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Circular RNAs: Therapeutic Uses in Colorectal Cancer

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Abstract: Circular RNA (circRNA) emerges as a significant sub-type of single-stranded non-coding RNA within colorectal cancer (CRC), boasting high abundance. Delving into research, numerous pivotal roles of circRNA in therapeutic contexts within CRC have come to light, encompassing areas such as metastasis, apoptosis, and proliferation. Moreover, circRNAs exhibit significant involvement in the advancement of therapeutic strategies, demonstrating unique correlations with tumor staging, size and overall survival rates in colorectal cancer. These associations position circRNAs as potential candidates for both anticancer interventions and prognostic biomarkers. Among all cancers, colorectal cancer is the second most prevalent cause of cancer-related death and the third most common disease to be diagnosed worldwide. To gain deeper insights into the impact of circRNA-based therapeutic developments on CRC and its progression, this comprehensive review aims to synthesize the roles of specific therapeutic applications targeting circRNAs in CRC. It also aims to evaluate circRNAs' potential as useful therapeutic targets and prognostic indicators in the context of colorectal cancer. The overarching goal of this review is to illuminate the landscape of therapeutic strategies and aid in clinical decision-making processes related to CRC. By elucidating the intricate interplay between circRNAs and therapeutic interventions, this review seeks to contribute to the advancement of therapeutic modalities and improve patient outcomes in the realm of colorectal cancer management.

Introduction

Colorectal cancer (CRC) poses a formidable challenge to global health, standing as the third most common cancer and the second leading cause of cancer-related death worldwide (Siegal et al., 2013). The burden is substantial, with over 1.9 million new cases and approximately 93,000 CRC-related fatalities recorded in 2020 alone. These figures underscore CRC's significant impact, comprising approximately 10% of all cancer diagnoses and contributing to 9.4% of cancer-related mortality globally (Sharma et al., 2022; Madhu et al., 2022, 2023; Halder, 2024; Nath et al., 2024). One of the challenges in managing CRC is its often-asymptomatic nature in the early stages, leading to delayed diagnosis and treatment initiation. As a result, numerous cases of CRC are detected in the late stages, potentially restricting treatment choices and leading to a less favourable prognosis. Therefore, identifying novel therapeutic targets and biomarkers is crucial for individualized treatment, early diagnosis, and CRC surveillance. This pursuit aims to enhance patient outcomes and prognosis significantly. By focusing on early detection strategies and advancing our understanding of CRC pathogenesis, we can potentially reduce morbidity and mortality rates associated with this devastating disease.

Colorectal cancer (CRC) arises from a complex interplay of genetic and epigenetic changes, which can propel tumor onset and advancement. Among the

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emerging players in cancer biology, circular RNAs (circRNAs), a unique class of non-coding RNAs that have garnered attention for their roles as initiators and enhancers of tumor growth. Unlike linear RNAs, circRNAs possess a closed-loop structure, endowing them with remarkable stability and evolutionary conservation (Pritchard et al., 2011). Recent progression in RNA sequencing and bioinformatics has enabled numerous circRNAs discovered across eukaryotic species, revealing their tissue-specific expression profiles (Hus et al., 1979; Nahand et al., 2020; Guo et al., 2014). Research endeavors have revealed dysregulated expression of circular RNAs (circRNAs) as a contributing factor in various cancer types, spanning colorectal (CRC), pulmonary, hepatic, and urothelial malignancies (Kristensen et al., 2019; Liu et al., 2021; Shang et al., 2020). Specifically, in CRC, ongoing research has unveiled several circRNAs whose dysregulation contributes to disease progression (Wang et al., 2020). Moreover, circRNAs abound in exosomes, human peripheral blood, and other bodily fluids, indicating their prospective application as diagnostic biomarkers and therapeutic targets (Zhang et al., 2023; kumar et al., 2023). In recent, progression in RNA sequencing technologies has facilitated the identification of specific circRNA associated with different stages of CRC, enhancing their utility in disease stratification and prognosis prediction. Thus, circRNAs emerge as auspicious biomarkers for CRC, paving novel avenues for early detection, prognostication, and therapeutic intervention in combating this complex disease.

Properties of circRNA and mechanistic principles

circRNA and Biogenesis

The production of circular RNAs (circRNAs) during transcription can be mediated by three primary mechanisms, each offering insights into the intricate processes governing circRNA biogenesis (Li et al., 2021; Huang et al., 2018). First, base-pairing of adjacent introns causes intron-pairing-driven circularization, which produces a circularized RNA molecule. Second, by attaching to certain sequences or motifs in the pre-mRNA and encouraging back-splicing processes that produce circRNAs, RNA-binding proteins (RBPs) or trans-factors can promote circularization. Lastly, lariat-driven circularization occurs when splicing machinery generates a lariat structure during canonical mRNA splicing. Subsequent back-splicing within the lariat results in the formation of a circRNA. These mechanisms collectively underscore the complexity and diversity of circRNA biogenesis, shedding light on the regulatory networks governing their production and function within cells.

