unfortunately, with all these techniques, the mortality rate of CRC remains high, and similarly, every year, 1.3 million new cancer cases of CRC are reported [9]. This is mostly due to the increased resistance of CRC against treatments, which can be seen in nearly all CRC patients [10].

The management of primary malignancy is not the only condition that is complicated by the development of resistance; it also affects associated conditions, such as respiratory disorders. Respiratory metastasis or chemotherapy-induced toxicity are two common causes of respiratory disorders in colorectal cancer patients. For example, drug-resistant CRC cells can metastasize to the lungs, leading to secondary respiratory disorders [11], or chemotherapeutic agents used to treat CRC can cause pulmonary toxicity, leading to conditions such as interstitial lung disease, pneumonitis, and pulmonary fibrosis [12].

Various mechanisms, including the upregulation and down-regulation of different kinds of ncRNAs, including circRNAs, can cause drug resistance. In some cases, dysregulation of circRNAs can also help increase chemosensitivity in various types of cancer in which the expression of those circRNAs has been changed [2,13]. Consequently, circRNAs are crucial for radiotherapy and chemotherapy purposes, either by increasing chemo-resistance or chemo-sensitivity, and being used to establish therapeutic approaches. Even circRNAs can be regarded as targets for CRC diagnostic and prognostic markers [14].

In 1976, circRNAs were found for the first time under an electronic microscope. Recently, they have been regarded as a distinct subclass of single-strand ncRNAs, which are described as covalently closed structures without 3′ and 5′ ends. Their specific structure will give them resistance against digestion by exonuclease and RNase. As a result, it increases their stability and half-life compared to linear RNAs. Due to their distinctive structure, they are also suitable as new therapeutics and predictive markers [15,16].

CircRNAs are synthesized in eukaryotic cells through the back-splicing of exons from pre-mRNA, and they have a significant proportion of miRNA binding sites. CircRNA classifications, based on the origin of the sequence, are categorized into four groups: exonic, intronic, exon-intron, and tRNA intronic circRNAs [6,17].

Recently, we highlighted the critical roles of circRNAs in different kinds of cancer, such as lung cancer [18], CRC [19], breast cancer [20,21], hepatocellular carcinoma [22], ovarian cancer [23], pancreatic cancer [24], bladder cancer [25] and prostate cancer [26], and retinoblastoma [27]. Additionally, they are also involved in other non-carcinogenic disorders such as Alzheimer's, diabetes, cardiovascular disease, epilepsy, and tuberculosis (TB) [8,28,29]. CircRNAs have critical functions in CRC cell progression, such as cell proliferation, invasion, migration, metastasis, and apoptosis [30]. Furthermore, advancing numbers of studies show that circRNAs play a significant role in the progression and regulation of chemoresistance in tumors [31].

In this study, we provide a comprehensive review of the primary roles of circRNAs in CRC progression, the molecular processes by which circRNAs either promote or inhibit drug resistance in CRC, and therapeutic strategies to overcome treatment resistance to improve clinical outcomes.

2. Biogenesis of circRNAs

Synthesis of circRNAs, known as biogenesis, occurs in eukaryotic cells through exon skipping during back-splicing processes or by skipping exons from pre-RNA. Spliceosomal machinery, including group I and II ribozymes, is often involved in this biological process (Fig. 1). Compared to linear RNAs, circRNAs lack 3′ and 5′ ends, making them resistant to exonucleases and evading RNA turnover [32].

CircRNAs are classified into four subgroups based on their chemical appearance: exonic circRNAs (ecircRNSs), intronic circRNAs (ciRNAs), exon-intron circRNAs (EIciRNAs), and tRNA intronic circRNAs (tricRNAs), which were synthesized from pre-tRNA introns [33]. The bulk of ciRNAs and EIciRNAs have been located in the nucleus, while ecircRNAs are the most abundant type in the cytoplasm. In addition, during the biogenesis of ecircRNAs, direct back-splicing is more prevalent than the skipping of exons [17].

Generally, RNA-binding proteins (RBPs) mediated circularization, intron pairing-driven circularization, and lariat-driven circularization are the three models approved for the biogenesis of circRNAs. The two processes involved in these three models' mechanisms are direct back-splicing and exon skipping [34]. The RBP-mediated circularization model can be divided into three steps: RBP binding, circularization, and exonucleolytic trimming. In the first step, specific RBPs bind to complementary sequences in the pre-mRNA, bringing together the downstream and upstream exons. This interaction stabilizes the exons in a conformation that facilitates circularization.

The exons are covalently joined in the second step to form a circRNA molecule. This can occur through a spliceosomal-dependent mechanism or by the action of an unknown enzyme. Once circularization occurs, the circRNA resists exonucleases and can accumulate in the cell. In the third step, the ends of the circRNA are trimmed by exonucleases, resulting in a mature and stable circRNA. The degree of exonucleolytic trimming can vary depending on the specific circRNA and affect its stability and function [33–35].

Exon skipping has little impact on the generation of circRNAs in the second model of circRNA biosynthesis, which is driven by intron pairing. Still, base pairing across both sides of the introns can result in various circularization pathways, which create a variety of circRNAs, such as ecircRNAs and EIciRNAs. Longer introns are also seen in the bordering sequences of circRNAs because pre-mRNA-bordering introns include reversed complementary sequences, and changed complementary sequences in longer introns promote circRNA synthesis [17].

In the third hypothetical model, which shows that an exon skipping event happens after pre-mRNA splicing, allowing 'lariat-driven circularization' to take place and interaction between 3'OH of the upstream exon and 5'PO4 of the downstream exon, allowing ecircRNAs to be produced, in some cases, their formation consists of only one exon (single-exon circRNAs). In contrast, in most cases, they are multi-exon (multi-exon circRNAs). Similarly, in other instances, the circularization happens between exon and intron, and the sequences can be kept in this case, which helps to produce a mixture of exon and intron, known as EIciRNAs [36,37]. Interestingly, during all of the mechanisms that happen in the lariat-driven circularization, a piece of circRNAs is removed to form another type of circRNA known as ciRNAs [38].

Despite this, recent studies revealed that the creation of circRNAs that are made by the exons of other genes according to their chromosomal translocation and other factors in vivo is known as fusion circRNAs (F-circRNAs), and the majority of them are oncogenes [39]. Read-through circRNAs (rt-circRNAs), a different kind of circRNA that has been identified, are composed of two nearby genes on the same DNA strand. This type of circRNA makes up a tiny portion, about 2.5 percent of the total circRNA in each sample, and their generation is correlated with RNA polymerase II (RNA pol II) [40]. The splicing of pre-tRNA results in the production of tricRNAs by a splicing enzyme, which cuts the pre-tRNA. As a result, two new structures are formed, known as the tricRNA and tRNAs [33]. The synthesis of circRNAs is a heavily dynamic

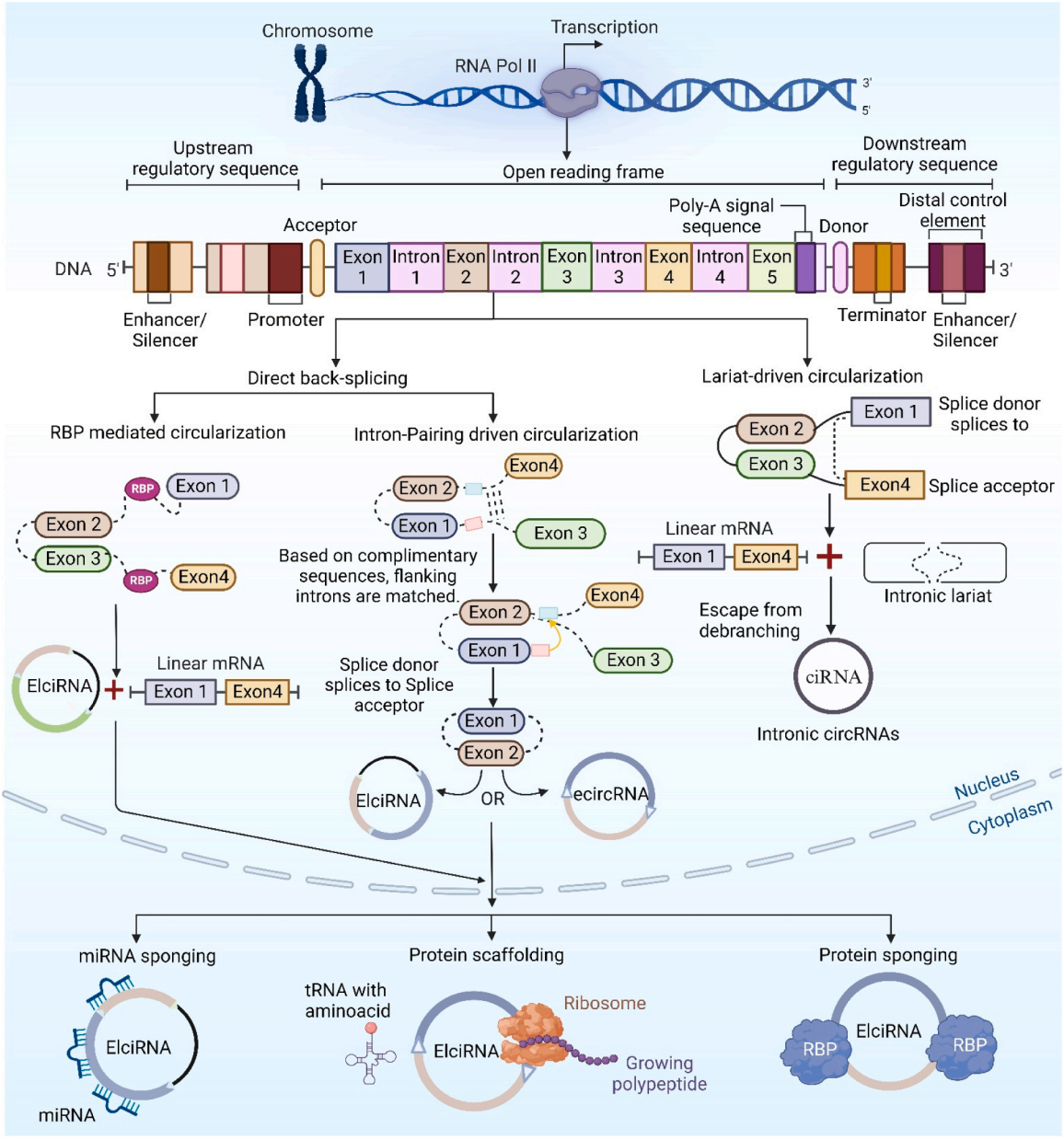

Fig. 1. This illustration shows the process of circRNA biogenesis from precursor mRNA (pre-mRNA). In the beginning, linear RNA is created due to the transcription of the pre-mRNA in the nucleus. A back-splicing event occurs in which an upstream splice acceptor site (3′) and a downstream splice donor site (5′) in the pre-mRNA sequence combine to produce a covalently closed circular RNA (circRNA). The circRNA's preserved introns are known as "lariat structures." Following lariat formation, circRNAs can be transported to the cytoplasm, where they can regulate gene expression in several ways.

mechanism influenced by many different cellular and extracellular factors.

