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REVIEW

Circular RNA, A Molecule with Potential Chemistry and Applications in RNA-based Cancer Therapeutics: An Insight into Recent Advances

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Abstract

Non-coding RNAs (ncRNAs) are functional RNA molecules that do not code for proteins. Among these, circular RNAs (circRNAs) represent a recently identified class of endogenous ncRNAs with a pivotal role in gene regulation, alongside short ncRNAs (e.g., microRNAs or miRNAs) and long non-coding RNAs (lncRNAs). CircRNAs are characterized by their single-stranded, covalently closed circular structure, which lacks polyadenylated tails and 5'-3' ends. This unique circular conformation makes them resistant to exonuclease degradation, rendering them more stable than linear RNAs, such as mRNAs in human blood cells, which highlights their potential as biomarkers. Both linear and circular RNAs are derived from pre-mRNA precursors. However, while linear RNAs are produced through conventional splicing, circRNAs are primarily formed through a process known as reverse splicing. CircRNAs can be categorized into five basic types: exon circRNAs, circular intronic RNAs, exon–intron circRNAs, intergenic circRNAs, and fusion circRNAs. These molecules have been shown to significantly influence key hallmarks of cancer, including sustained growth signaling, proliferation, angiogenesis, resistance to apoptosis, unlimited replicative potential, and metastasis. This article will delve into the biogenesis and functions of circRNAs, explore their roles in cancer, and discuss their potential applications as therapeutic options and diagnostic biomarkers.

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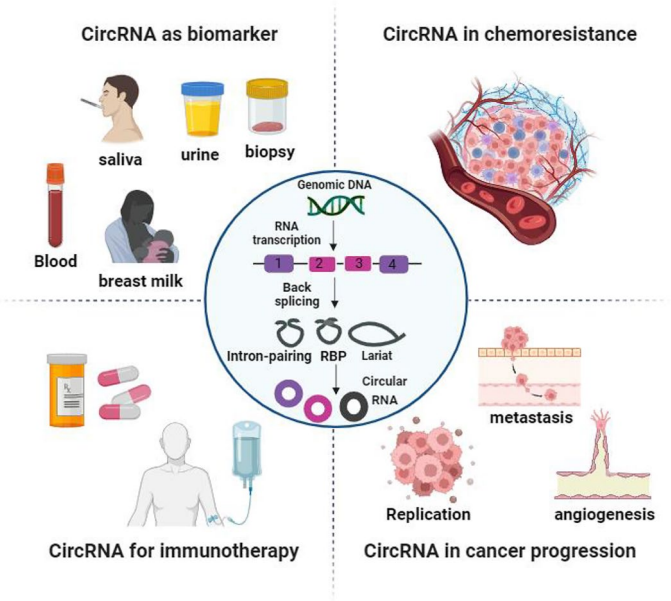
Graphical Abstract



Keywords CircRNA · Cancer · Biomarker · Immunotherapy · Therapeutic targets

1 Introduction

Non-coding RNAs, or ncRNAs, refer to a category of RNA molecules that possess functional roles while not encoding proteins. ncRNAs include several types, such as small nucleolar RNAs, tRNA, and housing-keeping ribosomal RNAs [1, 2]. It is known that the major part of the genome from mammals is transcribed to non-coding RNAs rather than coding type [3]. An endogenous form of ncRNA is CircRNA, progressively becoming recognized due to their crucial role in gene expression besides small RNAs [microRNAs, miRNAs] and LncRNAs [4, 5]. CircRNAs are one type of non-coding regulatory transcript that has gotten a lot of focus for study in the past few years [6]. They are considered unusual because of their less frequent being in nature and the logic of occurrence rather than the conventional linear RNA [7]. They are a unique class of RNA with a restricted covalent structure, high stability, and potential in gene regulation activity. Sanger HL et al. first identified these uncommon molecules in 1976 in RNA viruses and by electron microscopy. They demonstrate a high thermal tolerance, prominent cooperative effect, and self-complementarity [8–11]. In eukaryotic cells, circRNAs were first discovered in 1979 as an endogenous RNA splicing product after hepatitis delta infection

[12]. They are a rare expression product finding in the cells and exhibit a low sequence conservation. In 1993, it was found that a gender-related gene, sex-determining region Y (SRY), conducts circular transcription in adult mouse testicles [13]. Later on, it was revealed that circRNAs in human cells comprise the exons of RNA transcripts [14]. circRNAs were initially treated as a product of the erroneous splicing in pre-mRNA [15]. Later, high-throughput sequencing was used to disclose circRNA abundance and their assumed roles. Till recently, numerous circRNAs have been discovered in different eukaryotes, and their tissue-specific expression patterns have been found using RNA sequencing [RNA- seq] and circRNA-specific bioinformatics algorithms [16]. Because of their structural specificity and low abundance, circRNAs were first found in a few genes, including ETS-1, SRY, cytochrome P450 (CYP450), 2C24 and 2C18, and circular ANRIL (Canril) [17]. More than 20,000 distinctive circRNAs originating in many different genes are recognized, and the number will continue to increase [15]. It is a fact that most circRNAs are primarily conserved across species, making them an ideal tool in evolutionary approaches [18]. CircRNAs are single-stranded and covalently closed circle structures that lack 5′–3′ ends and a polyadenylated tail [6, 12, 15]. These molecules, ranging from 100 bp to 4 kb, were initially considered non-functional byproducts of distorted RNA joining [19]. The transcription efficiency of circRNAs by RNA polymerase II is equivalent to linear RNAs [20]. They are the product of non-sequential back-splicing of pre-mRNA transcripts, linked to reversed complementary sequences such as inverted repeating Alu pairs, exon skipping, and RNA-binding protein [RBP] [4, 21]. In this event, the abnormal binding of alternative RNA is mediated by spliceosome and is controlled by a combination of cis-elements and trans-acting factors [6]. Quaking and ADAR are examples of trans-acting factors that may either activate or inhibit the production of mammalian circRNAs [22]. A wide range of distinct genes encodes them, each with a unique size, expression level, and flanking introns. circRNAa may have one exon or several exons [23]. Due to their particular closed-circle structure, circRNAs are conserved from debasement by exonucleases and are more protected than linear RNAs [21]. Stable circRNAs are, therefore, prevalent in peripheral blood and may function as disease biomarkers [24] (Fig. 1). CircRNAs are excellent tumor biomarkers because of their great sensitivity and specificity. [25]. However, due to technical insufficiencies, only a limited number of specific circRNAs were proposed for the detection, and their function and diagnostic potentials are still under consideration [26]. Some Studies have reported them in body fluids such as saliva, blood, urine, breast milk, and membrane-bound vesicles like exosomes [18]. They can be found intracellular in various cells and have characteristics including stability, sequence conservation, and expression selectivity [27]. Most circRNA are detected primarily in the cytoplasm, whereas just a few circRNAs are located in the nucleus [8, 12]. Notably, there is not a consistent link between the expression level of circRNAs and their host genes. This suggests that circRNAs result from a different type of controlled alternative splicing rather than steady-state leftovers of mRNA splicing [28]. The high abundance, exceptional stability, and unique expression

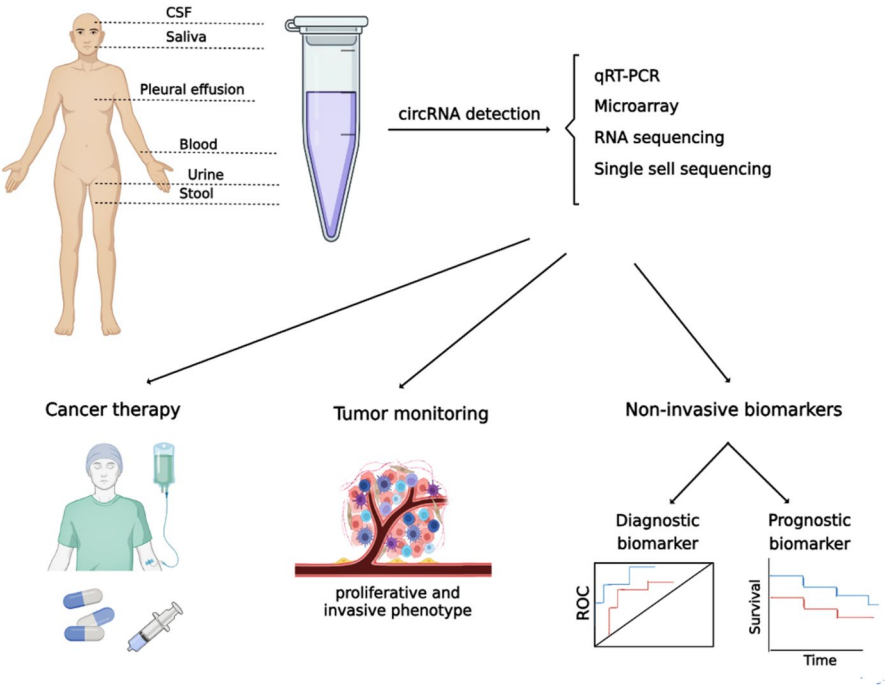


Fig. 1 The Schematic representation of various body fluids containing circRNAs, particularly cerebrospinal fluid (CSF), saliva, pleural effusion, blood, urine, and stool. As previously mentioned, analysis of circRNA content from biological fluids can be used to detect cancers and further predict susceptibility to therapeutic agents. The advancement of tumors and the effectiveness of therapy can be tracked longitudinally via circRNA monitoring. The distinct and significant divergence of circRNA expression between cancer patients and controls underscores their critical potential as fluid-based biomarkers, offering a vital tool for tracking cancer progression and spread

profiles of circRNAs, closely linked to cancer progression and patient outcomes, underscore their significant potential as both diagnostic and prognostic biomarkers. Additionally, certain circRNAs have been identified as key functional molecules driving cancer progression, making them promising candidates for targeted therapeutic strategies [29].

