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Functional Roles of Circular RNAs in Tumorigenesis and Clinical Applications

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Abstract: Circular RNAs (circRNAs) are a recently recognized group of RNA molecules with a closed loop structure, lacking a 5' cap and a 3' poly(A) tail. Once thought to be splicing errors, they are now known for their stability, conservation, and specific expression in different cell types. Research has shown that circRNAs play important roles in cancer development and progression. This review summarizes current knowledge about circRNA formation, properties, and functions in cancer. We describe how circRNAs can act as oncogenes or tumor suppressors by sponging microRNAs, interacting with RNA-binding proteins, regulating transcription, or being translated into peptides. We also list examples of circRNAs altered in cancers such as glioblastoma, lung, breast, gastric, and colorectal, and explain how they affect key cancer traits like uncontrolled growth, evading growth suppression, spreading, and forming new blood vessels. In addition, we discuss the strong potential of circRNAs as clinical tools. Because they are stable and found in body fluids like blood and saliva, circRNAs could serve as non-invasive biomarkers for early cancer detection, prognosis, and monitoring treatment response. Finally, we consider targeting harmful circRNAs or restoring beneficial ones as new cancer therapies, and outline the challenges and future directions in this fast-moving field.

Keywords: *Circular RNA (circRNA), Tumorigenesis, Biomarker, microRNA Sponge, Non-coding RNA, Cancer Therapeutics, Liquid Biopsy, Gene Regulation*

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1. Introduction

The discovery that much of the human genome produces RNA that does not code for proteins has changed our understanding of molecular biology. Among these non-coding RNAs, circular RNAs (circRNAs) have become a key focus in cancer research. First seen in RNA viruses and later in eukaryotic cells, they were once thought to be rare splicing mistakes. Advances in RNA sequencing and bioinformatics have revealed thousands of circRNAs, showing they are a large, stable, and conserved group with important regulatory roles (Memczak et al., 2013; Salzman et al., 2012).

CircRNAs are formed by a non-canonical splicing event called "back-splicing," where a downstream 5' splice donor site is covalently linked to an upstream 3' splice acceptor site, resulting in a continuous, closed loop structure. This unique configuration renders them resistant to degradation by RNA exonucleases, conferring remarkable stability and often a longer half-life than their linear counterparts. Initially, the function of circRNAs was enigmatic. The landmark discovery that the cerebellar degeneration-related protein 1 antisense transcript (CDR1as) acts as a potent sponge for miR-7 unveiled a primary mechanism of action: sequestration

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of miRNAs, thereby derepressing miRNA target genes (Hansen et al., 2013).

Further studies have shown that circRNAs have diverse functions. They can bind RNA-binding proteins and change their activity, help regulate transcription by interacting with RNA polymerase II, and serve as templates to make small proteins or peptides, despite lacking the usual cap structure (Legnini et al., 2017). Changes in circRNA levels are now often seen in human diseases, especially cancer. In tumors, circRNAs are often present at different levels than in normal tissues, and they can act as oncogenes or tumor suppressors, affecting many aspects of cancer development.

This review brings together current knowledge about how circRNAs function in cancer. We begin by examining how circRNAs are made and their main features. Next, we discuss how they control gene expression and contribute to cancer, using examples from several cancer types. We also focus on their potential clinical use, especially as biomarkers in liquid biopsies and as new treatment targets. Finally, we discuss the main challenges and future directions for circRNA research, and how these molecules might become part of cancer care.

2. Biogenesis, Characteristics, and Detection of CircRNAs

Understanding the unique biology of circRNAs is fundamental to appreciating their role in disease.

2.1. Mechanisms of Biogenesis

The formation of circRNAs is a co-transcriptional process primarily driven by back-splicing, which competes with canonical linear splicing. Three main models have been proposed (Figure 1):

Lariat-Driven Circularization: This model involves the formation of a lariat structure during splicing that contains exons. If the 3' tail of the lariat (the branch point) is brought into proximity with a downstream 3' splice site, back-splicing can occur, resulting in an exon-containing circRNA (ecircRNA) and a lariat containing introns.