Figure 1 illustrates the process of back-splicing RNA transcripts at conventional splice sites, which is the primary source of circular RNAs (circRNAs). Two primary processes drive the process of back-splicing: intron-pairing-driven circularization and RBP/trans-factor-driven the circularization process (Qu et al., 2015; Eger et al., 2018) By connecting an upstream splice-acceptor site with a downstream splice-donor site, a chemically closed circular structure is formed between these sites (Salzman et al., 2012). The successful formation of a circRNA is contingent upon the dynamic interplay between back-splicing and canonical mRNA splicing mechanisms. In intron-pairing-driven circularization, extensive intronic sequences harboring inverted repeats, such as ALU elements, play a pivotal role by facilitate base pairing, promoting circularization (Ashwal et al., 2014; Zhang et al., 2014). This process can give rise to two distinct types of circRNAs: exonic circRNAs (ecircRNAs) or exon-intron circRNAs (EIciRNAs), contingent upon whether introns are excised or retained within the circularized segment. These mechanisms highlight the versatility of circRNA biogenesis, governed by intricate molecular interactions and structural features within the genome (Li et al., 2015; Conn et al., 2015; Tay et al., 2017). On the other hand, RNA-binding proteins (RBPs) such as Quaking (QKI) and FUS form dimers with trans-factors in RBP/trans-factor-driven circularization, which allows them to bind to particular motifs inside flanking introns. This connection aids the circularization process. Additionally, the recruitment of RBPs and trans-factors to the target sites is guided by sequence-specific recognition motifs, ensuring precise regulation of circRNA formation (Zhang Y et al., 2013; Kramer et al., 2015; Kelly et al., 2015). Moreover, studies in Drosophila have unveiled the potential influence of various heterogeneous nuclear ribonucleoproteins (hnRNPs) and serine-arginine (SR) proteins, highlighting the intricate regulatory mechanisms governing circRNA formation further, studies have been conducted in several animal models (Ivanov et al., 2015). These insights provide a deeper understanding of the diverse pathways underlying circRNA biogenesis and their potential implications in cellular function and disease processes.

In lariat-driven circularization, alternative exons are removed from the mRNA during traditional RNA splicing, which results in the production of lariats. This process is known as exon skipping (Wang et al., 2014; Barrett et al., 2015). Subsequently, these lariats undergo

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internal back-splicing and intron removal, producing exonic circRNAs (ecircRNAs) (Wu et al., 2020). Furthermore, intronic lariats possessing a 7-nucleotide GU-rich motif at the 5' splice site and an 11-nucleotide C-rich sequence near the branchpoint have the capability to resist debranching, allowing them to generate intronic circRNAs (ciRNAs). This intricate process elucidates the diverse mechanisms by which circRNAs are synthesized, emphasizing the significance of lariat-driven circularization in broadening the diversity of circRNA populations within cellular environments. Additionally, recent studies suggest that lariat-driven circularization may regulate gene expression and cellular processes beyond circRNA formation, further highlighting its significance in cellular physiology and disease pathogenesis.

circRNAs across six vertebrate species, including humans, macaques, mice, rats, pigs, and chickens, highlighting the pervasive nature of circRNA expression in vertebrate genomes (Suzuki et al., 2006). This comprehensive database provides valuable insights into the diversity and abundance of circRNAs across different species and serves as a valuable resource for further understanding their roles and functions in biological systems.

Circular RNAs (circRNAs) exhibit widespread expression across a multitude of human cell types, indicating their ubiquitous presence and potential functional significance. Remarkably, the circ2GO database has cataloged a staggering number of circRNAs-specifically, 148,811 circRNAs derived from 12,251 genes within pulmonary cells, highlighting the richness