This article will introduce circRNAs, their biogenesis and function, and review their significance in cancer and their possibility as biomarkers and therapeutics. By addressing the current knowledge gaps and highlighting the relevance of circRNAs in cancer therapy, this work aims to contribute to the development of more effective, targeted approaches to cancer diagnosis and treatment.

2 The Characteristics and Classifications of CircRNAs

2.1 Characteristics of circRNAs

CircRNAs, a part of the non-coding RNA family, have some critical features [15].

(1) Stability: Due to the lack of a 5′ cap and 3′ end, circRNAs resist being digested by ribonucleases like RNase R and have a lengthy half-life of up to 10 times longer than linear RNAs [30]. (2) Sub-cellular Localization: They are produced in the nucleus, but most are found in the cytoplasm, implying that particular circRNA transit or localization criteria exist [29]. According to reports, 5.8–23% of human active genes create circRNAs [25]. However, the expression of circRNA is exclusive to specific cells and tissues, indicating that circRNAs have distinct biological functions and can be utilized for detecting different types of cancers [8]. (3) Expression levels: Several circularization methods may influence a circRNA's level of expression [21] . These molecules are extensively expressed, and their expression levels often outnumber those of linear mRNAs [31]. CircRNAs show greater expression in human peripheral whole blood than linear mRNAs, suggesting that circRNAs might be employed as biomarkers in routine clinical blood specimens [4]. Genomic study indicates that circRNA has greater expression levels in low-proliferating cells, such as those found in the brain, compared to actively proliferating cells. Red blood cells and platelets, which have had their nuclei removed, contain more circRNAs than hematopoietic cells that still have their nuclei intact. Platelets, in particular, have been shown to express the most circRNAs, like twice the erythrocytes and five times the granulocytes [7, 32]. (4) Degradation: The number of circRNAs inside cells is regulated by a balance mechanism between their synthesis and destruction. CircRNA degradation should initially emerge by particular nicking endonucleases to open the circle and cleave the linear RNA from the 3′ or 5′ ends [29].

2.2 Classifications of CircRNAs

In general, there are four primary forms of circRNAs: concise exon circRNAs [ecircRNAs], circular intronic RNAs [ciRNAs], Exon–intron circRNAs [EIciRNAs], intergenic circRNAs or fusion circRNAs [f-circRNAs] [21, 33]. Around 85% of circRNAs are ecircRNAs, which exclusively have exon sequences with 3′→5′ bound [15, 34, 35]. The nucleus contains ciRNAs, which have a 2′→5′ bound with a lariat composition. Exon and intron sequences with 3′→5′ bound form EIciRNAs, which are nuclear-localized [35]. According to certain studies, ecircRNAs are primarily detected in the cytoplasm [15]. It is believed that EIcircRNAs may be able to leave the nucleus during mitosis [34]. Various group circular intronic RNAs (ciRNAs), formed from alternative intronic sequences, have been discovered and characterized in human cells. EIciRNAs are different kinds of circRNAs made up of circularized exons with introns retained between exons [36].

3 Mechanisms for circRNA Generation

CircRNAs come from several sources. Most of them are derived from coding exons, while the remainder are derived from introns, intergenic regions, 3′ UTRs, 5′ UTRs, and antisense RNAs [37]. Both circRNAs and linear RNAs are made up of pre-mRNAs; however, unlike linear RNAs made by traditional splicing, circRNAs are mainly made through back-splicing [12] (Fig. 2), a specialized non-conventional alternative splicing [6]. Back-splicing requires the spliceosome machine to connect a 5′ splice site (donor) of an exon to an upstream 3′ splice site (acceptor) of another exon, resulting in the formation of a closed loop structure with a specific junction site for the majority of circRNAs [29]. Circular RNAs are abundant inside cells despite having a significantly lower back-splicing efficiency than linear RNAs because of their stability and extended half-life [14, 16]. Arthrobacter luteus elements (Alu elements), found upstream and downstream of the flanking introns of circularized exons, are involved in circular RNA synthesis [38]. The complementary nature of Alu sequences, a short-repeated sequence of DNA recognized by the Alu restriction enzyme, allows efficient pairing between the downstream 50 splice site and upstream 30 splice site. The presence of repeating sequences in the flanking introns enables the formation of a loop structure, which effectively handles the issues of opposite directionality and discontinuity [1]. A 7-nt GU-rich sequence at the 5′ splicing site and an 11-nt C-rich motif near the 3′ branch point site is required to produce ciRNAs [12, 39]. Although the

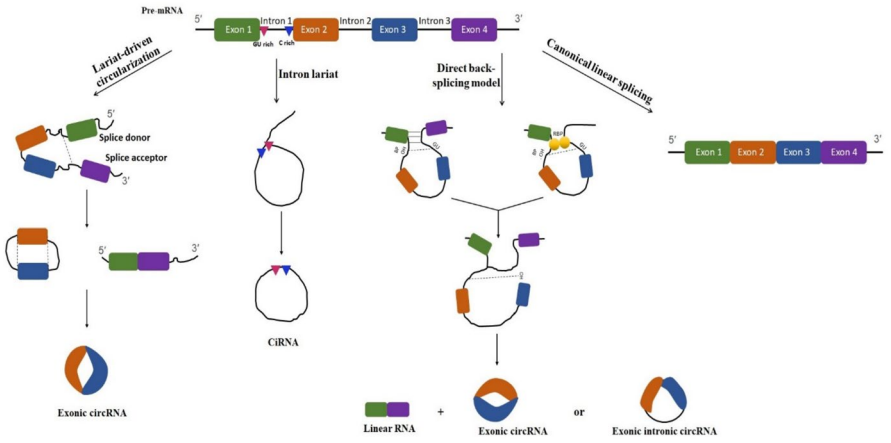


Fig. 2 The circRNA splicing. Unlike linear RNAs, which are made by traditional splicing, circRNAs are mainly made through back-splicing, which is a specialized, non-conventional alternative splicing. Accordingly, they are classified into three types: (1) EcircRNA comprises exons. They reside primarily in the cytoplasm, harbor miRNA response elements (MREs), and function as miRNA sponges. These can include single-exon circRNA and multi-exon circRNA. (2) EIciRNA is circularized, with introns positioned between exons. (3) CiRNA consists of introns. Both EIciRNA and ciRNA are abundant in the cell nucleus and can play important roles in gene transcription and post-transcription

precise mechanism of circRNA synthesis is unknown, three models—including a spliceosome-dependent lariat-driven circularization, direct back-splicing model, and resplicing-driven circularization—have been put forth to understand better the interaction between back-linking and traditional grafting in circRNA biogenesis [6, 34, 40].

3.1 Spliceosome-Dependent Lariat-Driven Circularization

According to this hypothesis, the back-splicing site is where the spliceosomes are put together to facilitate the merging of the upstream 3′ acceptor sites and the downstream 5′ donor sites. Internal splicing is then used to process the lariat, which ultimately leads to the production of EIciRNAs. Canonical splicing and circRNA biogenesis compete with one another [35]. These two methods are part of this mode: (a) Exon skipping: a huge lariat with the skipped exon can form during alternative linear splicing. By back-splicing, these exon-containing lariats can develop into mature circRNAs. Even though alternative splicing, particularly exon skipping, is considered a key regulator of circRNA synthesis, the primary mechanism of generating circRNAs is still unknown [20]. (b) Long intron lariat: Canonical linear splicing produces pre-mRNAs from linear mRNA. The debranched intron lariat is then further back-spliced to create mature circRNA [13].