3. Characteristics and functions of circRNAs

Non-coding RNAs (ncRNAs) are RNA molecules without encoding proteins; however, they play essential roles in gene expression regulation, RNA processing, and other cellular processes. NcRNAs are categorized based on their length, with small ncRNAs (<200 nucleotides) and long ncRNAs (>200 nucleotides) being the two main categories [41, 42]. NcRNAs have essential roles in various cellular processes, and their dysregulation has been implicated in many disorders, including cancerous diseases such as CRC, and non-carcinogenic diseases such as neurodegenerative disorders and cardiovascular disorders [43]. CircRNAs are a kind of long ncRNA derived from linear pre-mRNA by the back-splicing mechanism (non-canonical splicing) [44], and several of them are translated into proteins. They were first found in the RNA of the plant-based virus and are considered viroid, smaller than viruses [45,46]. Furthermore, they are abundant in eukaryotic cells such as plants, yeast [47], and human cells [48]. Their covalently closed structure makes them more stable and has a greater half-life than liner RNAs because of their resistance against degradation by exonucleases and RNases [49]. Additionally, it makes them suitable for usage as therapeutic targets and diagnostic biomarkers [50]. CircRNA could also encode for micropeptides [51]. And according to a study, about 10 percent of the genes can generate circRNAs [52].

CircRNAs are classified into four subgroups: ecircRNSs, ciRNAs, eIciRNAs, and tricRNAs. They are primarily found in the cytoplasm, such as ecircRNAs, while some of them, like ciRNAs and EIciRNAs, have been located in the nucleus [17]. Furthermore, approximately 80 % of all circRNAs are ecircRNAs, made when the 3′ splice donors and 5′ splice acceptors of the pre-mRNA bind backward via covalent annealing [53,

54]. CircRNA regulation is highly stable in blood, saliva, and exosomes, and this could be associated with the quick and practical processes of their synthesis and degradation in cells [55].

Although circRNAs have been hypothesized to have multiple roles, those roles remain unclear. Several studies have revealed that several circRNAs can serve as sponges for miRNAs. For example, circRNA CBL.11 inhibits cell proliferation in CRC by miR-6778–5p sponging [56, 57]. Additionally, Through RNA post-transcriptional control, other types of circRNA serve as RNA-binding proteins (RBP) connected to the progression of CRC in different stages [58]. Interestingly, several circRNAs significantly impact managing transcriptional regulation and gene control. For instance, circEIF3J and circPAIP2 are two examples of EIciRNAs that promote their parent transcription through their reaction with RNA polymerase II [48]. Furthermore, studies have shown that circRNAs could have a significant impact in controlling transcription and translation, interacting with proteins, and generating pseudogenes [59].

4. Dysregulation and functions of circRNAs in colorectal carcinoma

Many studies have confirmed that circRNAs have a critical role in inducing or suppressing CRC progression, such as cell proliferation, invasion, migration, and cell death, through their oncogenic or suppressive roles. Numerous dysregulations of circRNAs have been shown to alter the progression of CRC, and several studies have identified specific circRNAs that are differentially expressed in CRC cells compared to normal cells. For example, overexpression of circPACRGL leads to cell proliferation, migration, and invasion processes and suppresses cell death in CRC patients by miR-300 sponging [60]. Similarly, the transforming growth factor-1 (TGF-1) is regulated by circRNA, and its up-regulation induces cell proliferation and tumor development in CRC patients. This occurs via miR-506–3p and miR-142–3p sponging, which can be utilized as a valuable treatment biomarker in CRC individuals [61]. Moreover, Chen and colleagues, in their investigation demonstrated that circHUWE1 was markedly up-regulated in CRC tissues and that its expression level was connected to negative clinicopathologic characteristics. By sponging miR-486, circHUWE1 promoted malignancy in CRC and could be useful as a CRC diagnostic biomarker and a viable target for CRC therapy [62]. Furthermore, according to research by Lei Chen et al., circRUNX1 targets the miR-145–5p/IGF1 signaling pathway in CRC cells to promote tumor growth [63]. This finding suggests that circRUNX1 may be useful as a prognostic marker and therapeutic target for CRC patients.

Additionally, down-regulation of the circ-ITGA7 promotes the process of apoptosis and inhibits tumor cell proliferation and migration in CRC via sponging miR-3187–3p through regulation of ASXL1, NF1, ITGA7, and RREB1 [64]. According to a study, it has been shown that circ_001569 is highly expressed in CRC. The study used real-time PCR analysis in thirty matching specimens of CRC patients. using different cell lines such as SW480, HCT116, SW620, and LOVO. This circRNA will function to immediately sponge miR-145 and suppress its transcription, as a result affecting E2F5, BAG4, and FMNL2a and inducing the progression of CRC cells [65]. Similarly, By blocking the Wnt/β-catenin signaling cascade and focusing on microRNA-1229, circular RNA 0001666 reduces the growth, invasion, and stemness of CRC cells [66]. Likewise, Lu et al., confirmed that there is a considerable decrease in the expression of circ_0021977 in colon cancer tissues, plasma, and cell lines, and this expression functions as a tumor suppressor in CRC. The mechanism underlying this action entails the control of P21 and P53 expression via the competitive binding of circ_0021977 to miR-10b-5p [67]. According to these results, CRC proliferation, migration, and invasion are inhibited by the circ_0021977/miR-10b-5p/p21&p53 axis.

Additionally, using SW620, SW480, HCT116, HT29 CRC cell lines, NCM460, and FHC colon cell lines, and 293 T cells shows that circ-0026344 is suppressed in CRC cells in comparison with normal cells. Yuan and his team found that both miR-21 and miR-31 were sponged by this circRNA, and the expression of both miRNAs was raised in CRC tissues [68]. Similarly, Zeng et al. revealed that circHIPK3 is significantly upregulated in CRC. They showed that circHIPK3 immediately binds to miR-1207–5p, and they observed that the miR-1207–5p seed areas in circHIPK3 increased FMNL2 protein production that leads to an increase in the proliferation and invasion of CRC cells [69]. Through the RNA-sequencing technique, it was found that circ-NSD2 plays a significant role in CRC progression. circ-NSD2 is noticeably overexpressed in CRC patients and promotes cancer proliferation by sponging miR-199b-5p. Further, circ-NSD2 sponges miR-199b-5p and decreases its level, activating DDR1 and JAG1 and promoting CRC cell-matrix contact, migration, and metastasis [70]. Likewise, Ren et al. confirmed that as a ceRNA for miR-382/587/616, hsa circ 0001178 increased the ZEB1 level, a crucial trigger of the EMT, which promoted the metastatic spread of CRC [71]. Moreover, human CRC tissues and cells have higher levels of circBANP, which is connected with the cancer's stage. As shown by Ni et al., let-7d-5p targeted HMGA1 mRNA while circBANP directly bound let-7d-5p, and the circBANP/let-7d-5p may have affected HMGA1 to control Wnt/-catenin signaling [72]. Additionally, Circ 0056618 was shown to be overexpressed in CRC tumor tissues and CRC cell lines, which was correlated with a bad prognosis for CRC individuals. Zheng et al. demonstrated that circ 0056618 increased CXCR4 and VEGF-A in CRC by sponging with miR-206 and eliminating its repressive effects. This boosted cell proliferation, migration, and angiogenesis [73] (Fig. 2).

Despite that, Li et al. found that the level of circ_ITGA7, which is located in the cytoplasm, was lower in CRC samples, HCT116, and DLD1 cells than in normal FHC cells and non-cancerous cell lines. In addition, they showed that this circRNA was immediately linked to miR-766, which functions as a carcinogen in various types of cancer, including CRC [74]. They also showed that circ_ITGA7 could bind to miR-766 in a way that would likely stop SMAD4 from breaking down. The results of this study showed that the miR-766/SMAD4 axis was responsible for circ_ITGA7's enhancement of radiotherapy sensitization and suppression of CRC progression [75]. Similarly, Xiang-Nan Li et al. revealed that circDDX17 is decreased in CRC patients. Their study used high-throughput sequencing and qRT-PCR on 60 paired CRC samples. They found that circDDX17 binds with hsa-miR-21–5p, which is linked with the KEGG signaling in CRC. Further, they demonstrated that suppression of circDDX17 might enhance the progression of CRC in vitro [76].

Based on the above studies, it seems likely that circRNAs play essential roles in controlling how CRC cells behave and could serve as therapeutic targets. However, further study is needed to fully understand the functions and mechanisms of circRNAs in CRC. Furthermore, (Table 1) shows numerous circRNA dysregulation and highlights their functions with targeted miRNAs and signaling pathways.

5. The key functions of circRNAs as therapeutic resistance in colorectal carcinoma

The treatment options for CRC are endoscopy, surgery, down-staging preoperative radiotherapy, systemic therapy, target therapy, immunotherapy, and chemotherapy. Also, the variety of expression of circRNAs has a critical role in CRC pathogenicity and treatment through their function as regulators of CRC drug resistance. Due to their role as promoters or inhibitors, circRNAs were extensively studied, and researchers frequently provided new studies on therapeutic resistance.