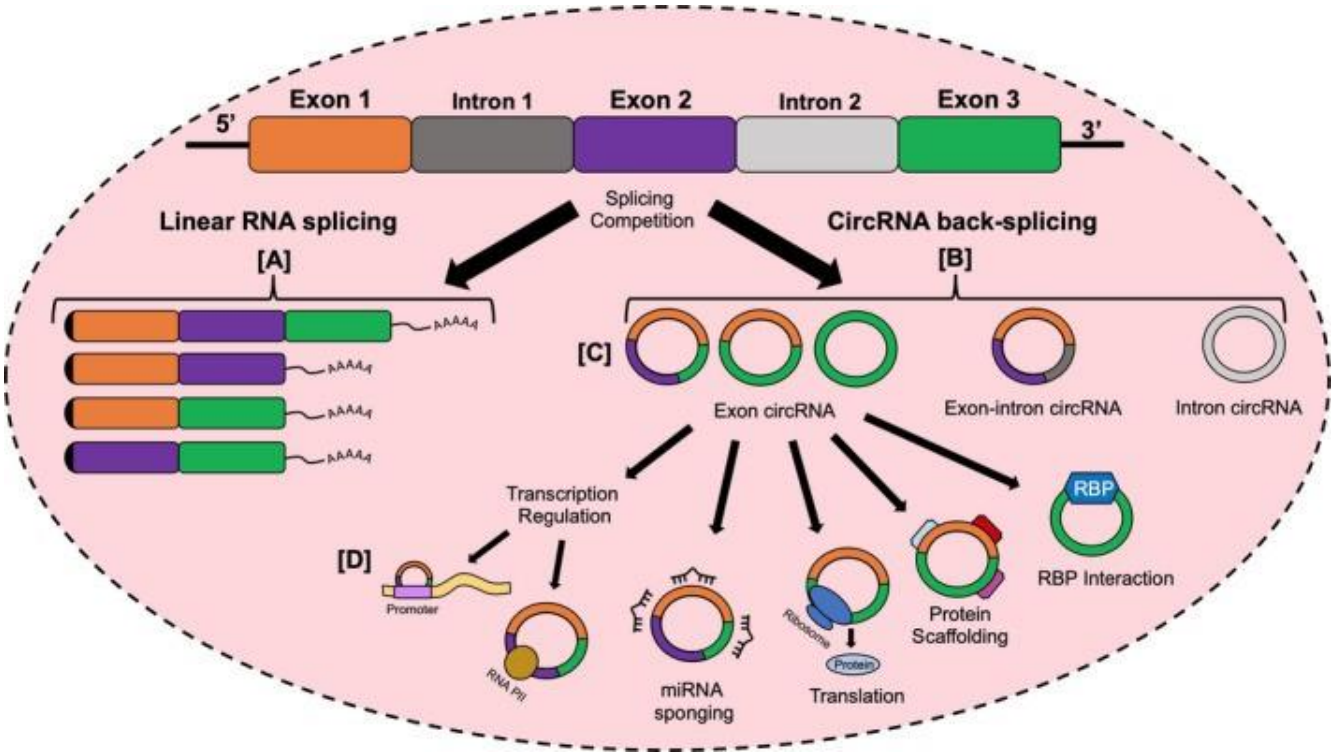

Figure 1. CircRNA biogenesis and interactions. Adapted: (Li et al., 2021). (A) To create linear RNA, pre-mRNA is spliced and introns are removed. (B) Pre-mRNA backsplicing creates circRNA, which competes with linear RNA splicing. (C) Exon circRNA, exon-intron circRNA, and intron circRNA are the three forms of circRNA. (D) CircRNA interactions with RNA polymerase II and regulator area binding, miRNA tapping, translation, protein structure and RNA-binding proteins (RBPs) in the control of transcription.

Abundance

Circular RNAs (circRNAs) exhibit widespread expression patterns across a broad range of eukaryotic organisms, spanning from mammals such as humans and mice to non-mammalian species, including zebrafish, Drosophila, and plants (Salzman et al., 2013). The extensive prevalence of circRNAs underscores their evolutionary conservation and suggests their potential significance in diverse biological processes. Notably, the circAtlas database has cataloged over one million

and complexity of circRNA expression profiles within this cell type as of 2020. Additionally, investigations conducted in human fibroblast cells have unveiled that approximately 14.4% of expressed genes have the capacity to produce circRNAs, highlighting the prevalence of circRNA biogenesis across the transcriptome. Moreover, certain circRNAs have been noted to exhibit expression levels up to 10 folds greater than their linear counterparts, emphasizing the regulatory significance and functional relevance of circRNAs in

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various cellular processes. Furthermore, estimations suggest that circRNAs constitute roughly 1% of the poly-adenylated RNA abundance in prominent cell lines such as A549, AG04450, and HeLa cells, indicating the substantial contribution of circRNAs to the cellular RNA pool. These findings collectively underscore the widespread presence and regulatory potential of circRNAs across various human cell types, prompting further exploration into their roles in cellular physiology and pathology (You et al., 2015).

In multiple cell lines, including A549, AG04450, and HeLa cells, it has been observed that circular RNA (circRNA) isoforms exhibit higher expression levels compared to their linear counterparts for approximately 50 genes in each cell line (Li Y et al., 2017, Zhang P et al., 2017). This suggests that circRNAs may play a predominant role in the regulatory landscape of these genes. However, for the majority of genes, circRNA expression levels typically range from 5% to 10% of their linear isoforms, indicating a more modest contribution to the overall gene expression profile. Moreover, circular isoforms comprise a substantial portion of spliced transcripts across hundreds of genes in leukocytes, underscoring the extensive prevalence and potential functional significance of circRNAs in cellular processes (Nicolet et al., 2018). The abundance of circRNAs represents a valuable and underexplored resource for investigating both physiological and pathological aspects of human biology. This highlights the importance of further research into the roles and functions of circRNAs in understanding the complexities of human health and disease.