3.2 Direct Back-Splicing Model (RBP-Induced Circulation)

The 'RBP-mediated circularization' model proposes that RBPs enhance circRNA synthesis by regulating neighboring splicing sites [39]. The circularized exons' 3′ and 5′ ends are brought together during RBP dimerization, facilitating their splicing by binding upstream and downstream of the circularized exon [35]. It has been demonstrated that circRNA synthesis is aided by several splicing factors, including Quaking and muscleblind. Moreover, circRNA production is regulated by the cooperation of serine-arginine [SR] proteins and heterogeneous nuclear ribonucleoprotein [hnRNP] with intronic repeats [41]. By linking the necessary intronic sequences, RBPs, such as Muscleblind (MBL), Quaking (QKI), and Fused-in Sarcoma (FUS), can speed up the rate of circularization [35]. As distinct trans-acting factors regulate circRNA synthesis, dysregulation of these factors might lead to abnormal circRNA biogenesis and expression [29].

3.3 Resplicing-Driven Circularization

Some exons from mature mRNAs may circularize and back-splice to create EcircRNAs. Introns may form lariats after canonical splicing to avoid the typical intron debranching and degradation; ciRNAs are then made [25]. Resplicing, which is commonly observed in cancers, is most likely only an aberrant pre-mRNA splicing

event. In cancer cells, for example, two unusual resplicing events were discovered on human TSG101 and FHIT mRNAs, which were considered to be caused by cancer-specific aberrant splicing. It is known that resplicing does not always produce circRNAs, yet the details are unclear [42].

4 Functional Mechanism of circRNAs

Based on the target genes, circRNAs may be divided into two types: target the other genes and those that target the host genes [43]. Several functions are attributed to cicrcRNA, including acting as endogenous RNAs for sponge miRNAs, regulating parental gene expression, modifying alternative splicing, modulating RNA–protein interactions, and functioning as scaffolds in the building of protein complexes, according to new findings [12] (Fig. 3). Circular RNAs are thought to have activities different from those of their host genes, which might be due to their significantly longer half-life compared to linear RNA transcripts [28]. Many circRNA activities are determined and affected by their cellular location, whether in the nucleus or the cytoplasm [44]. Aberrant synthesis of circRNAs leads to the development of some human disorders, notably cancer, as an indicator of their significant roles [45].

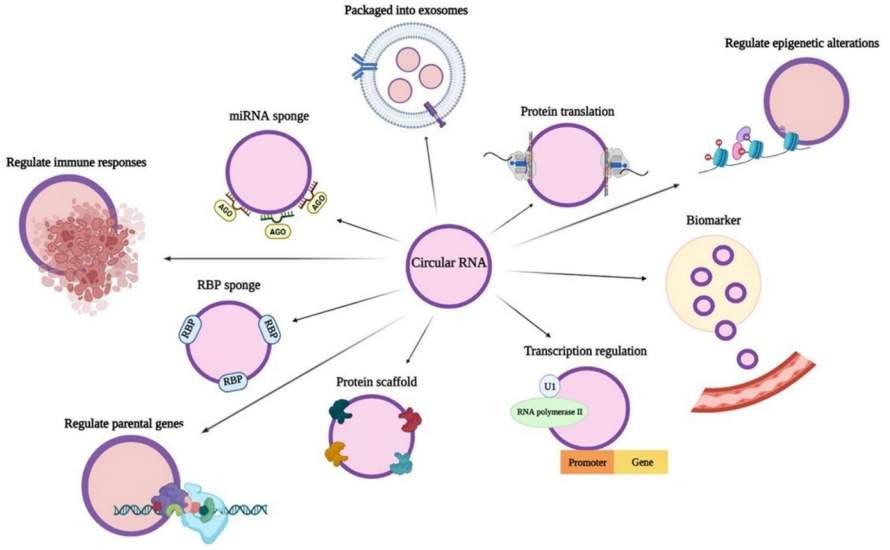


Fig. 3 The Schematic diagram of biological roles of circular RNAs. circRNAs have various roles, and their biological role is probably determined by their intracellular localization, i.e., in the nucleus or cytoplasm. CircRNAs exhibit diverse biological roles, ranging from miRNA sponging in the cytoplasm to regulating splicing in the nucleus; their specific function is largely dictated by their intracellular localization. This localization influences their interactions with proteins and other RNAs, ultimately determining their impact on gene expression and cellular processes

4.1 Act as miRNA Sponges

The concept of circRNAs acting as "sponges" for miRNAs was first proposed in 2013 [40]. miRNAs are a short non-coding RNA family (approximately 22 nucleotides) that post-transcriptionally modulate gene expression through base pairing to target sites within mRNAs [37]. They can bind to mRNA via complementary sequences in the 3′ UTR of target mRNA, limiting mRNA translation or boosting mRNA degradation to regulator gene expression [15]. CircRNAs have been revealed to function as miRNA sponges, acting as competitive endogenous RNAs [ceRNAs]. In this way, they can regulate gene expression by binding to miRNAs and inhibiting them from regulating their downstream target genes [3, 12, 29]. For example, CircEIF3M was markedly upregulated in both triple-negative breast cancer (TNBC) cells and tissues, where it played a key role in promoting cancer progression. Some findings reveal that circEIF3M acts as a ceRNA for miR-33a, thereby upregulating CCND1 expression, which subsequently drives TNBC progression. These results suggest that circEIF3M could serve as a promising therapeutic target for TNBC [46]. The competing endogenous RNA hypothesis suggests a mechanism by which different types of RNA regulate gene expression at the post-transcriptional level. This theory suggests that mRNAs, pseudogene transcripts, lncRNAs, and circRNAs influence the stability or translation of target RNAs by competitively binding to the same miRNA [27]. These molecules can regulate miRNAs adversely [4] by attaching to preferentially conserved target sites in miRNA and inhibiting their activity [33]. CircRNAs are also known as “super sponges” because of their increased propensity for binding to miRNAs compared to other competing endogenous RNAs, such as lncRNA or pseudogenes [18, 22]. A single circRNA has the ability to absorb several miRNAs. For example, circHIPK3 may sponge nine miRNAs, all of which have been shown to act as tumor-suppressive miRNAs and control cancer cell development [33, 47]. CircHIPK3, generated from exon 2 of the HIPK3 gene, is one of the discovered circRNAs that are widely expressed and have a high back splice efficiency [1].

4.2 Interact with RNA Binding Proteins

RBPs are primarily responsible for controlling the transcriptional regulation of genes. A family of proteins known as RBPs is crucial to the transcription and translation phases of gene expression [18]. They contain RNA-binding motifs as the primary binding site of RNAs [43] and can bind to circRNA junctions. In this way, they function in splicing, processing, folding, stabilizing, and localizing circRNA [48]. Some circRNAs have a high density of binding to a single or several RBPs besides their binding activities as miRNA sponges [49]. In this role, circRNAs behave as protein decoys or sponges [12] to participate in regulating gene expression in various physiological processes [20]. Additionally, circRNA can sort, store, and sequester RBPs and control their intracellular locations. Also, RBPs may control how circRNAs function and, to some extent, their half-life [18]. According to some in vivo and in vitro research, RBPs have been implicated in the development of circRNA

configuration. The most prominent example is the RNA binding protein QKI, which was discovered to be a key modulator of circRNA synthesis and a member of the STAR family of KH domain-containing RNA binding proteins. As mentioned, circRNAs can regulate the expression of RNA-binding proteins, and RBPs can govern the synthesis of circRNAs. In this regard, p53 is an encoded protein by the tumor suppressor gene TP53. This protein functions as an RBP to bind to circRNAs and their deficient mutual interactions lead to the development and progress of a range of malignancies. Because of this, certain circRNA-binding proteins are being targeted as therapeutic targets by modulating their interactions in circRNA-RBP complexes or by controlling their activity. Future research on the role of circRNAs in disease pathophysiology will benefit from exploring the relationship between RBPs and circRNAs [48].

By acting as decoys for RNA-binding proteins (RBPs), circRNAs can regulate the expression of their host genes and subtly alter the function of RBPs and their interacting proteins [50, 51].

4.3 Regulate Transcription or Splicing and Protein Translation

Some circRNAs, including ciRNAs and EIciRNAs, are found in the nucleus, even though most are found in the cytoplasm. The portion of the nucleus circRNA has a small number of microRNA target sites, and its activity is restricted to nuclear processes like transcription regulation. This subset of circRNAs controls alternative splicing and transcription by acting as transcriptional or splicing regulators to suppress gene expression [15, 18, 29]. EIciRNAs were discovered to be maintained in the nucleus after being produced by conventional splice signals, according to a study by Shan and his colleagues [1]. Furthermore, nuclear resident EIciRNAs bind with RNA polymerase II (pol II), interact with U1 snRNP and the Pol II transcription complex at the promoter of their parental genes, and thereby regulate parental gene expression. It has been shown that circRNAs work together as transcriptional regulators to regulate the expression of host genes [29, 41, 45]. Some ciRNAs are confined to transcriptional regions and can bind RNA pol II complexes, influencing RNA pol II transcription by an unknown mechanism. So, they perform a cis-regulation on their parent genes following a DNA/RNA duplex in situ hybridization [17]. It has been found that pol II and the ciRNA generated by the ANKRD52 gene can combine, and the complex can attach to the promoter region of this gene to increase its transcription [44]. Some certain ciRNAs, such as ci-ankrd52 and ci-sirt7, are known for the positive regulation of Pol II transcription and are crucial for the effective transcription of their parent coding genes. MBL protein can directly attach to its related circRNA, circMbl, and encourage the formation of circMbl. In this case, it has a harmful impact on canonical splicing and reduces the amount of produced parental mRNA. Furthermore, exon 2 of HIPK2/3 undergoes “alternative” splicing to circularize rather than canonical splicing and create a linear transcript from which numerous circRNAs originate. The typical synthesis of transcripts encoding proteins is negatively regulated by HIPK2/3 circularization [49].