Different classes of medications are used in CRC patients, including topoisomerase inhibitors like irinotecan [97], antimetabolite medications like 5-fluorouracil (5-FU) [98], platinum medications like cisplatin (DDP) and oxaliplatin (OXA) [99]. Therefore, monoclonal antibodies targeting EGFR are the most frequently used therapy for metastatic CRC. For instance, panitumumab and cetuximab are two monoclonal antibodies that have been shown to suppress pathways of Ras\Raf\MEK

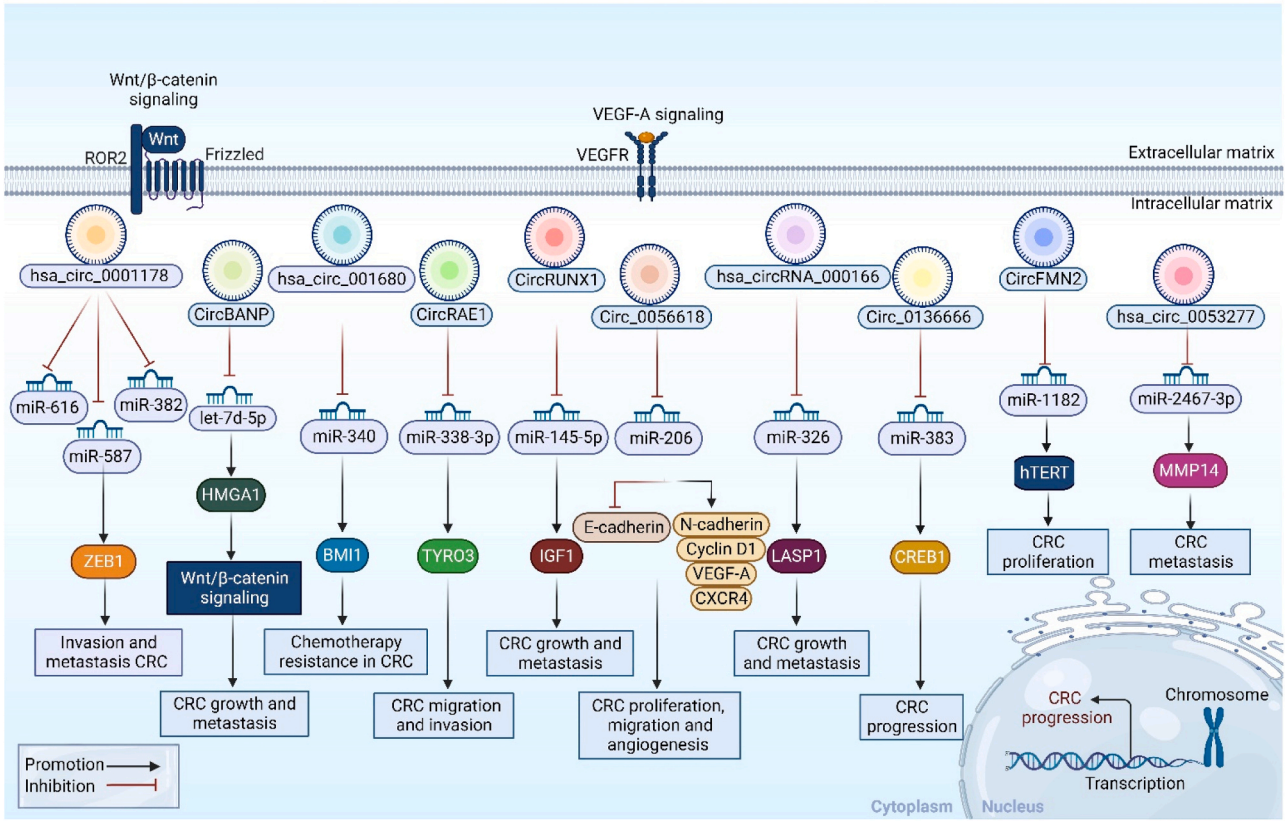

Fig. 2. A schematic illustration represents circRNA dysregulation in the progression of CRC through sponging different miRNAs and targeting several genes and pathways.

\ERK and cause a decrease in the development of CRC by targeting EGFR [100,101]. In addition, both medications could be used alone or with other chemotherapeutic courses. In comparison to chemotherapy alone, they have more advantages [102].

Recently, several circRNAs, such as circ-CD44, have raised CRC cells and enhanced oxaliplatin resistance by modulating miR-330–5 P, which, in effect, controls ABCC1 expression. In addition, ABCC1 contributes to the CRC's multidrug resistance and serves as a gene that causes various types of cancer [103]. According to research, it has been shown that circ-32993, which synthesizes from the *EML5* gene, was overexpressed in HCT-116 CRC cells and promotes resistance to 5-FU and oxaliplatin by modulating the miR-130b/PI3K/AKT pathway [104].

According to the microarray analysis, it has been shown that 1505 circRNA expression was dysregulated. Through this dysregulation, circRNAs are essential for the induction or suppression of chemoresistance and chemosensitivity in the HCT116 CRC cells. As a result of this dysregulation, it has been demonstrated that 773 circRNA examples were overexpressed; similarly, 732 of them were suppressed. The biotarget circ 32883 was highly overexpressed in oxaliplatin-resistant cells compared to chemosensitive CRC cells, leading the researchers to conclude that this specific biotarget represents a biomarker for CRC therapy resistance [105].

It has been shown that circRNAs significantly impact the CRC cell sensitivity to various treatments such as 5-FU, DDP, OXA, and FOLFOX (a combination of different types of cancer treatments). According to a recent study, circ-0001313, which is increased in radioresistant CRC 42 samples, is knocked down to promote response to therapy by inducing apoptosis, removing miR-338–3p, and ultimately enhancing the action of caspase-3. As a result, circ-0001313 signified both an efficient treatment target to eliminate radioresistance in CRC and a possible cancer indicator of radioresistance [106,107]. By using microarray hybridization analysis, it has been discovered that 71 circRNAs had various roles in 5-FU-resistant CRC cells. Of these circRNAs, 24 showed downregulation, while 47 showed upregulation. These circRNAs were found on all chromosomes, most of which were found on chromosomes 1, 8, and 9, indicating that these three chromosomes had a stronger correlation with 5-FU resistance than other chromosomes [108]. Another study focused on the most overexpressed circRNA, circ-PRKDC, which was overexpressed 116-fold in resistance to 5-FU. It was found in the survey that miR-885–3p is linked to the 5-FU resistance because it interacts with circ-PRKDC, which is a circRNA with a significant relationship to the resistance to 5-FU. As a result, the study showed that suppressing this circRNA can promote sensitivity to 5-FU by targeting the miR-375/FOXM1 axis and the Wnt/β-catenin signaling [109]. Suppressing circDDX17 has also been linked to the progression of CRC, and its overexpression makes cells more sensitive to 5-FU and slows the growth of CRC. By miR-31–5p sponging, circ_DDX17 prevented the evolution of CRC and reduced 5-FU resistance. Also, by binding with miR-31–5p, circDDX17 controlled the regulation of KANK1. Additionally, 5-FU sensitivity was increased, and tumor development was inhibited by circDDX17 overexpression in vivo [110].

As a targeted therapy, Irinotecan is a chemotherapeutic drug used to manage and treat several solid cancers, particularly CRC [97]. Using dual-fluorescence reporter assay, Jian et al. proved that circ_001680 modulates BMI-1 expression by regulating miRNA-340 [82]. More notably, they observed that by controlling the miRNA-340 and BMI-1, circ 001680 may increase the cancer stem cell (CSC) population in CRC and cause Irinotecan drug resistance. Circ_001680 has been demonstrated to be elevated in CRC cells, and its effects on regulating miR-360 can regulate BMI-1.

In addition to this, it has been revealed, according to the sphere formation tests, that circ-001680 overexpressed in HCT116 and SW480 cells generated higher numbers of stem cell spheres since being treated with irinotecan and showed a more powerful capacity for cell

Table 1
Dysregulation and function of circRNAs in CRC cells with their expressions and targeting signals.