Stability

Circular RNAs (circRNAs) stand out for their exceptional stability, a feature that distinguishes them from their linear mRNA counterparts. CircRNAs exhibit a significantly higher resistance to degradation by exonucleases compared to linear mRNAs. Because circRNAs are circular in structure, exonuclease RNase R, which is well known for requiring a minimum 3' residual of seven nucleotides for efficient binding and consequent nuclease activity, finds it extremely difficult to degrade them. This makes circRNAs unique since they don't have the required 3' overhang, which prevents them from being broken down by RNase R. Moreover, two well-known exonucleases, ribonuclease II and polynucleotide phosphorylase, have the remarkable property of maintaining the integrity of circRNA while breaking down their linear counterparts (Westholm et al., 2014; Liang et al., 2013). Moreover, experimental findings provide compelling evidence that circRNAs possess remarkably extended half-lives, surpassing 48 hours, which stands in stark contrast to their associated linear transcripts that typically endure half-lives of less than 20 hours. This heightened stability of circRNAs, particularly evident in studies where Hs68 cells were treated with actinomycin D, underscores the robustness and resilience of circRNA molecules. Such stability confers upon circRNAs a crucial role in cellular processes and regulatory networks, emphasizing their potential significance as key players in gene expression regulation and cellular homeostasis.

Expression unique to a cell, tissue, developmental stage, and illness

Numerous investigations have underscored the cell-type-specific expression patterns exhibited by circular RNAs (circRNAs), shedding light on their dynamic regulation and potential functional roles within different cellular contexts (Fang et al., 2018; Garikipati et al., 2019). Notably, circRNAs exhibit a striking up-regulation in mouse neuronal tissue when compared to cardiac, hepatic, pulmonary and testicular tissues. Several factors may underlie the observed enrichment of circRNAs in the brain. One contributing factor could be the exclusive expression of parent genes for many circRNAs in the brain, indicating a tissue-specific regulation of circRNA expression (Rybak-wolf et al., 2015). Furthermore, compared to other tissues, the brain has a larger ratio among the percentage of circRNA transcripts and the overall transcriptional output of the parent gene locus, which raises the possibility of increased circRNA creation or stability in brain tissues. Furthermore, studies examining circRNA expression profiles across distinct developmental stages of the human heart have revealed stage-specific expression patterns, highlighting the dynamic regulation of circRNA expression during cardiac development (Li et al., 2018). These findings underscore the complexity and specificity of circRNA expression across different tissues and developmental stages, suggesting their potential involvement in tissue-specific functions and developmental processes. A worldwide tendency of circRNA up-regulation was seen in mouse studies during the ageing process of brain tissues, but there was no consistent pattern of linear RNA up-regulation (Tang et al., 2017). CircRNAs accumulate in brain tissues with age in both mice and Drosophila, where expression of circRNAs is significantly higher in adult heads than in other larval, pupal, and adult tissues (Zhang et al., 2019; Tan et al., 2017). Furthermore, in contrast to healthy individuals, circRNAs have been shown to express differently in a variety of illness situations, including diabetes mellitus, cardiovascular disease,

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neurological disorders, and cancer (Zhao et al., 2019; Zaphiropoulos et al., 1966) Specifically, in cancer, circRNAs play significant roles across various stages of disease progression, including colorectal cancer (CRC), where their expression profiles have demonstrated correlations with different disease stages (Conn et al., 2015; Jeck et al., 2013). These findings underscore the diverse and dynamic roles played by circRNAs across physiological and pathological contexts, indicating their promise as biomarkers and targets for therapy in various disease states.