Although circRNAs are primarily classified as non-coding RNAs, emerging evidence suggests that some of them can indeed be translated into proteins [15]. This characteristic was first identified by Pamudurti et al. in 2017 when they discovered circMbl, marking a significant advancement in our understanding of circRNA functionality [40]. Since then, circZNF609 has been recognized as the first protein-coding circRNA in eukaryotes [45], with subsequent research indicating that several other circRNAs in various eukaryotic cells, including Drosophila, are also involved in translation [25]. Traditionally, the presence of 5′ and 3′ untranslated regions (UTRs) has been considered essential for initiating translation in eukaryotic cells. The lack of these regional ends was the initial reason to consider circRNAs as non-coding [30]. CircRNAs lack the 7-methylguanosine (m7G) cap at the 5′ end and the poly(A) tail at the 3′ end, which are crucial elements of linear mRNA that facilitate the recruitment of translation initiation factors; however, circRNA translation is carried out in an IRES-dependent or m6A-dependent manner [29]. IRES elements enable cap-independent translation by directly recruiting initiation factors and ribosomes, which is essential for circRNAs since they do not possess the 5′ cap and 3′ poly(A) tail typically found in linear mRNAs [52]. N6-methyladenosine (m6A) modifications on circRNAs also play a role in facilitating translation initiation. These modifications are recognized by reader proteins such as YTHDF3, which recruits eukaryotic translation initiation factors like eIF4G2. This process allows circRNAs to be translated via a cap-independent mechanism, similar to that used in IRES-mediated translation [53].

Circular RNAs contain open reading frame [ORF] and internal ribosome entry site [IRES] sequences that enable them to code peptides as a hybrid class of RNAs with structural and functional significance [22, 31, 33] (Fig. 4). For instance, circ-FBXW7 has a conservative IRES element that can be translated to a peptide FBXW7-185aa [44]. Additionally, Chen et al. (2018) showed that N6-methyladenosine (m6A), the most common base modification of RNA, may successfully promote the start of protein translation from circRNA [54].

4.4 Regulate Epigenetic Alterations

Epigenetic changes significantly impact gene expression and the occurrence and progression of various diseases [55]. Among these changes, DNA methylation is a crucial mechanism that affects both DNA and non-coding RNAs [56]. While DNA and non-coding RNAs are well-known for their roles in epigenetic modifications, structural proteins of the genome, such as histones, heterochromatin components, and Polycomb proteins, also play vital roles in these processes [55]. CircRNAs play a significant role in the regulation of cellular processes through their involvement in epigenetic changes. They have been found to influence DNA methylation and histone modifications, thereby impacting gene expression and disease progression. For instance, circFECR1 can attract TET1 DNA demethylase to the FLI1 promoter, leading to CpG DNA demethylation, which is crucial for regulating gene activity [47]. CircRNA expression is dynamically controlled to exert an epigenetic regulatory impact on its downstream targets pertinent to the illness mechanism at each stage of disease advancement. However,

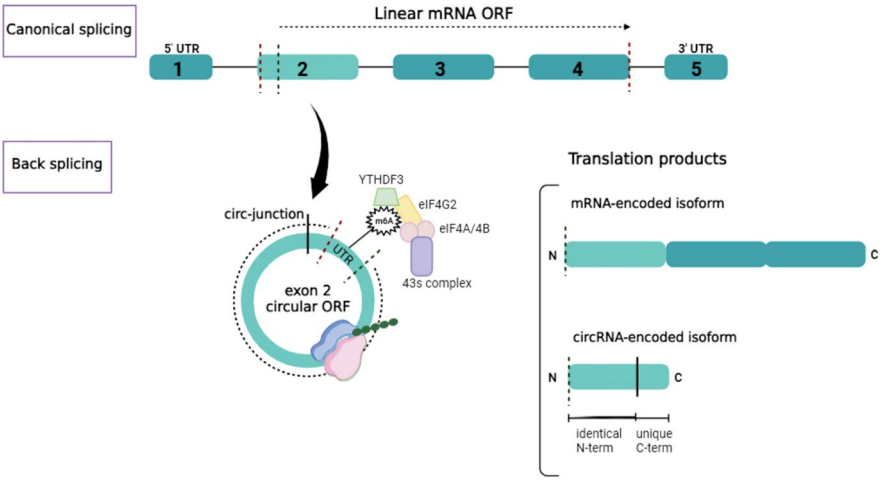


Fig. 4 The translation of circular RNAs involves the canonical splicing of pre-mRNA, which produces a linear RNA containing an open reading frame (ORF) that encodes the standard protein. Alternatively, circular splicing can generate a covalently closed circular RNA (circRNA) with a continuous ORF spanning the splice site. This circular ORF encodes a truncated protein isoform with an N-terminus similar to that of the standard protein and a distinct C-terminus encoded downstream of the splice site

the epigenetic regulatory implications of miRNAs in the pathogenesis of some diseases are studied; circRNAs may have a greater regulatory impact than miRNAs [57].

CircRNAs not only influence disease processes but also contribute to regulating immune responses through changes in methylation. Variations in the type and quantity of circRNAs associated with epigenetic methylation highlight the connection between non-coding RNA molecules and epigenetics [56]. Conversely, epigenetic alterations can also affect the biological development of circRNAs [47]. The most common epigenetic modification of RNAs in eukaryotes is N6-methylation of adenosine (m6A). Multiple studies have demonstrated that m6A is frequently observed in circRNAs [56]. The primary pathway for circRNA degradation involves cleavage by endonucleases. In this context, m6A modification promotes the recruitment of endonucleases, accelerating circRNA degradation through the YTHDF2-HRSP12-RNase P/MRP axis [55].

4.5 Protein Scaffolding

In addition to acting as miRNA sponges, circRNAs can function as scaffolds by directly binding to one or more proteins. Such protein-scaffolding circRNAs are referred to as “protein decoys" [22, 40]. Moreover, they can mediate protein–protein interactions and, in some cases, regulate gene expression [18, 41]. CircRNAs with binding sites for enzymes and their substrates are believed to act as scaffolds, facilitating interactions between two or more proteins [18, 28]. These molecules, containing multiple protein-binding sites, may serve as dynamic scaffolds to mediate

various protein–protein interactions and form large RNA–protein complexes. [29]. The co-localization of circRNAs and proteins indicates that some circRNAs possess conserved, protein-binding sequence regions. CircRNAs and proteins can interact to alter the subcellular localization of proteins, regulate the transcription of parental genes, and enhance the interaction of multiple proteins [35]. For example, circFOXO3 serves as a bridge between MDM2 and p53 proteins, accelerating p53 degradation. Notably, circFOXO3 protects FOXO3 from MDM2-mediated polyubiquitination and proteasome degradation through weak interactions with FOXO3 [1].

4.6 Exosomal circRNAs and Tumor Environments

Exosomes are extracellular vesicles with a diameter of 30 to 100 nm that can transport circRNAs to physiological fluids and cells, both nearby and distant. These vesicles, nanoscale membrane vesicles, play a crucial role in mediating intercellular communication, particularly within tumor microenvironments. They contain various RNAs, including mRNA and non-coding RNAs [58]. Initially, exosomes were thought to primarily function in removing cellular waste. However, their ability to carry and present circRNAs in body fluids has drawn attention to their potential as biomarkers for assessing cellular health. Exosomal circRNAs (exo circRNAs) have been shown to be more stable in exosomes compared to parental cells, as demonstrated by genome-wide RNA sequencing analysis [59]. Exo circRNAs are found in both blood and saliva [60], providing a rapid and accessible biomarker platform. Due to their site-directed and targeting capabilities, exo circRNAs have been proposed to enhance the efficacy of treatments targeting malignant cells and tumor environments. For instance, exosomal circPTGR1 has been shown to influence the growth of hepatocellular carcinoma, where exo circRNAs are upregulated and promote tumor invasion [61].

Survival analysis revealed a negative correlation between circ-IARS expression and survival time in pancreatic cancer patients, suggesting that circ-IARS in serum exosomes could serve as a promising non-invasive biomarker for both early diagnosis and prognosis [62]. Furthermore, Li et al. demonstrated that the expression of exosomal circPDE8A in plasma was closely associated with disease progression and prognosis in PDAC patients, highlighting exosomal circPDE8A as a potential key indicator for early detection and prognosis of PDAC [63].