CircRNAs	Location of circRNAs	Expression	Cell line studies	Animal studies	Clinical studies	Clinical characteristics	Targets/ signaling pathways	Roles in CRC hallmarks	Ref.
Circ-0001178	-	Up	LoVo and SW620	Nude mice	CRC tissue= 102 case	Advanced TNM stage, metastatic clinical features, adverse prognosis	miR-382/ 587/616, ZEB1	↑ Circ-0001178, ↓ miR-382/587/616, ↑ZEB1: ↑ Metastasis and invasion	[71]
CircPPP1R12A	Cytoplasm	Up	HT-29, SW48, HCT-116, SW620, SW480, LoVo, DLD-1, NCM460Caco2, HCT-15	Nude mice	CC tissue=20 pairs	Shorter overall survival	LAST1, YAP, MST1, TAZ, Hippo-YAP signaling	↑ CircPPP1R12A, ↑ Hippo-YAP signaling: ↑ Growth and metastasis	[77]
Circ-BANP	Cytoplasm	Up	HCT116, HT29	-	CRC tissue=35 pairs	Age, gender, location, differentiation, tumor invasion , LNM, TNM stage, serum CEA	-	↑ Circ-BANP: ↑ Proliferation	[78]
	Primarily in cytoplasm	Up	SW620, DLD1, SW480, HT29, HCT116, FHC	Nude mice	CRC tissue=60 case	TNM stages	let-7d-5p, HMGA1/ Wnt/ β-catenin signaling	↑ Circ-BANP, ↓ let-7d-5p, ↑ HMGA1, ↑ Wnt/ β-catenin signaling: ↑ Growth and metastasis	[72]
CDR1as/CiRS-7	Cytoplasm	Up	HCT-116, DLD-1, NCM460, CCD841	-	CRC tissue=40 pairs	Tumor size, T stage, LNM, poor OS	miR-7, EGFR, IGF-1R	↑CDR1as, ↓miR-7, ↑EGFR and IGF-1R: ↑ Cancer progression	[79]
			HCT116, HT29	Nude mice	CRC tissue= 448 case	Poor patient survival	miR-7, EGFR, RAF1	↑ CiRS-7, ↓ miR-7, ↑EGFR and RAF1: ↑ CRC growth	[80]
Hsa_circ_0053277	Nucleus	Up	HCT116, SW480, SW620, HT29, RKO, LOVO, HCoEpiC	-	CRC tissue=3 pairs	-	miR-2467–3p, MMP14	↑Hsa_circ_0053277, ↓ miR-2467–3p, ↑MMP14: ↑ CRC development	[81]
Hsa_circ_001680	Cytoplasm	Up	FHC, HCT8, HCT116, SW480, LOVO, HCT15, CACO2, DLD1, SW620, HT29, RKO	BALB/c athymic nude mice	CRC tissue=42 pairs	-	miR-340, BMI1	↑Hsa_circ_001680, ↓miR-340, ↑BMI1: ↑ Chemotherapy resistance	[82]
CircHUWE1	Cytoplasm	Up	HCT116, SW480	-	CRC tissue=58 pairs	lymphovascular invasion, LNM, distant metastasis, TNM stage	miR-486	↑CircHUWE1, ↓miR-486: ↑ Proliferation, migration, and invasion	[62]
CircVAPA	Cytoplasm	Up	HEK-293 T, HCT116, SW480, HT29, SW620, RKO, LoVo	-	CRC tissue=60 pairs	TNM stage, distant metastasis, LNM, depth of invasion, differentiation, lymphovascular invasion, tumor size, tumor site, age, gender	miR-101	↑CircVAPA, ↓miR-101: ↑ CRC growth	[83]
Has-circ-000984	Cytoplasm	Up	SW480, SW620, HT29, CCD-18Co, InEpC	Nude mice	CRC tissue=76pairs	Advanced CRC	miR-106b	↑Has-circ-000984, ↓miR-106b: ↑CRC growth and metastasis	[84]
CircAPLP2	-	Up	LoVo, HCT-116, SW620, SW480, FHC	BALB/c nude mice	CRC tissue=42pairs	-	miR-101–3p, Notch1, Notch signaling	↑CircAPLP2, ↓miR-101–3p, ↑Notch signaling: ↑ CRC proliferation and metastasis	[85]
			SW480, HCT116, SW620, LOVO, HT29, HIEC6	Nude mice	CRC tissue=3pairs	-	HELLS, miR-335–5p	↑CircAPLP2, ↓miR-335–5p, ↑HELLS: ↑ CRC progression	[86]
CircRAE1	Cytoplasm	Up	HCT116, NM460, SW620, SW480, HT29, HEK293T	-	CRC tissue= 80 pairs	Advanced tumor stage, LNM, size of the tumor	miR-338–3p, TYRO3	↑CircRAE1, ↓miR-338–3p, ↑TYRO3: ↑ Migration and invasion	[87]
Hsa-circ-0026416	Primarily cytoplasm	Up	HCO, HCT-116, HEK297T, HCT-8, DLD-1, SW480	BALB/c athymic nude mice	-CRC tissue= 169 pairs - Preoperative plasma=212 case - Postoperative	Gender, tumor differentiations, age, tumor diameter, tumor location, pN stage, pT stage, lymphovascular invasion, distant	miR-346, NFIB	↑Hsa-circ-0026416, ↓miR-346, ↑NFIB: ↑ Proliferation and migration	[88]

(*continued on next page*)

Table 1 (*continued*)

CircRNAs	Location of circRNAs	Expression	Cell line studies	Animal studies	Clinical studies	Clinical characteristics	Targets/ signaling pathways	Roles in CRC hallmarks	Ref.
					plasma=64 case	metastasis, pTNM, perineural invasion			
Circ-0060745	Primarily cytoplasm	Up	NCM460, LOVO, PKO, HT29, SW480	-	CRC tissue=28 pairs	Shorter survival time, advanced clinical stage, nodal classification, metastasis classification, liver metastasis	miR-4736, CSE1L	↑Circ-0060745, ↓miR-4736, ↑CSE1L: ↑Proliferation and metastasis	[89]
CircRUNX1	Cytoplasm	Up	SW480, LoVo, SW620, HT29, HCT116, RKO	BALB/c nude mice	CRC tissue=52 pairs	LNM, distant metastasis, TNM tumor stage	miR-145–5p/ IGF1 Signaling	↑CircRUNX1, ↓miR-145–5p, ↑IGF1 signaling: ↑Tumor growth	[63]
Circ-0056618	-	Up	NCM460, HCT116, LoVo, SW620, SW480, HT29	-	CRC tissue=60 pairs	Age, gender, tumor site, tumor size, LNM, TNM stage, distance metastasis	miR-206, CXCR4, VEGF-A, cyclin D1, E-cadherin, N-cadherin	↑Circ-0056618, ↓miR-206, ↑CXCR4 and VEGF-A: ↑Proliferation, migration and angiogenesis	[73]
Circ-000166	-	Up	SW1116, HCT116, DLD-1, SW620, SW480, HCoEpiC	-	CRC tissue=40 pairs	-	miR-326, LASP1	↑Circ-000166, ↓miR-326, ↑LASP1: ↑ tumor growth	[90]
Circ-0001666	-	Down	HT-29, SW480, HCT-116, SW-620, HIEC	-	-	-	miR-1229, Wnt/ β-catenin signaling	↓Circ-0001666, ↑miR-1229, ↓Wnt/ β-catenin signaling: ↓ Proliferation, invasion, and stemness	[66]
Circ-ZNF609	Mainly in cytoplasm.	Up	HCT116	-	CRC tissue=24 case	TNM staging	miR-150, Gli1	↑Circ-ZNF609, ↓miR-150, ↓Gli1: ↑Migration	[91]
Hsa-circ-0136666	-	Up	LoVo, DLD1, SW480, SW620, HCT116, HCT8, HT29, FHC	Nude mice	CRC tissue=52 cases	Poor overall survival	miR-136/ SH2B1	↑Hsa-circ-0136666, ↓miR-136, ↑SH2B1: ↑ Proliferation and invasion	[92]
			NCM460, SW480, LOVO, 293 T	Mice	CRC tissue=37 cases	Tumor size, distant metastasis, TNM stages, lymphatic metastasis	miR-383, CREB1	↑Hsa-circ-0136666, ↓miR-383, ↑CREB1: ↑Progression	[93]
CircRNA-100876	-	Up	LoVo, HCT-8, SW480, SW620, HT-29, Caco-2, FHC	-	CRC tissue=64 pairs	Gender, age, primary tumor site, differentiation, vascular invasion, tumor size, T stage, lymphatic metastasis, distant metastasis	miR-516b	↑CircRNA-100876, ↓miR-516b: ↑ Proliferation and metastasis	[94]
CircFMN2	Cytoplasm	Up	HCT116, HCoEpiC, SW480, DLD1, HT-29, RKO, 293 T	BALB/C nude mice	CRC blood=62 cases	Tumor size, advanced tumor stage, gender, TNM stage, age, distant metastasis, LNM, histological grade	miR-1182, hTERT	↑CircFMN2, ↓miR-1182, ↑hTERT: ↑ Proliferation	[95]
Hsa-circ-001569	-	Up	SW480, HCT116	-	CRC tissue=30 pairs	Differentiation, TNM classification	miR-145, E2F5, BAG4, FMNL2	↑Hsa-circ-001569, ↓miR-145, ↑E2F5, BAG4 and FMNL2: ↑ Proliferation and invasion	[65]
CircRNA CBL.11	-	Down	NCM460, HT29, HCT116, SW620, HEK293T	-	-	-	miR-6778–5p, YWHAE	↓CircRNA CBL.11, ↑miR-6778–5p: ↓ Proliferation	[57]
CircCSNK1G1	Mainly in cytoplasm	Up	HCT116, SW620, NCM460	Nude mice	CRC tissue=55 pairs	-	miR-455–3p, MYO6	↑CircCSNK1G1, ↓miR-455–3p, ↑MYO6: ↑ tumor development	[96]
Circ-0021977	Cytoplasm	Down	SW480, HCT8, HCT116, DLD1, HCoEpic	BALB/c nude mice	CRC tissue=63 pairs	Age, gender, tumor size, histological grade, LNM, TNM stage	miR-10b-5p, P21, P53	↓Circ-0021977, ↑miR-10b-5p, ↓P21 and P53: ↓ Proliferation, invasion, and metastasis	[67]

MST1 macrophage stimulating 1, *EGFR* epidermal growth factor receptor, *IGF-1R* insulin-like growth factor 1 receptor, *RAF1* rapidly accelerated fibrosarcoma 1, *MMP14* matrix metalloprotease-14, *BMI1* B cell-specific moloney murine leukemia virus integration site 1, *HELLS* helicase- lymphoid specific, *TYRO3* tyrosine-protein kinase receptor 3, *NFIB* nuclear factor 1 B-type, VEGF-A vascular endothelial growth factor A, LASP1 LIM and SH3 protein 1, *Gli1* glioma-associated oncogene family

zinc finger 1, *CREB1* cAMP responsive element binding protein 1, *hTERT* human telomerase reverse transcriptase, *BAG4* Bcl2-associated athanogene 4, *FMNL2* formin-like protein 2, *MYO6* myosin VI, *CRC* colorectal cancer, *CC* colon cancer.

proliferation than control cells [82,108]. Additionally, overexpression of Hsa_circ_0079662 has been demonstrated in the development of CRC; this elevation in expression also promotes the resistance of CRC cells to OXA by their reaction with hsa-miR-324–5p as a miRNA sponge [111] (Fig. 3). According to the study that has been done on 60 CRC patients, with SW480 and HCT116 cells, the study showed that expression of circ_000338 will cause resistance to 5-FU in CRC through the regulation of miR-217 and miR-485–3p [112].