Intron-Pairing-Driven Circularization: This is the predominant model. Complementary sequences within flanking introns, such as Alu repeats or other inverted repeat elements, base-pair with each other, bringing the upstream and downstream splice sites into close proximity. This facilitates the direct back-splicing event, looping out the intervening exons to form a circRNA.

RNA-Binding Protein (RBP)-Driven Circularization: Specific RBPs, such as Muscleblind (MBL) and Quaking (QKI), can dimerize and bridge the flanking introns, acting as a protein scaffold to promote back-splicing and circRNA formation.

Most circRNAs are derived from exonic sequences (ecircRNAs), but circular intronic RNAs (ciRNAs) and exon-intron circRNAs (EIciRNAs) also exist and have distinct nuclear functions.

2.2. Key Characteristics of CircRNAs

Covalently Closed Loop: The defining feature, lacking free ends.

High Stability: Resistance to RNase R exonuclease digestion makes them exceptionally stable, with half-lives exceeding 48 hours in some cases, compared to a few hours for linear mRNAs.

Conservation: Many circRNAs are evolutionarily conserved across species, suggesting important biological functions.

Cell-Type, Tissue-, and Development-Specific Expression: CircRNA expression is highly specific to cell type and developmental stage, making them ideal candidates for disease-specific biomarkers.

2.3. Detection and Validation Methods

The unique structure of circRNAs necessitates specific detection methods. RNA-Seq with RNase R treatment enriches for circRNAs and allows for genome-wide discovery through algorithms that identify back-splicing junction

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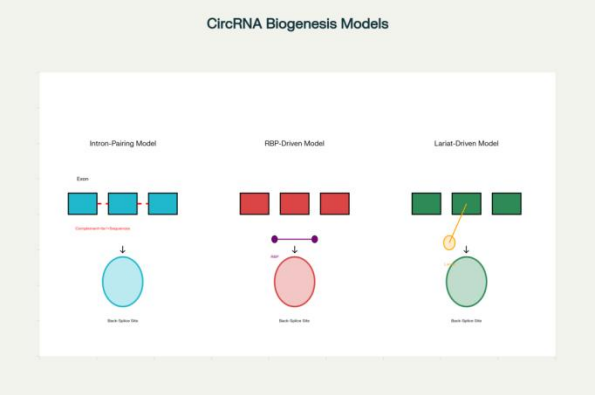
(BSJ) reads. Validation is typically performed using:

Divergent Primer PCR: Primers that face away from each other are designed to span the BSJ, allowing for specific amplification of the circular, but not the linear, transcript.

Northern Blotting: Can distinguish circRNAs based on their size and resistance to digestion.

Fluorescence In Situ Hybridization (FISH): Used to visualize the subcellular localization of circRNAs.

Figure 1. Models of circRNA Biogenesis.



(1) Intron-Pairing-Driven: Complementary sequences (e.g., Alu repeats) in flanking introns base-pair, bringing splice sites together for back-splicing. (2) RBP-Driven: Dimerizing RNA-binding proteins (RBPs) bridge the introns to facilitate circularization. (3) Lariat-Driven: A lariat structure formed during splicing undergoes internal back-splicing to form a circRNA.

3. Multifaceted Functional Mechanisms in Tumorigenesis

CircRNAs influence cancer hallmarks through a diverse array of molecular mechanisms (Figure 2).

3.1. miRNA Sponging

This is the most extensively characterized function. CircRNAs can act as competitive endogenous RNAs (ceRNAs) by harboring multiple binding sites for a specific miRNA, sequestering it and preventing it from repressing its target mRNAs. For example:

ciRS-7 (CDR1as) sponges miR-7, a tumor suppressor miRNA that targets oncogenes like EGFR and RAF1. High ciRS-7 expression promotes growth and invasion in glioblastoma and lung cancer.

circHIPK3 sponges multiple miRNAs, including miR-124, to promote proliferation in a variety of cancers.