4.7 Immune Responses Regulation

Numerous studies have identified non-coding RNAs (ncRNAs), particularly long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), as potential novel regulators of immune responses and immunological disorders [64], despite the dominant role of proteins. Research on circRNAs in immune cells primarily focuses on macrophages, which are essential players in immune responses [65]. CircRNAs, in combination with double-stranded RNA-activated protein kinase, can form a 16–26 bp double-stranded RNA stem-loop structure, a configuration involved in immune

response regulation [44]. CircRNAs can influence genes associated with immune responses through the circRNA-microRNA-gene axis, where they interact with specific microRNAs to regulate host antiviral immune reactions. However, experimental validation of findings from large-scale bioinformatics analyses remains necessary [66]. In an attempt to generate circRNAs for cell transfection, Chen et al. used in vitro transcription and auto-splicing circulation. Unexpectedly, their results showed that in vitro-generated circRNAs could activate cellular immune response pathways and inhibit RNA virus infections via the retinoic acid-inducible gene-I (RIG-I) pathway. In contrast, endogenous circRNAs do not activate this pathway, likely due to their interaction with specific RNA-binding proteins [66].

4.8 Regulation of Parental Genes

CircRNAs are byproducts of gene transcription; however, it has been understood that they have an important role in control of their parental gene expression where they have been transcripted [67]. CircRNAs may control parental gene expression through various mechanisms, including post-translational modifications, miRNA sponging, mRNA trapping, translational regulation, and the modulation of transcription and splicing [68, 69]. Dong and colleagues mentioned that circRNAs are numerous in the nucleus and have a low enrichment for miRNA target sites; besides, knocking down ciRNAs may reduce the expression of their parental genes [37]. Some nuclear circRNAs may induce DNA hypomethylation at promoter sites or regulate intronic enhancers, thereby affecting parental gene transcription. For example, FECR1, a novel FLI1 exonic circRNA, activates FLI1 transcription through a positive feedback mechanism that induces DNA hypomethylation at CpG islands within the promoter. This mechanism enables FLI1 to inhibit metastasis in breast cancer by employing epigenetic regulation via its exonic circular RNA [68]. CircRNAs may regulate parental genes at both transcriptional and post-transcriptional levels [67]. They can exert direct control by interacting with RNA polymerase II or indirect control through the ceRNA (competing endogenous RNA) mechanism [33]. In some nuclear human cells, ciRNAs have been shown to modulate the transcription of parental genes in cis by enhancing RNA polymerase II activity [69]. However, the precise mechanisms underlying these regulatory processes remain unclear, and they are not consistently well-regulated in certain pathological conditions.

5 The Functions of circRNA in Cancer

CircRNAs appear to play a role in various aspects of cancer development, with two main research areas gaining prominence. The first is the identification of suitable biomarkers, and the second is the exploration of circRNA regulatory functions in cancer development, particularly how these functions are influenced by changes in circRNA expression patterns [44]. CircRNAs regulate key cancer hallmarks, including sustained growth signals, proliferation, angiogenesis, resistance

to apoptosis, limitless replicative potential, and metastasis [6]. Furthermore, by participating in alternative splicing, transcription, translation, cell autophagy, and interactions with RNA-binding proteins, circRNAs play significant roles in regulating the biological processes of malignancies [70]. Due to their exceptional stability in blood and other bodily fluids, circRNAs are considered promising biomarkers for diagnosing, predicting the risk of, and monitoring various cancers [20, 40]. CircRNAs are also closely associated with clinical aspects of cancer, such as TNM stage, lymph node metastasis, differentiation, tumor size, and overall survival [29]. Evidence suggests that dysregulation in circRNA expression is linked to molecular processes involved in carcinogenesis [31]. Although the exact causes of circRNA dysregulation remain unclear, chromosomal abnormalities and defective circRNA synthesis have been proposed as potential explanations [29]. CircRNAs have been shown to play roles in cancer cell proliferation, invasion, and drug resistance in malignancies such as colorectal, gastric, and esophageal cancers. Additionally, studies have identified these molecules in hematologic malignancies, such as acute myeloid leukemia, suggesting their utility for diagnostic, therapeutic, and prognostic purposes [4, 33, 71].

5.1 CircRNAs as Biomarkers in Cancer

CircRNAs are now recognized as multifunctional molecules that play a crucial role in cancer development [72]. Tumors cannot spread or harm the host unless malignant cells evade immune surveillance and immune responses through various immune evasion mechanisms. Due to its inherent properties, circRNA has significant potential to regulate tumor immunity. Additionally, circRNAs have been proposed to function as competing endogenous RNAs (ceRNAs) that assist tumors in evading immune surveillance [27].

The tissue- and malignancy-specific expression patterns of circRNAs make them promising biomarkers for cancer detection and monitoring. Compared to proteins, circRNAs offer several advantages for cancer recognition, including easier extraction using advanced protocols and higher tissue specificity [27] (Table 1). As previously mentioned, unlike linear RNAs, circRNAs are resistant to ribonuclease enzymes, enabling their stability and extraction from tissues, serum, and urine. This stability is a critical feature of circRNAs, positioning them as valuable biomarkers for a range of human cancers [14].

There are some challenges in using circRNAs as Biomarkers. (1) Specificity and Stability in Clinical Samples: Although circRNAs are typically stable due to their circular structure, their stability in clinical samples can be influenced by RNA integrity, which in turn affects their reliability as biomarkers [73]. (2) Delivery Mechanisms for circRNA-Based Therapies: Translating circRNA-based therapies to the clinic requires the development of efficient delivery systems. Current advances in vector systems and technologies are being developed to deliver circRNAs specifically to tumor sites, minimizing off-target effects [74]. (3) Regulatory and Ethical Considerations: As circRNAs advance towards clinical

Table 1 Expression and biological Functions and roles of circular RNAs in cancer diagnostics and therapeutics

Type of cancers	circBase ID	Name of the host gene	Regulation [Up, Down] in cancer	Target genes	Mode of functions	Target mir	References
Colorectal cancer	hsa_circ_0000598	B2M	Upregulated	BMI1	miRNA sponge	miR-340	https://doi.org/10.1186/s12943-020-1134-8
	hsa_circ_0001492	ERBIN	Upregulated	4EBP-1	miRNA sponge	miR-125a-5p	https://doi.org/10.1186/s12943-020–01272-9
	hsa_circ_0001666	FAM120B	Downregulated	PCDH10	miRNA sponge	miR-576-5p	https://doi.org/10.1002/ctm2.565
	has_circ_0084615	ASPH	Upregulated	ONECUT2	miRNA sponge	miR-599	https://doi.org/10.1186/s13046-021–02029-y
Esophageal squamous cell carcinoma	hsa_circ_0001666	FAM120B	Downregulated	PPM1L	miRNA sponge	miR-661	https://doi.org/10.1038/s41419-022–04818-5
	has_circ_0023984	NOX4	Upregulated	REV3L	miRNA sponge	miR-433-3p	https://doi.org/10.1007/s10620-021–06916-4
	has_circ_0003340	OGDH	Upregulated	PRKAA1	miRNA sponge	miR-940	https://doi.org/10.1111/1759–7714.14377
	hsa_circ_0001741	TNPO3	Upregulated	NOTCH3	miRNA sponge	miR-491-5p	PMID: 35,693,080
Gastric cancer	hsa_circ_0110389	SORT1	Upregulated	SORT1	miRNA sponge	miR-127-5p, miR-136-5p	https://doi.org/10.1038/s41419-021-03903-5
	hsa_circ_0000936	SHKBP1	Upregulated	HUR, VEGF	miRNA sponge	miR-582-3p	https://doi.org/10.1186/s12943-020–01208-3

Table 1 (continued)

Type of cancers	circBase ID	Name of the host gene	Regulation [Up, Down] in cancer	Target genes	Mode of functions	Target mir	References
	has_circ_0004872	MAPK1	Downregulated	Smad4, ADAR1	miRNA sponge	miR-224	https://doi.org/10.1186/s12943-020–01268-5
	hsa_circ_0000437	CORO1C	Upregulated	SRSF3 PDCD4	miRNA sponge	–	https://doi.org/10.1038/s41388-022–02449-w
Hepatocellular carcinoma	hsa_circ_0001445	SMARCA5	Downregulated	TIMP3	miRNA sponge	miR-17-3p, miR-181b-5p	https://doi.org/10.1016/j.jhep.2018.01.012
	hsa_circ_0098181	SOX5	Downregulated	PPARA	miRNA sponge	miR-18a-3p	https://doi.org/10.3389/fphar.2022.819735
	hsa_circ_0017114	GPR137B	Downregulated	FTO	miRNA sponge	miR-4739	https://doi.org/10.1186/s12943-022–01619-4
	Hsa_circ_0000098	SLC30A7	Upregulated	MCUR1	generation of ATP in HCC	miR-383	
Breast cancer	hsa_circ_0000043	PUM1	Upregulated	Smad3	Interact and repress	miR-136	https://doi.org/10.1139/bcb-2020–0219
	hsa_circ_0087784	RNF20	Upregulated	HIF-1α	miRNA sponge	miR-487a	https://doi.org/10.1038/s41419-020–2336-0
	has_circ_0089153	NUP214	Upregulated	E2F6	miRNA sponge	miR-2467-3p	https://doi.org/10.1002/tox.23498