According to research that has been done by quantitative real-time PCR, circHIPK3, for which its involvement in the initiation and growth of various cancers, enhances OXA resistance in HEK293T and HT29, and HCT116 CRC cells via miR-637 sponging. This is based on suppressing apoptosis of associated autophagy via signaling the STAT3/Bcl-2/beclin1 pathway [113]. Recent research has demonstrated that CRC cells can generate resistance to cisplatin by the upregulation of circ_0071589. Interestingly, by downregulating circ_0071589, cisplatin-resistance (CDDP-resistance) and even induce apoptosis of the resistant cells by miR-526b-3p/KLF12 axis regulation. It can be inhibited. Furthermore, by suppression of Cyclin D1 and Bcl-2 and overexpression of cleavage caspase-3 through circ_0071589 suppression, scientists can make cisplatin-resistant CRC cells proliferate less and decrease the progression of CRC [114]. Similarly, according to recent research that has been done in 100 CRC and normal samples with different cell lines such as LoVo, HT-29, HCT116, SW480, and SW620. It has been demonstrated that upregulation of circ_101277 promotes the CRC cells' cisplatin resistance via blocking miR-370, thereby significantly controlling the expression of IL-6. Additionally, the knockdown of circ_101277 stimulates CRC cisplatin sensitivity [115].

Markedly, by using HCT116 and HT-29 cell lines, Li et al. found that CRC cells resistant to OXA have higher levels of circ_CCDC66 expression. Interestingly, circ_CCDC66 knockdown inhibited cellular proliferation, enhanced the apoptosis of induced oxaliplatin, and prevented the resistance of OXA in CRC cells by blocking phosphorylation through PI3KK inhibitors or by non-phosphorate mutants of DHX9 [116]. Similarly, Pan and his group showed that circ_ATG4B was upregulated in the CRC cells that have resistance to OXA through increasing autophagy. By removing organelles degraded by chemotherapy, autophagy can serve as a barrier in tumor cells, preventing their apoptosis and increasing resistance [117]. Furthermore, recent research using LOVO and HCT116 cells has demonstrated that circ_CSPP1 and FZD7 are highly upregulated in CRC cells, and miR-944 is suppressed, which leads to doxorubicin (DOX) resistance (Table 2). By knocking down circ_CSPP1, doxorubicin

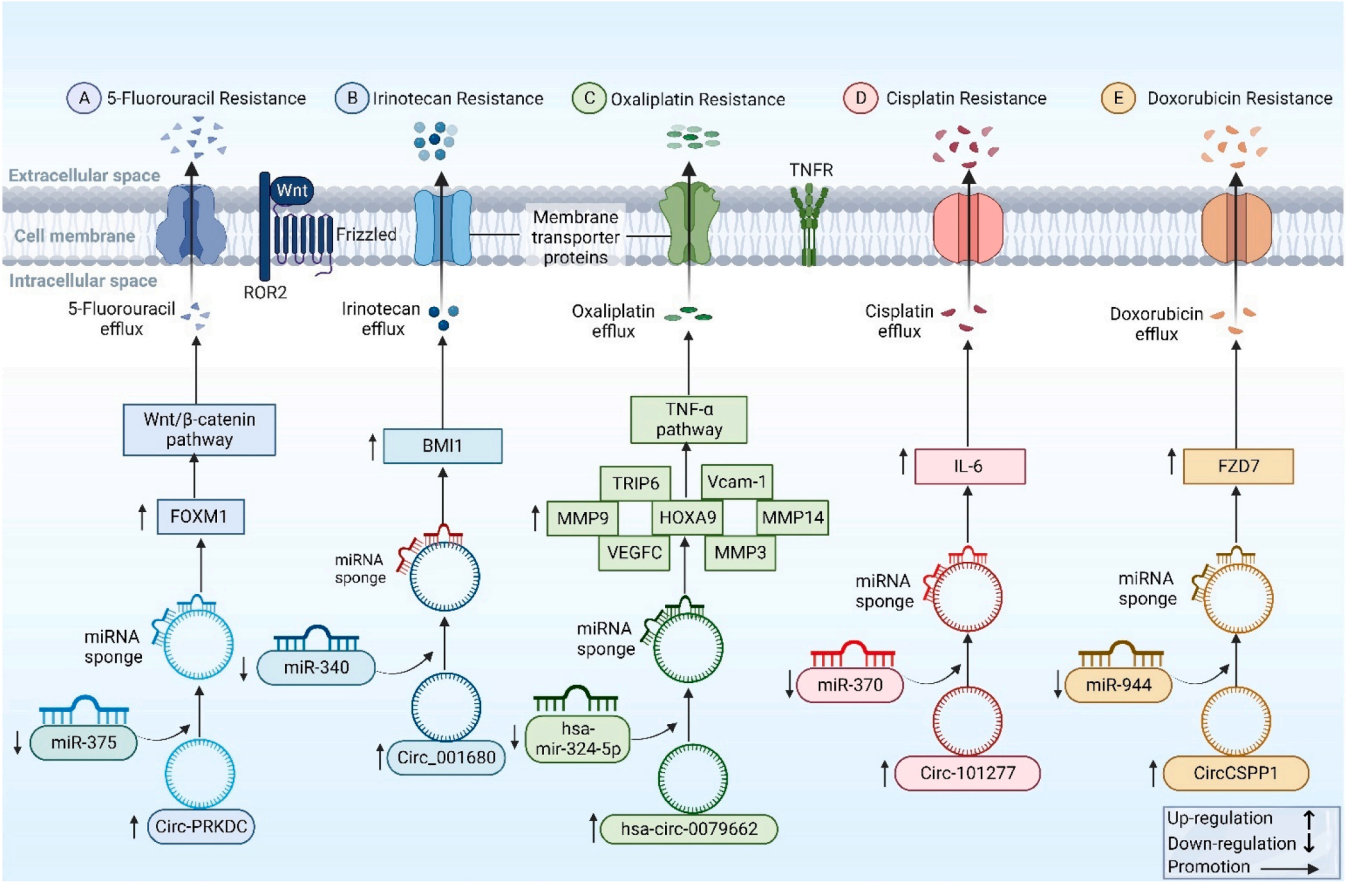

Fig. 3. A schematic illustrates the role of circRNAs in CRC drug resistance. **(A)** Circ-PRKDC in CRC enhanced 5-FU resistance by activating the Wnt/β-catenin signaling and increasing forkhead box protein M1 (FOXM1) expression by sponging miR-375. **(B)** Circ_001680 induces resistance to irinotecan therapeutics in CRC through B cell-specific Moloney murine leukemia virus integration site 1 (BMI1) upregulation by regulating miR-340. **(C)** As a ceRNA that binds to hsa-mir-324–5p, hsa circ 0079662 can increase the expression of Homeobox A9 (HOXA9), vascular cell adhesion molecule 1 (Vcam-1), thyroid receptor-interacting protein 6 (TRIP6), vascular endothelial growth factor C (VEGFC), matrix metalloproteinase-9 (MMP9), matrix metalloproteinase-3 (MMP3), and matrix metallopeptidase 14 (MMP14) and generate oxaliplatin resistance via activating the TNF-α pathway. **(D)** CircRNA 101277 acts by trapping miR-370, upregulating its target gene Interleukin 6 (IL-6), and enhancing cisplatin resistance. **(E)** CircCSPP1 mediates doxorubicin-resistant progression in CRC cells by directly downregulating miR-944 expression and increasing FZD7 levels.

Table 2
Summary of circRNA-related drug resistance in CRC.

CircRNAs	Expression	Types of drugs	Targets/ signaling pathways	Clinical samples	Cell line	Animal model	Functional role in CRC	Ref.
Circ-PRKDC	Up-regulation	5-Fluorouracil	miR-375, FOXM1 and Wnt/β-catenin	30 pairs of tumor and ANTs	FHC, SW480, SW620	Nude mice	↑Circ-PRKDC, ↓miR-375, ↑FOXM1, ↑Wnt/β-catenin: ↑ 5-Fluorouracil resistance	[109]
CircDDX17	Down-regulation	5-Fluorouracil	miR-31–5p, KANK1	30 pairs of tumor and ANTs	NCM460, HCT116, SW480	BALB/c nude mice	↓CircDDX17, ↑miR-31–5p, ↓KANK1: ↓ Chemosensitivity	[110]
Circ-001680	Up-regulation	Irinotecan	miR-340, BMI1	42 pairs of tumors and ANTs	Caco2, SW620, DLD1, SW837, Lovo, HT29, RKO, HCT8, SW480, HCT116, FHC	BALB/c athymic nude mice	↑Circ_001680, ↓ miR-340, ↑BMI1: ↑ Irinotecan resistance	[82]
Hsa-circ-0079662	Up-regulation	Oxaliplatin	HOXA9, TRIP6, Vcam-1, VEGFC, MMP3, MMP9, MMP14, IL-1, IL-6, TNF-α pathway	-	HT29- HCT116-LOHP, LOHP, HCT8-LOHP	Nude mice	↑Hsa-circ-0079662, ↓hsa-mir-324–5p, ↑ (HOXA9, TRIP6, Vcam-1, VEGFC, MMP3, MMP9, MMP14, IL-1, IL-6 TNF-α pathway): ↑ Oxaliplatin resistance	[111]
CircHIPK3	Up-regulation	Oxaliplatin	miR-637, Bcl-2, beclin1, STAT3 signaling	49 CRC patients	HT29, HCT116, HEK293T	BALB/c athymic nude mice	↑CircHIPK3, ↓miR-637, ↑Bcl-2, ↑beclin1, ↑STAT3 signaling: ↑ Oxaliplatin resistance	[113]
Circ-0071589	Down-regulation	Cisplatin	miR-526b-3p, KLF12	-37 patients with CDDP-resistant and 19 patients with CDDP-sensitive	HCT116, LOVO, FHC	BALB/c nude mice	↓Circ-0071589, ↑miR-526b-3p, ↓KLF12: ↓ Cisplatin resistance	[114]
Circ-0005963 (ciRS-122)	Up-regulation	Oxaliplatin	miR-122, PKM2	6 oxaliplatin-sensitive patients' serum and 13 oxaliplatin-resistant patients	SW480, HCT116, HEK293T	BALB/c-nude mice	↑Circ-0005963, ↓miR-122, ↑PKM2: ↑ Oxaliplatin resistance	[119]
Circ-101277	Up-regulation	Cisplatin	miR-370, IL-6	100 pairs of tumors and ANTs	CCD 841 CoN, LoVo, HT-29, HCT116, SW480, SW620	-	↑Circ-101277, ↓miR-370, ↑IL-6: ↑ Cisplatin resistance	[115]
CircCCDC66	Up-regulation	Oxaliplatin	PI3KK, DHX9	-	HCT116, HT-29	-	↑CircCCDC66, ↑PI3KK, ↑DHX9: ↑ Oxaliplatin resistance	[116]
CircATG4B	Up-regulation	Oxaliplatin	TMED10, autophagy	-	HCR116, SW480, HT29, DLD1	BALB/c nude mice	↑CircATG4B, ↑TMED10, ↑autophagy: ↑ Oxaliplatin resistance	[117]
CircCSPP1	Up-regulation	Doxorubicin	miR-944, FZD7	36 patients with CRC doxorubicin sensitive or resistant	LoVo, HCT116	Nude mice	↑CircCSPP1, ↓miR-944, ↑FZD7: ↑ Doxorubicin resistance	[118]