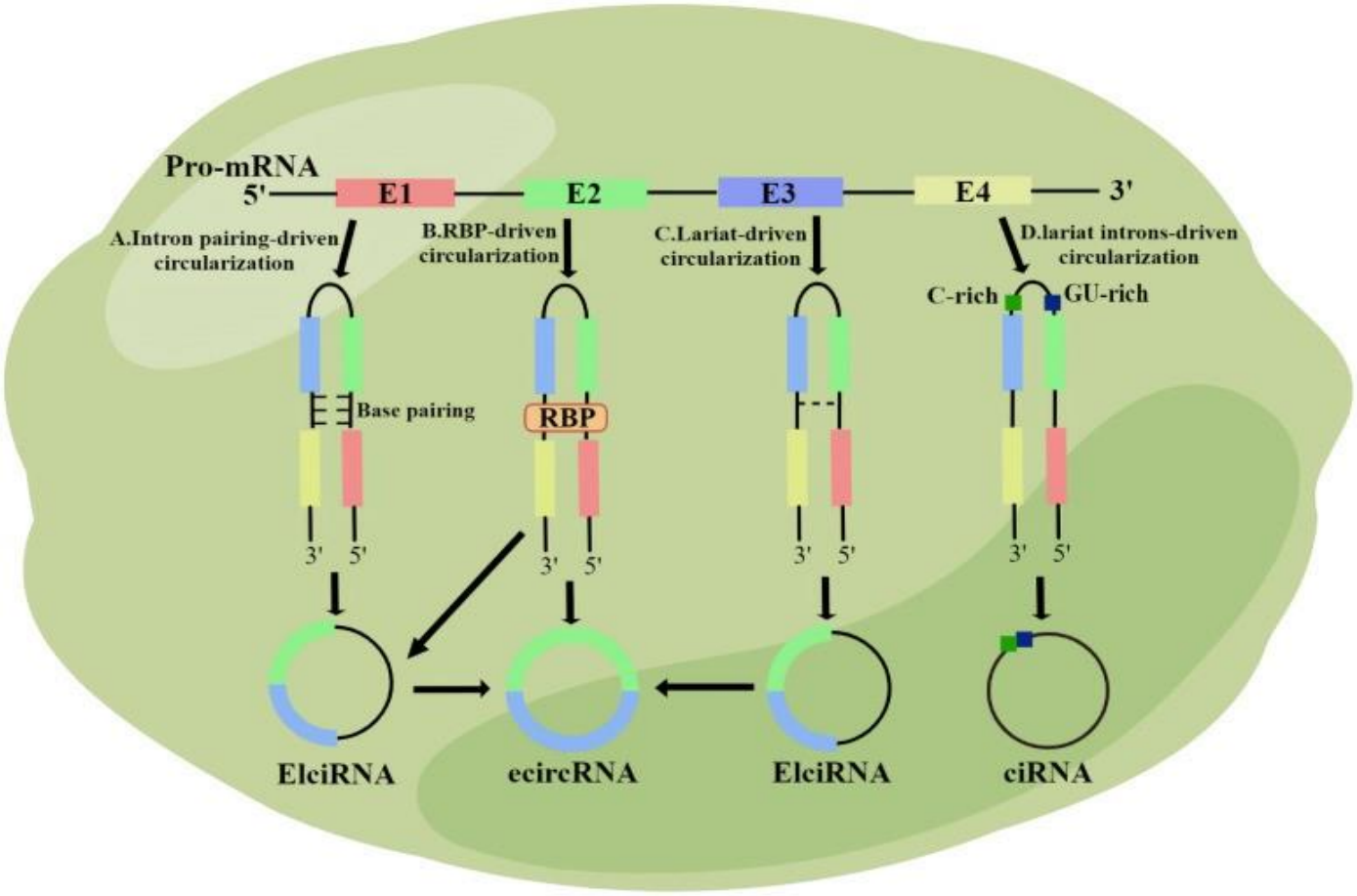

Figure 2. The biological origin of circular RNA [Adapted from Fang et al. (2023)]. There are four different types of circularization: (A) driven by intron pairing; (B) driven by RNA binding protein (RBP); (C) driven by Lariat and (D) driven by lariat introns.

Exploring the Biological functions, Mechanisms, and Clinical Implication of circular RNA in colorectal cancer

The circular RNAs (circRNAs) are a subtype of RNA molecules that arise from the post-transcriptional splicing of pre-mRNA. Conventional splicing processes are used to eliminate introns in order to create mature mRNA. The amino acid sequence and domain binding of these circRNAs place them into four major subgroups: intronic circRNAs, exonic-intron ciRNAs, tRNA intron ciRNAs and exonic circRNAs. Among these, exonic circRNAs are the most prevalent type identified. The formation of circRNAs occurs through various mechanisms. Exon circRNAs are generated through two primary pathways: reverse splicing and cyclization triggered by lariats (Zhang et al., 2022). In the lariat-driven cyclization pathway, the lasso structure undergoes excision of all introns, resulting in the remaining exons binding together to form circular RNA molecules (Lin C et al., 2022). Conversely, the reverse splicing pathway involves the binding of RNA-binding proteins to two introns, resulting in the formation of exon circRNAs (Han et al., 2020; Wang et al., 2020; Wang et al., 2022). These intricate processes contribute to the diverse repertoire of circRNAs found within cells, underscoring their significance in post-transcriptional regulation and cellular functions. For example, the Alu complementary sequence promotes base pairing-driven cyclization, which fuses two introns (Starke et al., 2015), leading to reverse splicing and the production of EIciRNA. Furthermore, certain circRNAs have areas rich in 11 nucleotide C elements and 7 nucleotide GU elements, which prevents them from being broken down (Winkle et al., 2021; Okholm et al., 2020). Notably, eCircRNA, common within the cytoplasm, is not engaged in transcriptional activities, whereas CiRNA and EIciRNA, mostly found in the nucleus, are essential in gene transcription (Zhang et al., 2023). These distinctions highlight the diverse

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functionalities and cellular distributions of different circRNA subtypes.

CircRNAs as potential therapeutic targets:

In colorectal cancer (CRC), circular RNAs (circRNAs) have distinct correlations between the size of the tumor, the staged state, and overall survival rates. They also play a major role in the development of treatment resistance. These relationships highlight circRNAs' capacity to function as CRC diagnostic and prognostic markers, offering vital information about the course of the illness and how it responds to therapy. Additionally, circRNAs offer promising avenues for understanding the intricate mechanisms underlying drug resistance development, potentially paving the way for more effective therapeutic interventions in CRC management.