Table 1 (continued)

Type of cancers	circBase ID	Name of the host gene	Regulation [Up, Down] in cancer	Target genes	Mode of functions	Target mir	References
	hsa_circ_0000519	RPPH1	Upregulated	COL1A1	miRNA sponge	miR-328-3p	https://doi.org/10.1111/jcmm.14875
Lung cancer	hsa_circ_0008305	PTK2	Downregulated	TGF-β	Induce EMT	–	https://doi.org/10.1186/s12943-018-0889-7
	hsa_circ_0000190	CNIH4	Upregulated	PD-L1	Immune-related	–	https://doi.org/10.3390/ijms23010064
	hsa_circ_0010235	ALDH4A1	Upregulated	PD-L1	miRNA sponge	miR-636	https://doi.org/10.1111/1759–7714.14338
	hsa_circ_0001421	SEC31A	Upregulated	CDCA3	miRNA sponge	miR-4677-3p	https://doi.org/10.1186/s13000-020–01048-1
Bladder cancer	hsa_circ_0000799	BPTF	Upregulated	RAB27A	miRNA sponge	miR-31-5p	https://doi.org/10.18632/aging.101520
	hsa_circ_0001073	ACVR2A	Downregulated	EYA4	miRNA sponge	miR-626	https://doi.org/10.1186/s12943-019-1025-z
	hsa_circ_0072088	ZFR	Upregulated	WNT5A	miRNA sponge	miR-545, miR-1270	https://doi.org/10.3389/fonc.2020.596623
	hsa_circ_0006332	MYBL2	Upregulated	MYBL2	miRNA sponge	miR-143	10.18632/aging.102481
	hsa_circ_0004463	RPAP2	Downregulated	FOXO1	miRNA sponge	miR-380-3p	https://doi.org/10.1080/15384101.2020.1852746

Table 1 (continued)

Type of cancers	circBase ID	Name of the host gene	Regulation [Up, Down] in cancer	Target genes	Mode of functions	Target mir	References
Pancreatic cancer	hsa_circ_0007334	MBOAT2	Upregulated	p21 (RAC1) activated kinase 4	Cell cycle regulation	miR-433-3p	https://doi.org/10.1186/s13046-021-01894-x
	hsa_circ_0030167	TPT1	Downregulated	Wif1	miRNA sponge	miR-338-5p	https://doi.org/10.1016/j.canlet.2021.04.030
	hsa_circ_0074298	HARS	Upregulated	SMOC2	miRNA sponge	miR-519	https://doi.org/10.7150/jca.62927
Myeloid leukemia	hsa_circ_0059707	ID1	Upregulated		Promote cleavage of an oncogene	–	https://doi.org/10.3390/curroncol29090525
	hsa_circ_0040823	BANP	Downregulated	PTEN	miRNA sponge	miR-516b	https://doi.org/10.1002/jgm.3404
	hsa_circ_0009910	MFN2	Downregulated	B4GALT5	miRNA sponge	miR-491	https://doi.org/10.1111/ijlh.13742
	hsa_circ_0008305	PTK2	Upregulated	FOXM1	miRNA sponge	miR-330-5p	https://doi.org/10.1016/j.bcmd.2020.102506
Prostate cancer	hsa_circ_0003258	ZNF652	Upregulated	IGF2BP3	enhanced the stability of histone deacetylase 4	–	https://doi.org/10.1186/s12943-021-01480-x
	hsa_circ_0076305	PGC	Upregulated	PGK1	miRNA sponge	miR-411-5p	https://doi.org/10.1111/and.14406
	hsa_circ_0006156	FNDC3B	Downregulated	S100A9	stabilizes the protein by blocking the ubiquitination	–	https://doi.org/10.1038/s41417-022–00492-z

Table 1 (continued)

Type of cancers	circBase ID	Name of the host gene	Regulation [Up, Down] in cancer	Target genes	Mode of functions	Target mir	References
	hsa_circ_0008068	KATNAL1	Downregulated	WISP1	miRNA sponge	miR-145-3p	https://doi.org/10.1139/bcb-2019-0211
	has_circ_0081234	TRRAP	Upregulated	MAP 3 K1	miRNA sponge	miR-1	https://doi.org/10.1002/jgm.3376
Ovarian cancer	has_circ_0000554	LIN52	Upregulated	–	miRNA sponge	miR-567	https://doi.org/10.1007/s11356-021-13710-2
	has_circ_0063804	CELSR1	Upregulated	CLU	–	miR-1276	https://doi.org/10.18632/aging.203474
	hsa_circ_0078607	SLC22A3	Downregulated	Fas	miRNA sponge	miR-518a-5p	https://doi.org/10.1186/s13048-020–00664-1
	hsa_circ_0001756	HIPK2	Upregulated	RAB5A	interacting with RNA-binding protein (RBP)	–	https://doi.org/10.1080/15384101.2021.2010166
Papillary thyroid carcinoma	hsa_circ_0058124	FN1	Upregulated	NUMB	repression of NOTCH3/GAT-AD2A axis	miRNA-218-5p	https://doi.org/10.1186/s13046-019–1321-x
	hsa_circ_0039411	MMP2	Upregulated	SOX4	miRNA sponge	miR-423-5p	https://doi.org/10.1177/1724600821043128
	hsa_circ_0137287	SLC26A7	Downregulated	PPP2R2A	miRNA absorption	miR-183-5p	https://doi.org/10.1007/s10616-021–00473-4

Table 1 (continued)

Type of cancers	circBase ID	Name of the host gene	Regulation [Up, Down] in cancer	Target genes	Mode of functions	Target mir	References
	hsa_circ_0001658	ARID1B	Upregulated	PI3K-AKT	miRNA sponge	miR-671-5p	https://doi.org/10.21037/atm-22–3650
	hsa_circ_0059354	RASSF2	Upregulated	ARFGEF1	miRNA sponge	miR-766-3p	https://doi.org/10.1007/s40618-021–01713-2
Glioblastoma	hsa_circ_0072309	LIFR	Downregulated	p53	promoted autophagy	miR-100	https://doi.org/10.1111/cns.13821
	hsa_circ_0029426	RAN	Upregulated	–	miRNA sponge	miR-197	https://doi.org/10.1002/jcb.28313
	hsa_circ_0060055	EIF6	Upregulated	API5	miRNA sponge	miR-197-3p	https://doi.org/10.1007/s12640-022–00548-w
	hsa_circ_0006168	CNOT6L	Upregulated	IGF1R	miRNA sponge	miR-628-5p	https://doi.org/10.1080/15384101.2021.1930357
Osteosarcoma	hsa_circ_0001387	WHSC1	Upregulated	PI3K-AKT	miRNA sponge	miR-195-5p	https://doi.org/10.1186/s13046-021–02027-0
	hsa_circ_0088212	PAPPA	Downregulated	APOA1	miRNA sponge	miR-520 h	https://doi.org/10.1016/j.tranon.2021.101219
	hsa_circ_0001174	TCONS_l2_00016814	Upregulated	MACC1	miRNA sponge	miR-186-5p	https://doi.org/10.1186/s13018-022–03059-8

Table 1 (continued)

Type of cancers	circBase ID	Name of the host gene	Regulation [Up, Down] in cancer	Target genes	Mode of functions	Target mir	References
	hsa_circ_0056285	RALB	Upregulated	TRIM44	miRNA sponge	miR-1244	https://doi.org/10.2147/CMAR.S290645

translation, legal and ethical considerations become increasingly crucial. It is essential to explore regulatory frameworks for circRNA-based diagnostics and therapeutics, encompassing issues such as intellectual property rights, informed patient consent, and data privacy protection [75].

5.2 Resistance to Cell Apoptosis and Sustained Angiogenesis

A highly selective and essential mechanism known as programmed cell death, or apoptosis, maintains a balance between cell survival and death, helping to prevent diseases such as cancer [76]. The ability to evade apoptosis plays a critical role in cancer development by promoting unchecked cell division [77]. Cancer cells employ strategies to evade apoptosis, such as enhancing anti-apoptotic factors (e.g., Bcl-2, Bcl-xL, and Mcl-1) or reducing the tumor-suppressive activity of pro-apoptotic proteins (e.g., Puma and Bax). CircRNAs exhibit significant regulatory effects on several apoptosis-related components [29]. For example, endogenous circUBAP2 and has-circ-0001892 in myeloma and osteosarcoma cells compete to inhibit miR-143 activity. Since miR-143 activates the anti-apoptotic factor Bcl-2, its suppression decreases apoptosis in these cancers [27].