3.2. Interactions with RNA-Binding Proteins (RBPs)

CircRNAs can function as protein sponges, decoys, or scaffolds.

Sponge/Decoy: circFoxo3 can bind to the anti-senescence proteins ID-1 and E2F1, as well as the anti-stress proteins FAK and HIF1Î±, preventing their function and promoting cellular senescence and apoptosis in breast cancer.

Scaffold: circACC1 facilitates the formation of a ternary complex between the metabolic regulators AMPK Î² and Î³ subunits, stabilizing them and enhancing their activity to promote glycolysis and tumor survival under energy stress.

3.3. Regulation of Transcription

Nuclear-retained circRNAs, particularly EIciRNAs, can regulate the transcription of their parental genes. For instance, circEIF3J and circPAIP2 interact with the U1 small nuclear ribonucleoprotein (snRNP) and RNA Pol II at the promoters of their parental genes, enhancing their transcription.

3.4. Translation of Functional Peptides

Although considered non-coding, some circRNAs contain an internal ribosome entry site (IRES) and an open reading frame (ORF), enabling cap-independent translation. These circRNA-derived peptides can have significant roles in cancer.

circFNDC3B was found to encode a protein that inhibits the progression of bladder cancer.

circSHPRH encodes a protein termed SHPRH-146aa, which protects full-length

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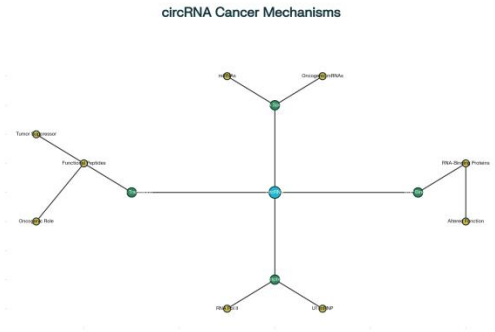
SHPRH from degradation and functions as a tumor suppressor in glioblastoma.

Figure 2. Multifaceted Functional Mechanisms of circRNAs in Cancer.



CircRNAs can: (1) Sponge miRNAs in the cytoplasm, derepressing oncogenic mRNAs. (2) Bind and sequester RNA-binding proteins (RBPs), altering their function. (3) In the nucleus, regulate transcription by interacting with Pol II and U1 snRNP. (4) Be translated into functional peptides that exert tumor-suppressive or oncogenic functions.

4. Dysregulation of CircRNAs in Specific Cancers

The context-dependent role of circRNAs is evident across cancer types, where they can act as either oncogenes or tumor suppressors (Table 1).

Table 1: Examples of Dysregulated circRNAs in Human Cancers.

circRNA	Cancer Type	Expression	Primary Mechanism	Functional Role
ciRS-7	Glioblastoma, NSCLC	Upregulated	Sponges miR-7	Oncogene: Activates EGFR/RAF1 pathway
circHIPK3	Liver, Lung, Colorectal Cancer (CRC)	Upregulated	Sponges miR-124, miR-558	Oncogene: Promotes proliferation, angiogenesis
circPVT1	Gastric, Oral Squamous Cell Carcinoma (OSCC)	Upregulated	Sponges miR-125 family; acts as a protein scaffold	Oncogene: Promotes proliferation and chemo-resistance
circFoxo3	Breast, Bladder	Downregulated	Binds and sequesters anti-senescence proteins (ID-1, E2F1)	Tumor Suppressor: Induces senescence and apoptosis
circZKSCAN1	Liver Cancer	Downregulated	Protein scaffolding (unknown partners)	Tumor Suppressor: Inhibits migration and invasion
circ-DNMT1	Breast Cancer	Upregulated	Binds to AUF1 and p53, promoting their interaction	Oncogene: Promotes tumorigenesis and autophagy
circ-PVT1	OSCC	Upregulated	Sponges miR-497-5p	Oncogene: Upregulates GALNT7, promoting growth

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Abbreviations: NSCLC (Non-Small Cell Lung Cancer), CRC (Colorectal Cancer), OSCC (Oral Squamous Cell Carcinoma).