Circular RNAs (circRNAs) play a pivotal role in the pathogenesis of atherosclerosis, obesity and metabolic disorders (Cao et al., 2020). Moreover, as a prognostic biomarker in the diabetics mellitus, lung fibrosis and cardiovascular-related diseases (Zaiou et al., 2020, Zaiou et al., 2020, Ma et al., 2020). More than 70 upregulated circRNAs have been identified to play active roles in colorectal cancer (CRC) tumorigenesis and progression, with their silencing demonstrating contrasting effects both in vivo and in vitro (Liu Z et al., 2019). Consequently, these oncogenic circRNAs emerge as viable therapeutic targets, with the degradation of their distinctive back-splice junctions via siRNAs holding promise for imparting anti-tumor effects (Zhang et al., 2016; Ding et al., 2023). Animal studies have validated these findings, illustrating that siRNAs or short hairpin RNAs (shRNAs) directed against oncogenic circRNAs effectively inhibit CRC growth, proliferation, and metastasis (Zheng et al., 2019; Obi et al., 2021).

For instance, in a study by Chen et al., treatment with a shRNA targeting circMETTL3 demonstrated significant inhibition of tumor growth and metastasis in nude mice xenograft models. This finding suggests that circMETTL3, known for its oncogenic properties, could potentially be targeted for therapeutic intervention. Additionally, Chen et al. (2019) utilized a patient-derived xenograft (PDX) model to validate their findings, showing that the knockdown of circNSUN2 notably decreased tumor metastasis in both hepatic and pulmonary metastasis models (Chen et al., 2019). These results underscore the therapeutic potential of targeting circRNAs in combating tumor progression and metastasis.

Similarly, colon cancer metastatic to distant organs was greatly reduced in-vivo by targeted modulation of circLONP2 through antisense oligonucleotide (ASO), leading to decreased nodular size and lower numbers (Wang et al., 2019). Additionally, Wang et al. showed that exosomal siRNA targets hsa_circ 0005963 sensitized mice that were resistant to oxaliplatin in colon cancer to the drug, presenting a viable approach for conquering oxaliplatin resistance in CRC. Furthermore, several medications and substances show potential as anticancer agents through their targeting of circRNA-associated pathways. One possible therapeutic strategy for the therapy of colorectal cancer is lidocaine medication, which has been shown to inhibit the growth, metastasis and cause death in CRC cells by modifying the circITFG2/miR-1204/SOCS2 axis (Qu et al., 2018). Furthermore, the circPPP1R12A-73aa-mediated proliferation and metastatic capacity of colon cancer cells were effectively inhibited by Peptide 17, an inhibitor that is specific to YAP (Wang et al., 2022; Hussen et al., 2024). These results demonstrate the many functions of circRNAs and the related pathways in developing and managing colorectal cancer. Novel approaches to treating a variety of human illnesses, including as cancers, lipid-related disorders, and infectious diseases, are provided by NA-based therapies. Many RNA-based therapies have been investigated and shown to enhance patients' quality of life and extend their lifespan in various disease contexts (Li et al., 2022; Halloy et al., 2022). These therapies include small interfering RNAs (siRNAs), antisense oligonucleotide (ASOs), ASO anti-microRNAs (anti-miRNAs), miRNA sponges, circular RNA therapies, miRNA mimics, and CRISPR-Cas9-based gene editing. CircRNAs, like other RNA therapeutics, have the capability to modulate gene expression or exert modular functions. They can function as miRNA sponges, expanding the repertoire of strategies for inhibiting oncogenic RNA functions. This multifaceted role of circRNAs underscores their therapeutic potential in disease management and highlights their importance in the field of RNA-based therapeutics.

As an example, it was shown that hsa_circ_001783 sequesters miR-200c-3p, which promotes the growth of breast cancer (Ruan et al., 2021; Bai et al., 2022). Artificial circRNAs have attracted more attention because of their strong and long-lasting translation process in eukaryotic cells. Li et al. developed a unique circRNA vaccination platform that elicits strong innate and adaptive immune responses. Their work has been demonstrated to be efficient in inducing anti-tumor responses in a variety of animal tumor models (Li et al.,

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2024; Robbins et al., 2009; Yin et al., 2017). Qu et al. presented a unique strategy to provide protection against SARS-CoV-2 infection: circRNA vaccines that target the SARS-CoV-2 spike protein. They also looked at the potential of synthesizing circRNAs for building hACE2 decoys that are intended to neutralize pseudovirus particles and for generating antibodies that neutralize SARS-CoV-2 (Qu et al., 2022). Despite the promising potential of synthesized circRNAs, several challenges hinder their advancement as therapeutic agents. These challenges include the need to mitigate sustained overexpression resulting from their unique properties, the

colorectal (CRC) cells had higher expression levels of Circ 0006174. Surprisingly, in CRC cells, downregulation of Circ 0006174 results in reduced Dox resistance and decreased cell migration, invasion, and proliferation. Interestingly, exosomes derived from Dox-resistant cells with CRC had significant quantities of circ 0006174. Furthermore, Zhang et al. (2021) revealed the regulatory interaction between miR-1205/CCND2 or circ_0006174/miR-1205 (Wang et al., 2022). Exosomal Circ 0006174 increases CCND2 expression through miR-1205-mediated enhancement of Dox resistance. The therapeutic potential of circ_0006174 inhibitions is