FOXM1 forkhead box protein M1, *KANK1* KN motif and ankyrin repeat domain-containing protein 1, *HOXA9* homeobox A9, *MMP3* matrix metalloproteinase 3, *MMP9* matrix metalloproteinase 9, *MMP14* matrix metalloproteinase 14, *IL-1* interleukin 1, *IL-6* interleukin 6, *TNF-α* tumor necrosis factor-alpha, *Bcl-2* B-cell lymphoma 2, *KLF12* krüppel-like factor 12, *PKM2* pyruvate kinase M2, *PI3K* phosphoinositide 3-kinase, *DHX9* DExH-box helicase 9, *TMED10* transmembrane P24 trafficking protein 10, *FZD7* frizzled-7.

sensitivity increased and suppressed the CRC progression [118].

According to these findings, it is possible to assume that circRNA plays a significant role in the progression of CRC and its resistance to chemotherapy, offering novel pharmacological targets and biomarkers for the clinical management of CRC.

6. Strategies to overcome drug resistance by targeting circRNAs

The study of circRNA has made significant progress in recent years. Growing evidence suggests that circRNAs can be targeted for therapeutic reasons in vivo and in vitro through various techniques, including ASOs or RNA interference (RNAi), CRISPR/Cas9-mediated editing, exosome-mediated delivery, RNA-binding protein inhibition, and circRNA modification. A promising strategy for enhancing treatment results involves focusing on circRNAs in colorectal cancer (CRC) patients to overcome medication resistance. Here are some potential approaches that researchers are considering, even though this field of study is ongoing.

6.1. RNA interference-mediated circRNA knockdown

Utilizing the natural RNAi mechanism, whereby double-stranded RNA (dsRNA) molecules trigger the production of post-transcriptional silencing, a technique based on siRNAs works to silence genes [120]. In RNAi, short hairpin RNA (shRNA) or short interfering RNA (siRNA) are widely utilized to knock out circRNAs. RNAi typically employs short hairpin RNA or short interfering RNA (siRNA) to knockdown circRNAs [121]. ShRNAs are converted into siRNAs after being processed and are distinguished by their loop and base-paired stems [122]. Typically, circRNAs are knocked down by targeting their unique back-splice junction without affecting the associated linear mRNA. Further, through complementary pairing, antisense oligonucleotides (AON) can also target circRNAs [123]. Despite their effectiveness at blocking protein interaction sites on circRNAs, their length prevents them from being used to specifically target the back-splice junction and knockdown of circRNAs. In addition, the most practical approach to knocking down circRNAs in vivo currently is the use of siRNA and shRNA delivered in lipid-based polymers.

Interestingly, circRNA cleavage can be triggered by siRNA/shRNA directed at the back-splice junction. For instance, a group of circRNAs, including CDR1as/ciRS-7, were precisely silenced by targeting regions primarily used for back-splicing, with no detectable impact on producing their associated linear RNAs [124] (Fig. 4).

Exosomes from chemoresistant CRC cells have been reported to be enriched in ciRS-122 circRNA, which acts as a sponge for miR-122 and increases PKM2 [125]. PKM2 stimulates glycolysis and ATP synthesis. It has been hypothesized that PKM2 overexpression generates incredible energy for transporters, allowing CRC cells to expel drugs from their

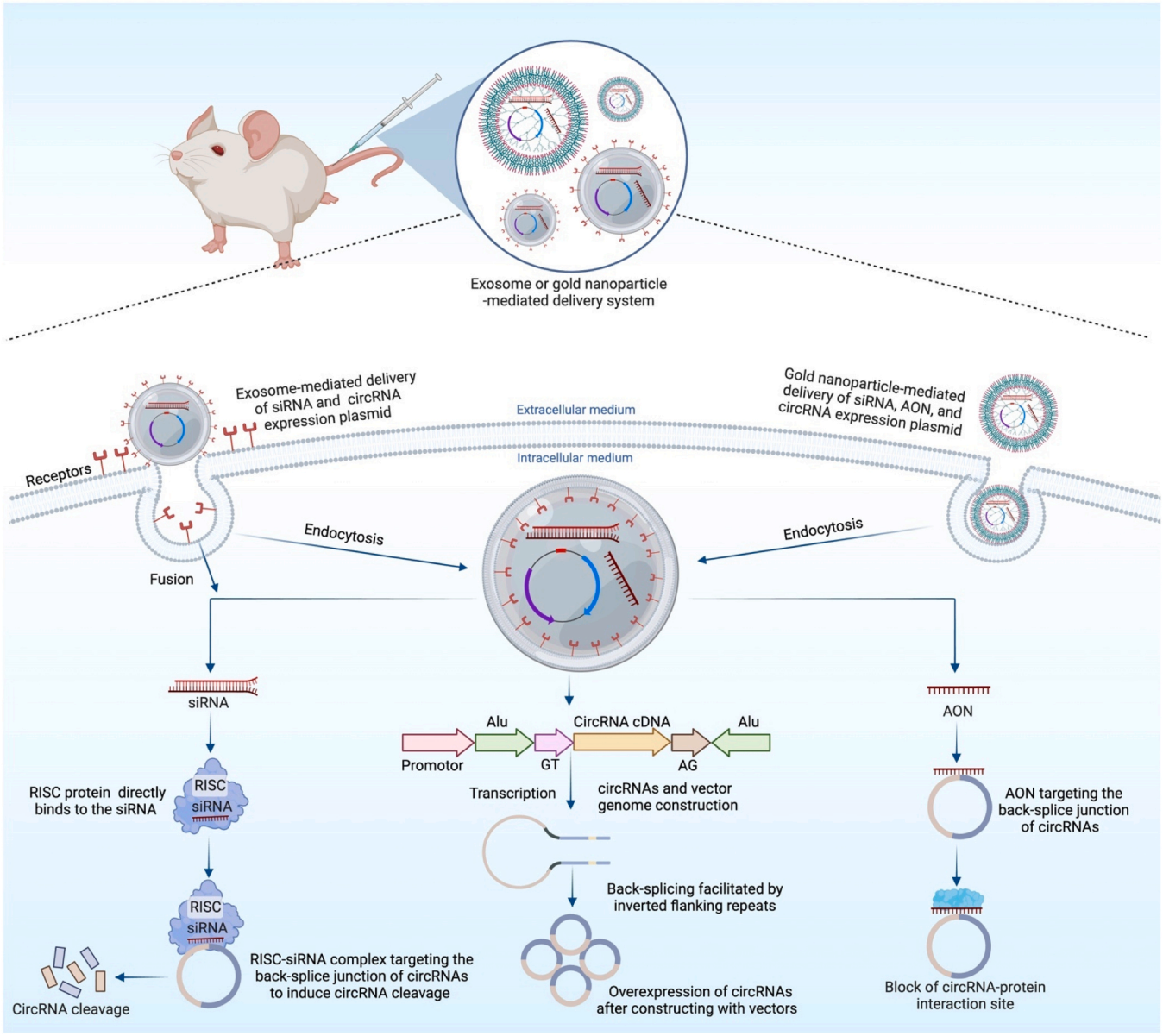

Fig. 4. Illustration of common ways to target circRNAs in vivo as a therapeutic way to knockdown or overexpress circRNAs, such as exosome-induced delivery small interfering RNA (siRNA) and circRNA expression plasmid, gold nanoparticle-induced delivery of siRNA, circRNA expression plasmid, and antisense oligonucleotides (AON).

mechanisms. It was demonstrated that chemoresistant CRC cells transfer their drug resistance by delivering ciRS-122 via exosomes to non-chemoresistant cells. In this study, siRNA targeting ciRS-122 was given through this approach, causing an increase in miR-122 and a decrease in PKM2, which in turn increased the susceptibility of CRC cells to oxaliplatin in a mouse model [125].

Nevertheless, RNAi molecules have some drawbacks that need to be addressed. These include their quick destruction by nucleases [126], inefficient cellular delivery [127], lack of cell selectivity [128], immunogenicity [129], and off-target consequences [130].

Thus, RNAi-based circRNA knockdown needs to undergo considerable research and optimization before it can be applied in the clinic to help cancer patients overcome medication resistance.

6.2. *CircRNA expression vectors*

The use of circRNA expression vectors is a unique approach that takes advantage of the characteristics of circular RNAs to reduce drug resistance [131]. Overexpressing specific circRNAs by circRNA expression vectors can modify cancer cell pathways associated with drug resistance [121].

After an expression cassette for circRNA was built, This cassette includes the target circRNA sequence and promoters, enhancers, and terminators for gene regulation [132]. Further, the circRNA is expressed only in the desired cells due to the regulatory components. For circRNA overexpression in vivo, lentiviral and adenoviral vectors are usually used [133]. The circRNA expression cassette is released from the lentiviral or adenoviral vectors once they have entered the target cells. Stable and prolonged production of the circRNA can be achieved with lentiviral vectors because the genomic material may integrate into the DNA of the host cell [132]. Whereas most viral vectors integrate, adenoviral vectors instead offer temporary, highly effective expression [134].