5. Clinical Applications: From Biomarkers to Therapeutics

The unique properties of circRNAs position them as powerful tools for clinical oncology.

5.1. circRNAs as Diagnostic and Prognostic Biomarkers

The stability, specificity, and detectability of circRNAs in bodily fluids make them superior candidates for liquid biopsies.

Early Diagnosis: Panels of circRNAs (e.g., a combination of hsa_circ_0000190, hsa_circ_0000745) in plasma have shown high sensitivity and specificity for detecting gastric cancer, outperforming traditional protein biomarkers like CEA and CA19-9.

Prognostic Stratification: High levels of circPVT1 in plasma are associated with poor overall survival in gastric cancer and can serve as an independent prognostic factor.

Monitoring Treatment Response: Changes in the levels of specific circRNAs in serum can reflect tumor burden and response to chemotherapy or targeted therapy, allowing for real-time adjustment of treatment regimens.

5.2. circRNAs as Therapeutic Targets and Agents

The functional centrality of many circRNAs in signaling pathways makes them attractive therapeutic nodes.

Targeting Oncogenic circRNAs: siRNA, antisense oligonucleotides (ASOs), or small molecules can be designed to specifically target and degrade oncogenic circRNAs. For example, knocking down circHIPK3 with ASOs has been shown to suppress tumor growth in mouse models.

Restoring Tumor-Suppressive circRNAs: Synthetic circRNAs mimicking tumor-suppressive functions could be delivered using nanoparticle-based systems to restore lost functions and inhibit tumor progression.

circRNA-Based Vaccines: The stable, non-immunogenic nature of circRNAs makes them an exciting platform for protein expression in vivo . Engineering synthetic circRNAs to encode tumor-specific antigens is a promising avenue for cancer immunotherapy.

6. Discussion

The translation of circRNA biology from bench to bedside, while promising, faces several significant hurdles.

Technical and Biological Challenges: A primary issue is the accurate and cost-effective quantification of circRNAs in complex clinical samples, distinguishing them from abundant linear isoforms. The functional annotation of most identified circRNAs remains incomplete; we have only scratched the surface of their mechanistic diversity. Delivering circRNA-targeting therapies or therapeutic circRNAs to specific tissues with high efficiency and low off-target effects also remains a major pharmacological challenge.

Context-Dependency and Complexity: The function of a circRNA can be highly context-dependent, acting as an oncogene in one tissue and a tumor suppressor in another. This complexity requires a deep understanding of the specific cellular environment before considering therapeutic intervention. The interplay between circRNAs and other components of the cellular RNA network (the "competing endogenous RNA" network) adds another layer of complexity that must be deciphered.

Future Directions: The future of circRNA research lies in the integration of multi-omics data (circRNA-seq, RBP-interactome, proteomics) to build comprehensive functional networks. The development of more sophisticated in vivo delivery systems, such as engineered extracellular vesicles, will be crucial for therapeutic applications. Large-scale, prospective clinical trials are urgently

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needed to validate the utility of circRNA biomarkers in diverse patient populations. Finally, exploring the role of circRNAs in the tumor microenvironment and therapy resistance will open new avenues for combination treatments.

7. Conclusion

Circular RNAs were once thought unimportant, but are now seen as key players in cancer biology. Their unique formation and stability, along with roles such as sponging microRNAs and making proteins, allow them to control important cancer pathways. Changes in circRNA levels are common in many cancers, showing their importance. Because they can be found in blood and other body fluids, circRNAs could become powerful biomarkers for diagnosing, predicting, and monitoring cancer without invasive procedures. Although challenges remain, ongoing research and new RNA therapies make it more likely that circRNAs will become a regular part of cancer care, bringing new possibilities for diagnosis and treatment.

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