Angiogenesis, the process of forming new blood vessels, is essential for supplying nutrients and oxygen to support tumor cell proliferation and survival [76]. Vascular endothelial growth factor (VEGF) is recognized as the most potent regulator of angiogenesis [12]. CircRNAs influence tumor angiogenesis by modulating VEGF-related pathways through miRNA sequestration. Specifically, circRNAs regulate angiogenesis by acting as sponges for microRNAs, competing with endogenous RNA molecules, or binding and suppressing them. MicroRNAs typically target the 3'UTR region of angiogenic or anti-angiogenic factor transcripts, inhibiting mRNA translation and promoting mRNA degradation. The identification of circRNAs associated with tumor angiogenesis as biomarkers or therapeutic targets offers promising opportunities for the development of novel anti-tumor treatments [78].

5.3 Limitless Replication Potential and Tissue Metastasis

In normal cells, replication potential is limited by two processes: senescence and crisis. Telomeres, located at the ends of chromosomes, are crucial for this finite replication capacity. Telomerase, an enzyme that adds telomeric sequence repeats to the ends of telomeric DNA, is overexpressed in 85–90% of human cancers, indicating that unlimited replication potential is essential for tumor growth and malignancy. As telomeres shorten with each cell division, their length determines the number of cell division cycles [12]. Evidence suggests that circRNAs influence telomerase activity and reduce the replicative ability of cancer cells. For instance, circWHSC1 recruits miR-145 and miR-1182, leading to increased expression of the telomerase reverse transcriptase enzyme. This activation enhances telomerase activity, supporting the infinite replication capacity of cancer cells [77].

Metastasis is a complex process involving local tumor growth, intravascular invasion, and colonization of distant tissues or organs, culminating in a lethal stage. The

epithelial-mesenchymal transition (EMT) is a critical initial step in promoting invasion and distant metastasis in many malignancies. CircRNAs have been shown to contribute to EMT through various pathways, including the regulation of TGF-β signaling, which affects the EMT program and tumor metastasis [29, 77]. For example, circPTK2 (hsa_circ_0008305) was significantly downregulated in non-small cell lung cancer (NSCLC) cells undergoing TGF-β-induced EMT [12].

5.4 CircRNAs in Phenotypic Plasticity and Metabolic Switching

Unlocking phenotypic plasticity and non-mutated epigenetic reprogramming have recently been proposed as a hallmark of cancer. Evidence suggests that phenotypic plasticity, defined as the ability of cells to transition into cancer through dedifferentiation, inhibited differentiation, or transdifferentiation, is a critical component in the pathophysiology of certain malignancies. Numerous studies have highlighted the role of circRNAs in facilitating phenotypic plasticity [77]. For example, circSH2B3 acts as a sponge for hsa-miR-4640-5p, increasing IGF2BP2 expression. This mechanism grants cancer cells dedifferentiation potential and drives cancer progression [79].

Another hallmark of cancer is the alteration of energy metabolism to support tumor growth. During carcinogenesis, cells often shift to anaerobic glycolysis to meet their energy demands. This glycolytic reprogramming is associated with several well-known oncogenes. However, the role of circRNAs in metabolic switching remains poorly understood [11]. A significant study found that circRPN2 promotes metabolic alterations favoring anaerobic glycolysis by influencing ENO1-mediated AKT/mTOR signaling [80]. This discovery underscores the importance of circRNAs in a crucial and rate-limiting process of energy supply within cancer cells.

5.5 CirRNAs and Cancer-Associated Chromosomal Translocations

A group of fusion circRNAs has recently been identified in cancer cells, arising from abnormal chromosomal translocations within the exons of different genes [36]. Cancer-associated chromosomal translocations rearrange specific non-homologous chromosomes, joining two otherwise distinct genes and resulting in the formation of a ‘fusion gene’ [81]. Oncogenic fusion proteins encoded by these fusion genes have been shown to play a causal role in carcinogenesis. Alongside fusion proteins, cancer-associated chromosomal translocations also produce fusion circRNAs. J. Guarnerio and colleagues identified two abnormal fusion circRNAs, f-circM9 and f-circPR, generated through chromosomal translocation. These fusion circRNAs have been linked to the development and progression of hematological malignancies. Moreover, the expression of f-circRNAs is crucial for the survival of cancer cells and their ability to resist treatment, highlighting their significant role in cancer biology [35]. In mouse embryonic fibroblasts, fusion circRNAs f-circPR and f-circM9_1 independently promote leukemia progression by increasing cell proliferation, suppressing apoptosis, and inducing resistance to arsenic trioxide (ATO), irrespective of their linear transcript or fusion protein products [82].

5.6 CircRNA as a Potential Target for Immunotherapy

Tumor immunotherapy, encompassing cellular therapy, checkpoint blockades, tumor vaccines, and cytokine administration, has gained increasing prominence. However, due to the heterogeneous nature of tumors, immunotherapy outcomes remain suboptimal and often lead to side effects. Studies have highlighted the role of certain ncRNAs, such as miRNAs, in inducing tumor immunity. Yet, circRNAs have not been extensively studied in regulating tumor immunity or explored for their potential clinical applications [83]. CircRNAs may expand the range of 'druggable' targets, offering new therapeutic opportunities [84]. Their expression profiles vary not only across different malignancies but also at various stages of immune responses to tumors. This dysregulated expression is notably significant in relation to different organ-specific cancers and their responses to immune therapies. Some strategies involve monitoring tumor stages by evaluating circRNA expression during immunotherapy [41].

Additionally, circRNAs have been proposed as novel tumor antigens, potentially facilitating cell-to-cell communication among anti-tumor immune components, thus presenting a promising target for immunotherapy [27]. An intriguing study by Zhang et al. identified elevated ciRS-7 levels in colorectal cancer. Higher ciRS-7 expression was associated with advanced tumor stages (II to IV), lymph node involvement, and distant metastases, all indicative of poorer tumor immunity [22]. These findings suggest that ciRS-7 may serve as a biomarker for tumor immune status and could be explored across various cancer types for its potential in cancer immunotherapy. Furthermore, recent research has identified enzymes capable of degrading circRNAs, which could impact their stability and function [85]. For instance, engineered circRNAs are being explored as platforms for RNA-based vaccines in cancer treatment, leveraging their stability and translational capabilities [86].

Exosomal circRNAs act as critical mediators of intercellular communication within the tumor microenvironment. Employing the circRNA-miRNA-mRNA axis, they selectively bind and transport tumor-specific miRNAs or mRNAs, facilitating their transfer between carcinoma cells and immunocytes. This exosomal encapsulation not only stabilizes miRNAs during intercellular transport [83] but also ensures their targeted delivery. Upon fusion with recipient immunocytes, the released circRNA cargo profoundly modulates tumor immunity. Notably, exosomal delivery of miRNA-155 has been shown to potentiate cancer immunotherapies by augmenting the cytotoxic activity of tumor-specific CD8 + T cells. Consequently, targeting exosomal circRNAs represents a compelling avenue for the development of next-generation tumor immunotherapeutic interventions [87].

5.7 CircRNAs in Predicting Response to Chemoradiotherapy

Growing data suggests that circRNAs are highly associated with tumor chemotherapy resistance. They could be critical in the development and the strategy to control this resistance [12, 88]. The amount of DNA damage in cancer cells, their capacity to balance the expression of genes linked to apoptosis induction and inhibition,

the expression level of genes controlling the induction of cell cycle arrest, and their DNA repair mechanism all affect how sensitive they are to radiation. Cancer cells resistant to radiotherapy tend to suppress cell death and increase DNA damage repair. The dysregulated gene expression in resistant cells is intimately connected to radiation adaptation. As mentioned, ncRNAs are distinguished for their function in controlling gene expression in cancer cells, particularly the regulatory ncRNAs. Because they play such a significant role, ncRNAs are thought to be related to radiation resistance and may control how sensitive cells can be to radiotherapy [89]. The inclusion of circRNAs in chemoresistance in several types of cancer has also been reported [90]. The underlying mechanisms of circRNA's implication in this procedure include drug efflux, apoptosis, glycolysis, interference with TME, autophagy, and DNA damage repair dysfunction, among others. Some other mechanisms still need to be explored further [88] (Fig. 5). Drug efflux, facilitated by ATP-binding cassette (ABC) transporters, is a critical mechanism of multidrug resistance (MDR) in cancer. Recent studies demonstrate that circRNAs can modulate this process. Specifically, circ_0076305 has been identified as a key regulator of cisplatin resistance in non-small cell lung cancer (NSCLC), functioning by sponging miR-186-5p and consequently upregulating the expression of the ABCC1 efflux transporter [91]. By modulating the balance of pro- and anti-apoptotic proteins, circRNAs play a role in drug resistance. For instance, circAMOTL1 confers paclitaxel resistance in breast cancer by regulating AKT and its downstream effectors, including the pro-apoptotic