It is crucial to validate the expression of the circRNA from the vector and ensure that it takes on the circular form before moving on to functional tests. Circularization can be verified using qRT-PCR, northern blotting, or RNase assays [135,136]. Then, drug-resistant cancer cells

are transfected with the verified circRNA expression vector. Numerous techniques, including lipofection, electroporation, and viral transduction, can induce transfection [137]. The drug sensitivity of the cancer cells should be assessed following a successful transfection. This can be accomplished by administering the desired medications to the transfected cells and observing how they react, such as by cell viability or apoptosis assays.

6.3. Synthetic circRNAs

Direct synthesis and processing of circRNAs are other methods for overexpressing circRNAs, in addition to using plasmids [138]. Circularization of RNA can be achieved via various techniques [139]. Splint ligation can be used to cycle single-stranded linear RNA that has been chemically or in vitro transcribed [140]. This process generates circRNA molecules that are highly pure and can be given to the tumor site [141]. Further, This technique has produced a successful miRNA sponge in vitro [142]. Insufficient circRNA production and adverse immune system activation prevent synthetic circRNAs from being used in vivo to their full potential [143].

Synthetic circRNAs can be delivered into cancer cells via various techniques, such as viral vectors or lipid-based nanoparticles, once they have been created [144,145]. Synthetic circRNAs function as potent gene-expression controllers inside cells [146], efficiently suppressing the activity of medication resistance-related genes or enhancing the expression of therapeutic targets.

6.4. Nanoparticle delivery of circRNA-based therapeutics

The delivery of circRNA-based therapeutics via nanoparticles is a cutting-edge method that could revolutionize cancer treatment [147]. Many of the drawbacks of conventional treatments can be avoided if circRNA molecules are carried to the appropriate cells or tissues via nanoparticles [148]. These nanoparticles have characteristics that guarantee stability, biocompatibility, and the capacity to avoid clearance systems, enabling them to travel through the body without incident and reach their designated location [149].

The most advanced carriers of nanoparticles, lipid-based nanoparticles (LNPs), enclose siRNA or circRNA and can target particular cells using either endogenous or exogenous ligands. When LNPs are ingested, the endosomal membrane becomes unstable, allowing nuclear cargo like circular RNAs and siRNAs to escape into the cytosol [150] (Fig. 4). Many of the issues that are affecting RNAi molecules can be addressed by transporting them in nanoparticles, making them more stable, and facilitating their uptake by cells [151].

CircRNA molecules are enclosed within the nanoparticles and maintain their integrity throughout transport [145]. The specificity and selectivity of the nanoparticles are increased due to surface modifications with targeting ligands that enable them to actively seek out and attach to receptors or biomarkers on the surface of tumor cells [152]. Once the circRNA-based therapies are released within the CRC target cells can exert their effects using a variety of ways [14]. They can function as potent regulators, affecting gene expression, altering signaling pathways, or absorbing microRNAs, which can potentially have therapeutic effects [153]. Furthermore, drug-resistant cells can be made more susceptible to therapy when they are given nanoparticles carrying circRNA therapies, which can enhance the effectiveness of treatment [154].

Furthermore, nanoparticles' biodegradability guarantees they will eventually leave the body, reducing long-term hazards [155]. Thus, the field of nanoparticle-based circRNA therapeutics is still in its infancy; it has the potential to provide highly effective, precise, and individualized treatments.

6.5. Exosome delivery of circRNA-based therapy

A novel approach called exosome delivery of circRNA-based therapies has excellent potential for the effective and targeted treatment of many disorders [156]. CircRNAs can be delivered naturally using exosomes, which are tiny extracellular vesicles produced by cells [157]. These vesicles keep circRNAs from degrading and make it easier for them to reach particular target cells [158]. Exosomes can be genetically modified or loaded with synthetic circRNAs to transport therapeutic cargo-specific to the target disease [159] (Fig. 4).

When released into the bloodstream, exosomes can cross several biological barriers, including the blood-brain barrier (BBB), and are intended to deliver circRNA-based therapeutics [160]. When exosomes reach the target cells, they take them in and immediately transport the circRNAs to the cytosol [161]. The circRNAs can interact with RBPs or act as sponges for miRNAs to control gene expression and signaling pathways linked to drug resistance or other pathological events [162].

Furthermore, functional recovery from stroke was significantly improved in nonhuman primates following administration of modified rabies virus glycoprotein-circSCMH1-extracellular vesicles [163]. Exosomes are a type of non-viral, non-immunogenic particle delivery that can prevent RNAi molecules from being degraded and increase their uptake by cells [164]. Additionally, exosomes can precisely target cancerous locations due to their natural homing abilities [165]. Although exosomes may be more biocompatible than manufactured nanoparticles, their production presents difficulties [166].

6.6. CRISPR/Cas-mediated circRNA knockdown

Over the past decade, the discovery of clustered regulatory interspaced short palindromic repeats (CRISPR) has revolutionized biomedical research and introduced novel analytical frameworks for studying all areas of the life sciences [167]. The CRISPR/Cas system allows researchers to target and silence circRNAs associated with drug resistance, suggesting that drug-resistant cancer cells may be reversible [168].

CRISPR-derived transcripts work with Cas proteins to target complementary nucleic acids for cleavage. Guide RNAs (gRNAs) can be created to instruct the Cas enzyme to cleave and degrade a target circRNA by targeting its back-splice junction [169,170]. In this way, drug resistance-related circRNA might be depleted, which weakens the resistance mechanisms.

For example, it attempted to utilize the CRISPR/Cas13d technique for depleting circular RNAs to fight drug resistance and create a more effective knockdown means to investigate the role of circRNAs (Fig. 5). To efficiently and specifically suppress various linear transcripts, the CRISPR/Cas13d system was created as an RNA-guided, RNA-targeting CRISPR system [171]. The most efficient Cas13d enzyme, CasRx, was used to target circRNAs in combination with an unprocessed pre-gRNA or a mature gRNA [171]. The transcribed pre-gRNA is converted into mature gRNAs that are 52 nucleotides long and have variable 3′ spacers that range in size from 14 to 26 nucleotides [172]. Pre-gRNA designs converted into mature gRNAs with different length spacers facilitated a more potent knockdown when compared to gRNAs with fixed 22 nucleotide spacers [172].

Over a thousand circRNAs with differential expression have been recently found after analyzing the genome-wide expression pattern of circRNAs in sorafenib-resistant HCC cells [173], showing that circRNAs may play a part in sorafenib resistance. Further, Zhang and his team used the Cas13d library to screen for circRNAs that could enhance sorafenib's effectiveness in Huh7 cells.

As a result, these circRNAs were important in sorafenib resistance since their knockdown reduced Huh7 cell growth solely in the presence of sorafenib [172].

On the other hand, circGCN1L1 was completely undetectable at the studied circRNA-producing locus when CRISPR/Cas9-mediated genome editing disrupted the intronic RNA pairing across the circle-forming

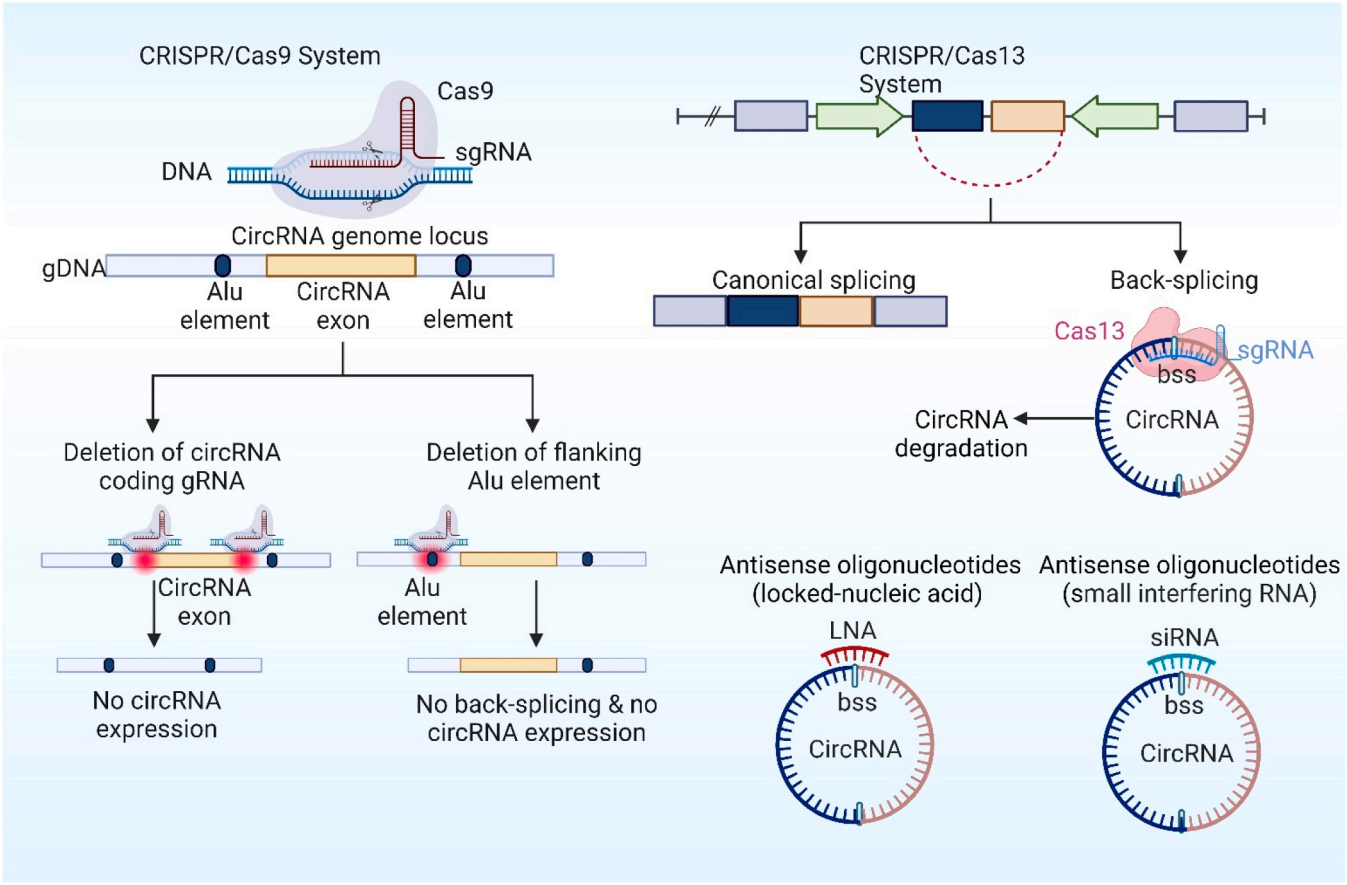

Fig. 5. A schematic illustrated the main strategies that could be used to knockdown or overexpress circRNAs in CRC cells, such as CRISPR/Cas-induced circRNA knockout or RNA interference-induced circRNA knockdown, and circRNA expression plasmids.

exons in vitro [174]. In addition, Rajewsky et al. effectively developed a Cdr1as loss-of-function model from the animal genes employing CRISPR-Cas9, a technique that involves Cas9 mRNA and two sgRNAs that are designed to bind upstream of Cdr1as splicing sites [175]. Thus, the CRISPR/Cas technologies, which may be used as cutting-edge cancer therapies and diagnostics in the future, will be completely comprehended by researchers.