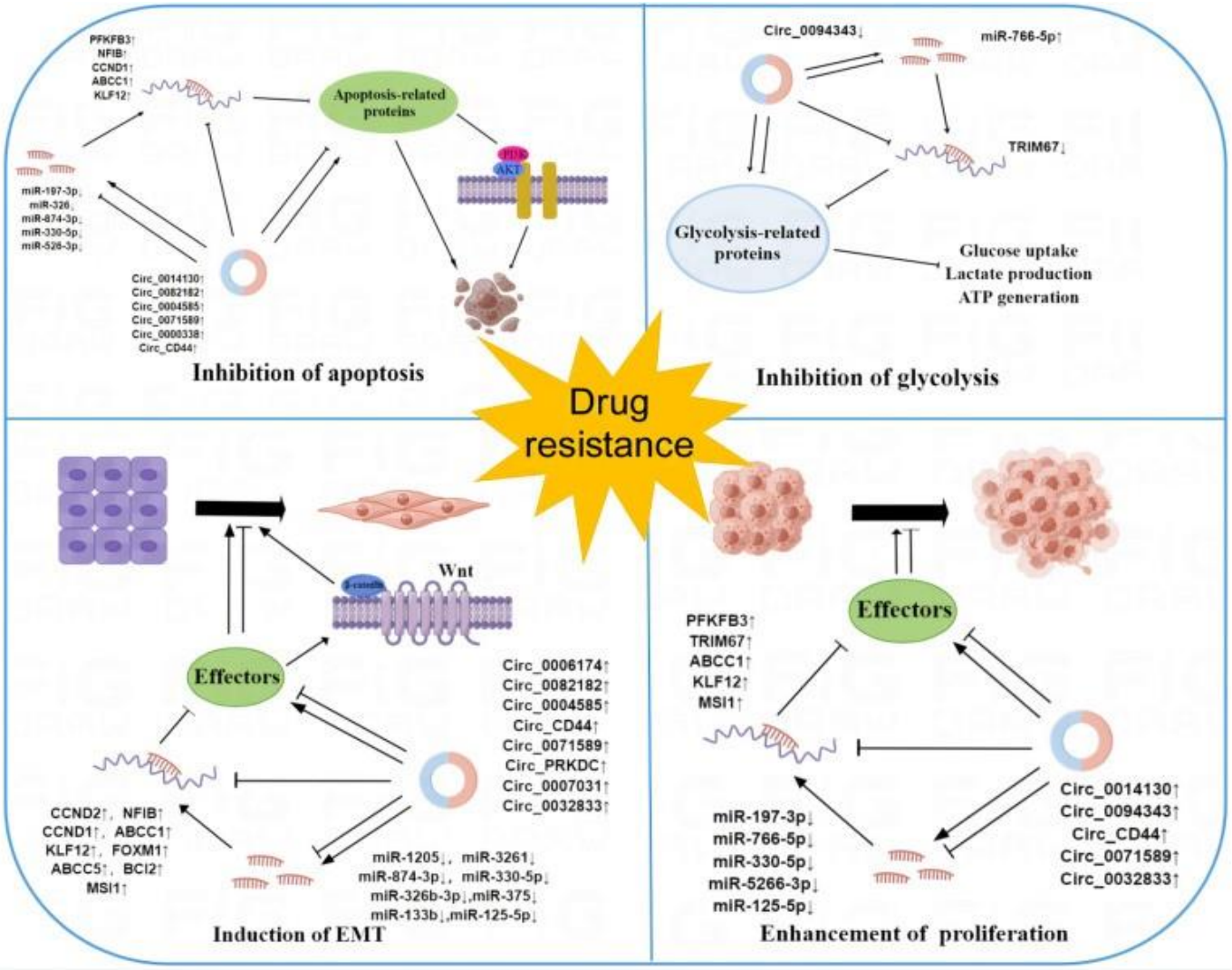

Figure 3. The role of circRNAs in cancer drug resistance involves their dysregulation, which influences various cellular processes in cancer cells, including apoptosis, epithelial-to-mesenchymal transition (EMT), glycolysis and cell proliferation (Adapted from Fang et al., 2023).

development of methods for producing highly purified artificial circRNAs and the establishment of efficient and specific delivery mechanisms. Furthermore, the discovery of distinct circRNA expression patterns between healthy and carcinoma tissue, as well as primary and metastatic tumors, illuminates the proliferating significance of circRNAs as potential therapeutic targets in the management of colorectal cancer (CRC). In tissues and cells resistant to doxorubicin (Dox), cancer of the

further demonstrated by in vivo investigations, which show increased tumor sensitivity to Dox with modification by the miR-1205/CCND2 axis. The body of research strongly suggests that exosomes with high Circ 0006174 concentrations can be used as markers for chemoresistance in colorectal cancer (Zhang et al., 2021).