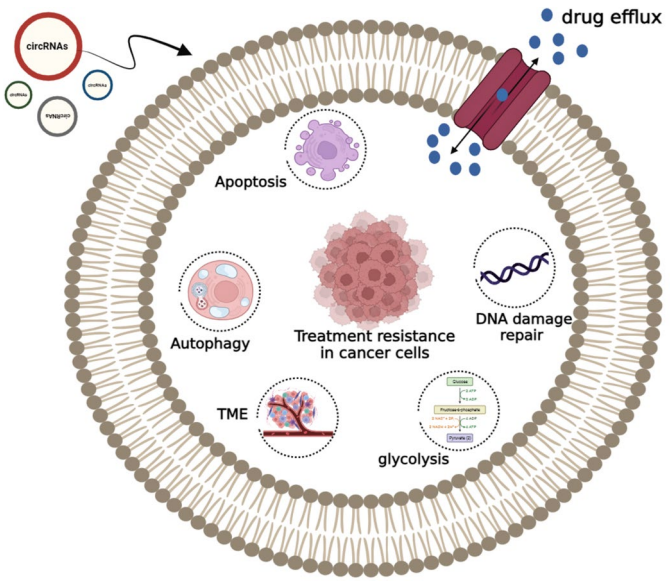


Fig. 5 The underlying mechanisms of circRNAs involved in chemoresistance in different types of cancers. By affecting cell apoptosis, drug efflux, autophagy, DNA damage repair, cell glycolysis, and epithelial-mesenchymal transition, circRNAs induce resistance to anti-tumor drugs in various types of cancer

BAX and BAK and the anti-apoptotic BCL-2 [92]. CircRNAs can contribute to chemotherapy resistance by regulating tumor cell glycolysis. For example, silencing circ_0008928 in cisplatin-resistant NSCLC cells increases cisplatin sensitivity and inhibits tumor progression and glycolysis by upregulating miR-488 and downregulating HK2 [93]. The circular RNA hsa_circ_0085131 contributes to resistance against cisplatin in NSCLC and doxorubicin in breast cancer by acting as a ceRNA. This action increases the expression of ATG7, a key protein in autophagy, thereby enhancing drug resistance [94]. CircAKT3 promotes cisplatin resistance in gastric cancer by both increasing the cancer cell's ability to repair DNA damage and suppressing their apoptosis [95].

It is understood that circRNAs may affect cell apoptosis and how responsive cancer cells are to radiation. The main function of lncRNAs and circRNAs to induce radioresistance is reducing the impact of specific miRNAs, which may bind to lncRNAs and circRNAs through base-pairing principles [89]. It has been found that circRNAs were differently expressed between parental control cells and 5-fluorouracil (5FU)-based chemoradiation-resistant colorectal cancer [CRC] cells using circRNA microarray analysis. Three of these circRNAs, including has_circ_0007031, has_circ_0000504, and has_circ_0007006, had overexpression in chemoradiation-resistant CRC cells. This variable expression was further validated by qRT-PCR, demonstrating their potential for chemoradiation resistance prediction and prevention in CRC [96]. Additionally, radioresistance of esophageal cancer and chemotherapy resistance of acute myeloid leukemia and breast cancer are found to be related to differential expression of circRNAs. These significant findings suggest that circRNAs can serve as biomarkers to monitor tolerance to cancer therapy [97]. Besides, they are susceptible target points to apply for conjunctive cancer therapy against drug resistance.

6 CircRNA Research Database

Researchers have recently devoted considerable effort to studying circRNAs, making the development of circular RNA databases essential. These databases, which include comprehensive annotations of protein-coding capabilities, significantly facilitate research and clinical applications related to circRNAs [98]. With rapid advancements in bioinformatics, the establishment and enhancement of various useful databases are anticipated. To date, investigations in this area of circRNA research, including sequence analysis, simulation, and docking studies, show great potential and demand. A selection of up-to-date databases for circRNA research is presented in Table 2.

Table 2 Database for circRNA research

Type of database		Website	Function	Refs
1	circRNADb	http://reprod.njmu.edu.cn/cgi-bin/circrnadb/circRNADb.php	providing comprehensive details on circRNAs, including exon splicing, IRES, and ORF	https://doi.org/10.1038/srep34985
2	circnet	http://circnet.mbc.nctu.edu.tw/	demonstrating the relationship between circRNAs, miRNAs, and genes	https://doi.org/10.1093/gigascience/gix118
3	ribocirc	http://www.ribocirc.com/index.html	A comprehensive repository of computationally predicted ribosome-associated circRNAs (Ribo-circRNAs)	https://doi.org/10.1186/s13059-021-02300-7
4	circinteractome	http://circinteractome.nia.nih.gov/	performing a bioinformatic investigation of the circRNAs' binding locations	https://doi.org/10.1038/s41419-018-0503-3
5	CSCD	http://gb.whu.edu.cn/CSCD/	circRNA, MRE, RBP, and associated gene variable splicing frequency in cells can all be predicted	https://doi.org/10.1093/nar/gkx891
6	TSCD	http://gb.whu.edu.cn/TSCD/	Provide a global view of tissue-specific circRNA in main tissues of human and mouse	https://doi.org/10.1093/bib/bbw081
7	circRNADisease	http://cgga.org.cn:9091/circRNADisease	circRNA and illness associations with evidence from experiments	https://doi.org/10.3390/ijms19020480
8	exoRBase	http://www.exorbase.org/	79,084 circRNAs were found in human blood exosomes, with information on their annotation, expression level, and potential originating tissues	https://doi.org/10.1093/nar/gkab1085
9	circpedia	http://www.picb.ac.cn/rnomics/circpedia/	circRNA annotation from six different species	https://doi.org/10.1016/j.gpb.2018.08.001
10	circbase	http://www.circbase.org/	circRNA data from several species is being offered	https://doi.org/10.1261/rna.043687.113
11	CircInteractome	http://circinteractome.nia.nih.gov/	Interacting miRNAs and RNA-binding proteins of circRNAs	https://doi.org/10.1080/15476286.2015.1128065

Table 2 (continued)

Type of database		Website	Function	Refs
12	circAtlas	https://ngdc.cncb.ac.cn/circatlas/	Incorporating the most comprehensive circRNAs and their functional and expression profiles in vertebrates	https://doi.org/10.1186/s13059-020-02018-y
13	circad	https://clingen.igib.res.in/circad/index.html	Circad is the most comprehensive and updated database of disease associated circular RNAs	https://doi.org/10.1093/database/baaa019
14	CircFunBase	https://bis.zju.edu.cn/CircFunBase/	Provide a high-quality functional circRNA resource including experimentally validated and computationally predicted functions	https://doi.org/10.1093/database/baz003
15	circbank	http://www.circbank.cn/index.html	is a comprehensive database of human circRNA that includes more than 140,000 annotated human circRNAs from various sources	https://doi.org/10.1080/15476286.2019.1600395
16	MiOncoCirc	https://mioncocirc.github.io/	It is the first extensive clinical, cancer-centric resource of circRNAs	https://doi.org/10.3389/fonc.2020.523342
17	circR2Disease	https://bio.tools/circR2Disease	Predicting circRNA-Disease Associations Based on Improved Collaboration Filtering Recommendation System With Multiple Data	https://doi.org/10.1093/database/bay044

7 Conclusion and Perspectives

CircRNA molecules interact with RNA-binding proteins, function as miRNA molecular sponges, and regulate gene transcription. However, several mechanisms of action remain unidentified and require further investigation. It is now evident that dysregulated circRNAs in various body fluids, such as urine and cerebrospinal fluid, may serve as effective non-invasive biomarkers for cancer detection. The discovery and functional analysis of these novel RNA molecules have not only enhanced our understanding of the complexity of eukaryotic transcriptomes and non-coding RNAs but also introduced innovative approaches and tools for diagnosing and treating human diseases. Recent evidence strongly supports the association between global circRNA expression profiles and tumorigenesis, with potential differentiation among specific cancer types. In conclusion, circRNAs hold great promise as novel biomarkers for cancer detection, therapy, and prognosis monitoring. They exhibit significant potential for broad clinical application in the future, with each type of circRNA and malignancy offering vast opportunities for further research.

Further elucidation of the molecular mechanisms underlying circRNA functions in cancer is crucial for designing targeted interventions. This includes understanding how circRNAs interact with other non-coding RNAs and proteins to modulate cancer hallmarks such as proliferation, metastasis, and drug resistance. Despite the potential of circRNAs, challenges such as specificity, sensitivity, and the complexity of circRNA interactions in different cancer types must be addressed. Overcoming these challenges will require interdisciplinary collaboration, innovative solutions, and a commitment to advancing our understanding of circRNA biology.

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