7. CircRNAs prospective CRC biomarkers towards diagnosis and prognosis

Early detection and CRC screening are essential for improving treatment outcomes and lowering CRC-related morbidity. Only a small percentage of CRC patients are diagnosed as a result of the classic symptoms of the disease, such as losing weight, irritable bowel syndrome, and perirectal bleeding, which might go unnoticed for a long time. Although the identification of CRC has improved due to stool examination, digital colonoscopy, and electronic rectal examination, effective biomarkers for CRC are still required for early diagnosis. Finding noninvasive, affordable blood/serum or urine-based epigenetic biomarkers may be a useful screening tool.

CircRNAs are an essential biomarker for diagnosing CRC because of their sensitivity and specificity. Firstly, circRNAs are highly stable and resistant to exonuclease destruction because they lack 5′ or 3′ prime ends [176]. Second, circRNAs are detected in solid tumors and human liquids like saliva, serum, plasma as well as exosomes [48]. For instance, circ1662 and circPACRGL were considerably increased in CRC patients, suggesting their cancer-specificity [61]. Similarly, in colon cancer and polyps, circCCDC66 expression was raised and was linked to a bad prognosis [177]. Likewise, functional research has shown that circMBOAT2 increases CRC cell proliferation, motility, and invasion by acting as a miR-519d-3p sponge; additionally, by competitively binding to miR-519d-3p and concentrating on TROAP in CRC cells, circMBOAT2 controlled cell proliferation and migration. These findings suggested that circMBOAT2 might be a brand-new candidate as a CRC biomarker [178]. Further, circRNAs offer great diagnostic potential because they are resistant to degradation and can be found in body fluids without causing any harm to the patient. Additionally, Patients with and without CRC can be differentiated based on the presence or absence of circ-KLDHC10 in their serum samples [176].

By using the reverse transcription quantitative real-time PCR (RT-qPCR) method, can be determined the expression of different types of circRNAs either in fluids or tissues [34]. Expression of various circRNAs according to their stability, the long half-life, and their resistance against digestion by exonuclease and RNase that comes from their specific covalently closed structure without 3′ and 5′ ends, which makes them be used significantly as biomarkers for different types of cancers such as CRC [179].

Dysregulation of circRNAs plays an essential part in identifying the occurrence and progression of CRC in patients. For example, Guo et al. have shown that the hsa-circ-0000069 was significantly overexpressed in CRC and strongly associated with the patient's TNM stage [180]. According to an investigation that has been done on 153 CRC samples and 44 normal samples, it has been shown that ciRS-7 is up-regulated. Functions firmly with sponge miR-7, correlated with poorer patient survival, can serve as a chemotherapeutic agent for colorectal cancer, and even up-regulation can serve as a predictive biomarker [80,181]. Another investigation found disruption of circRNAs in the progression of CRC.

Further, circALG1 expression was shown to be significantly higher in

peripheral blood and tumor tissues from CRC patients, and this was connected with CRC metastasis [182]. This study highlights the significance of circRNAs as a biomarker for CRC diagnostics because of their role in regulating cancer cell signaling. Previous research has shown that circRNAs play crucial roles in cancer cellular processes like TGF-β-Smad, PI3K-Akt, GEF-H1-RhoA, JAK-STAT, Wnt β-Catenin, and by increasing oncogenic activity, reducing the activity of tumor suppressor gene products, and decreasing subsequent proteins [183–186]. Therefore, circRNAs may serve as an effective biomarker in detecting CRC.

8. Conclusion

CRC is becoming increasingly common in all parts of the world, and it is incredibly challenging to treat because of treatment-induced resistance. CircRNA is one of the most abundant alterations in cancer and is responsible for cancer progression and therapeutic resistance. Additionally, due to their abundance, stability, conservation across species, and disease-specific circRNAs hold significant potential as biomarkers for diagnosis and prognosis in CRC patients. Targeting circRNAs to overcome drug resistance is a recent topic of discussion in colorectal cancer treatment. The expression of circRNAs can be inhibited via RNA interference (RNAi) or small chemical inhibitors, CRISPR/Cas techniques, exosome-mediated delivery, inhibition of RNA-binding proteins, or circRNA modification to reduce drug resistance. Although many promising approaches have been identified, there is still a significant distance before they can be used in clinical practice. Thus, more continuous research is needed to stand a chance against drug resistance in CRC patients.

Ethics approval and consent to participant

Not applicable.

Consent of publication

Not applicable

Authors' contributions

All authors contributed to the study's conception and design. BMH, MCG and MT supervised the study. AAM, MS, SE and SRA collected the data. BMH, MT and AAM wrote the first draft of the manuscript. SRA and MFR illustrated the figures. MFR and AMH designed and drew tables. MFR and AMH reviewed and edited the draft. All authors read and approved the final manuscript.

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Not applicable.

Table 3
Summary of dysregulation of several circRNAs potentially used as a biomarker in CRC.

CircRNAs	Parent gene	Location	Expression in CRC	Clinical samples	Assessed cell lines	Animal model	Potential use	Ref.
CircCCDC66	CCDC66	-	Up-regulation	CRC sample= 12 case	HT-29, HCT116	NOD/SCID mice	Diagnostic & prognostic	[177]
				CRC tissue=29 case	HCT116, SW620	-	-	[187]
Circ-100290	SLC30A7	Mainly cytoplasm	Up-regulation	CRC tissue=44 pairs	HCT116, SW480, HT29, SW620	-	Prognostic	[188]
CircMBOAT2	MBOAT2	Mainly cytoplasm	Up-regulation	CRC serum=107 patients & healthy people= 100	HCT-8, DLD-1, SW480, HCT-116	Nude mice	Diagnostic	[178]
Has-circ-0060927	CYP24A1	Mainly cytoplasm	Up-regulation	CRC tissue=83 pairs	HT-29, HCT-116	-	Diagnostic	[189]
				CRC tissue=68 pairs	HCT116, SW480	BALB/c nude mice	Diagnosis	[190]
Has_circ-0004585	KIAA1199	-	Up-regulation	CRC tissue=50 pairs, CRC blood= 142 samples & healthy individual= 142 samples	-	-	Diagnostic	[9]
Has-circ-0004771	-	-	Up-regulation	CRC =135 case	FHC, HCT-116, SW-480	-	Diagnostic	[191]
Circ-0002138	-	Mostly in cytoplasm	Down-regulation	CRC tissue=50 64 cases, Normal sample=37	RKO, HT29, HCT116, SW1116, SW480, SW620, LOVO, DLD1	-	Diagnostic	[192]
Circ-0001649	SHPRH	-	Down-regulation	CRC tissue=64 pairs	HCT116	-	Diagnostic	[193]
Circ-0000567	SETD3	Cytoplasm	Down-regulation	CRC tissue=102 pairs	FHC, SW480, RKO, CACO2, SW620, HCT116	-	Diagnostic	[194]
CircITGA7	ITGA7	Mainly cytoplasm	Down-regulation	-	SW480, RKO, Caco-2, SW620, LoVo, HCT116, DLD1, FHC	Mice	Diagnostic	[75]
Circ-FBXW7	FBXW7	-	Down-regulation	CRC tissue=20 patients	SW480, SW620	BALB/c nude mice	Prognostic	[195]
Circ-0026344	-	-	Down-regulation	CRC tissue=32 pairs	NCM460, FHC, 293 T, HCT116, SW480, SW620, HT29	-	Prognostic	[68]
Circ-0014717	-	-	Down-regulation	CRC=46 patients	HCT116, HT29, SW480	-	Prognostic	[196]
Has-circ-0002320	-	-	Down-regulation	CRC tissue=50 pairs and plasma samples= 100	-	-	Diagnostic & prognostic	[197]
Circ-MTO1	MTO1	-	Down-regulation	CRC tissue=63 pairs	SW480, SW620, HT-29, HCT-116, FHC	-	Prognostic	[198]

SLC30A7 solute carrier family 30 members 7, *CYP24A1* cytochrome P450 family 24 subfamily A member 1, *SETD3* set domain containing 3, *ITGA7* integrin subunit alpha 7, *MTO1* mitochondrial tRNA translation optimization 1 homolog.

CRediT authorship contribution statement

Mark C Glassy: Writing – review & editing, Writing – original draft, Supervision, Methodology. **Solat Eslami:** Writing – original draft, Funding acquisition, Formal analysis. **Ali M. Hussein:** Methodology, Investigation. **Mohammed Fatih Rasul:** Methodology, Investigation. **Abdulqahar Azizkhan Mohammed:** Investigation, Funding acquisition, Formal analysis. **Bashdar Mahmud Hussen:** Writing – original draft, Methodology, Investigation. **Snur Rasool Abdullah:** Methodology, Investigation. **Mohammad Taheri:** Writing – review & editing, Writing – original draft, Validation, Supervision.

Declaration of Competing Interest

The authors declare they have no conflict of interest

Data Availability

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

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Not applicable.

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