There is growing evidence that exosomes produced from drug-resistant cells have the capacity to provide chemosensitive cell resistance. Because of the unique

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structure of exosomes, circRNA is protected from destruction and may be concentrated effectively. Moreover, exosomes' size and membrane composition make it easier for cancer cells to absorb and fuse with them. Significantly less Circ_0094343 was expressed in colorectal tumor (CRC) connective tissues, chemoresistant CRC tissue, and metastatic CRC tissues. Furthermore, Circ_0094343 released by exosomes inhibits glycolysis, clone formation, and HCT116 cell growth. Surprisingly, Circ_0094343 increases the chemosensitivity of HCT116 cells to a variety of medications, such as irinotecan, cetuximab (Cet), bevacizumab, oxaliplatin (L-OHP), doxorubicin (Dox), and 5-fluorouracil (5-FU). Circ_0094343 naturally absorbs miR-766-5p and swells it, controlling TRIM67 (Tang et al., 2017; Zhang et al., 2022; Norguet et al., 2011). These results demonstrate that Circ_0094343 inhibits HCT116 cell growth, clone development, and glycolysis via the miR-766-5p/TRIM67 axis, hence enhancing chemosensitivity (Fang et al., 2023).

Circ_0082182 was shown to be increased in colorectal cancer (CRC) tissues and cells that were resistant to oxaliplatin (OXA) by Wang et al. They found that circ_0082182 downregulation promoted apoptosis while preventing drug resistance, OXA-resistant CRC cell growth, invasion, and migration. Furthermore, it was shown that miR-326 is an immediate target of NFIB, which functions to stop the growth of carcinoma and stop CRC cells from developing oxaliplatin (OXA) resistance (Martinez et al., 2015; Kang et al., 2020; Mauri et al., 2020; Ghanbarian et al., 2018). It was discovered that Circ_0082182 sequesters miR-326 to control NFIB expression. Circ_0082182 enhanced the miR-326/NFIB axis in xenograft carcinoma models of OXA-resistant cells, hence boosting tumor development. According to these results, Circ_0082182 sequesters miR-326 to increase NFIB expression, which in turn affects how OXA resistance develops and progresses in colorectal cancer. As a result, Circ_0082182 shows promise as a therapeutic target for OXA-resistant CRC patients (Ma et al., 2018; Yang et al., 2021; Lan et al., 2021).

These results offer fresh perspectives on the processes controlling resistance mediated by circRNA. Through various pathways, including the stimulation of the epithelial-to-mesenchymal transition (EMT), the encouragement of cell proliferation, the prevention of apoptosis, and the suppression of glycolysis, their abnormal expression adds to the development of cancer treatment resistance (see figure 2). However, the precise mechanism remains partially understood. As our understanding of circRNA progresses, it holds significant potential for clinical applications in the future.

In the field of colorectal cancer (CRC), circular RNAs (circRNAs) have shown great promise as therapeutic agents. These endogenous RNA molecules, which are characterized by their closed-loop configuration, have a substantial impact on the development and course of colorectal cancer. Research indicates that circRNAs are dysregulated in colorectal cancer tissues, and they actively participate in key cellular processes that are linked to the development of tumors, including invasion, metastasis, apoptosis, proliferation, and treatment resistance. CircRNAs are appealing therapeutic intervention possibilities because of their abnormal expression patterns in colorectal cancer.

In many trials, circRNAs have demonstrated therapeutic promise in colorectal cancer (CRC). For example, Liu et al. (2021) showed that circHIPK3 upregulates the level of expression of oncogenic targets by functioning as a miR-7 sponge, hence promoting the advancement of CRC. CRC cell migration and proliferation were dramatically reduced when circHIPK3 was inhibited, indicating circHIPK3's promise as a therapeutic target (Liu et al., 2020).

Conclusion

The therapeutic potential of circular RNAs (circRNAs) is progressively expanding as our comprehension of their functionalities improves. Their unique capabilities to attenuate microRNA (miRNA) activity and modulate protein function position circRNAs not just as pivotal regulators of gene expression in colorectal cancer (CRC) development and progression but also as promising targets for novel therapeutic interventions with potentially heightened efficacy. Despite significant strides, the intricate complexities surrounding circRNAs and their therapeutic applications present numerous unanswered questions that elude our current understanding. These complexities and uncertainties must become a focal point for future research endeavors, as unlocking these mysteries holds the promise of catalyzing ground breaking advancements in the field. By prioritizing investigation into circRNAs and their therapeutic implications, we aspire to usher in transformative changes in CRC treatment and management landscape.

Conflict of Interest

The authors affirm that there are no conflicts of interest to disclose concerning the publication of this work. This declaration ensures transparency and upholds the research findings' integrity.

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