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*Article*

# Circular RNAs in Tumor Therapy

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**Abstract:** Contrary to the common belief that circRNAs are "mistakes" in RNA splicing, mammalian cells really contain a large number of highly conserved circRNAs. CircRNAs may produce miRNA inhibitors that are stable and potent. Nevertheless, many questions regarding the role of circRNAs remain to be resolved. First off, circular RNAs have the same ability to stop the spread of cancer as long noncoding RNAs. Circular RNAs (circRNAs) are a subclass of non-coding RNAs that lack poly (A) tails on either the 3′ or 5′ ends. Over 100,000 genes are known to encode circRNAs. Clinical data indicates that circRNAs, which exhibit variable expression in several disorders, including cancer, may serve a regulatory role in some conditions and diseases. Recent studies demonstrate that As an endogenous competitive RNA, circRNA can control the invasion, growth, and other physiological functions of tumor cells. Additionally, some circRNAs located in the nucleus can regulate the translation of the parent gene by binding to RNA polymerase II.

**Keywords:** RNA, circRNAs, miRNA

## 1. Introduction

Sometimes referred to as "circRNAs," "circular RNAs" are physically stable, covalently closed circular RNA molecules. The circRNAs that exhibit tumor-suppressive characteristics could be potential targets for cancer treatments due to their significant involvement in the development and spread of cancer. In this instance, we examine our current knowledge of circRNA classification and provide an overview of the roles and mechanisms of circRNAs that restrict tumor growth in various forms of cancer. Circumstances covered include liver cancer (circARSP91, circADAMTS13, circADAMTS14, circMTO1, hsa_circ_0079299, and circC3P1), bladder cancer (circFNDC3B, circITCH, circHIPK3, circRNA-3, cdrlas, and circLPAR1), gastric cancer (circLARP4, circYAP1, hsa_cric_0000096, hsa_circ_0000993, and circPSMC3), breast cancer (circ_000911, hsa_circ_0072309, and circASS1), lung cancer (hsa_circ_0000977, circPTK2, circ_0001649, hsa_circ_100395, and circ_0006916), glioma (circ_0001946, circSHPRH, and circFBXW7), and colorectal cancer (circITGA7 and hsa_circ_0014717). These tumor-suppressive circRNAs may be useful as viable and effective treatment targets because of their physical stability. We also introduce a brand-new approach to circRNA classification. Depending on whether they can be translated or not, circRNAs are classified as noncoding or coding 2019 [1]. Recently, cRNAs, or named circ-RNAs, have garnered a lot of attention due to their important contributions to several areas of cancer biology. Furthermore, mounting data suggests that circular RNAs may play a role in the effective implementation of tailored cancer therapies. This brief study introduces CircRNAs, discusses their potential applications as therapeutic targets and biomarkers, and suggests potential targeted approaches. The obstacles that circ RNAs

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need to get beyond in order to be recognized as official accepted for use in a therapeutic setting. It is evident that our growing knowledge of circRNAs broadens our comprehension of the molecular makeup of cancer and offers a plethora of innovative treatment options [2].

A family of incredibly common endogenous RNAs known as circular RNAs (CrcRNAs) have a unique entire ring shape, are covalently closed, and do not have free 3′ or 5′ ends. Because the majority of circRNAs in the cytoplasm are resistant to RNase, they are highly abundant and robust. Circular RNAs (CrcRNAs) can be produced by a range of gene designs, mostly by the use of an alternate RNA splicing mechanism known as "back-splicing" [3], managed by canonical splice signals [4]. Sanger et al. completed a study in 1976 to examine circRNA's presence in viroid [5]. Over the next decades, numerous c RNAs discovered among human cells, but They were long believed to be nothing more than waste products of RNA splicing errors [3]. The transcriptional profile of the whole human genome was not made public until recently, owing to advancements in sequencing technology. When these substances became accessible, people were interested in them. CircRNAs play important roles that have been revealed by the breakthroughs in RNA sequencing and a number of efficient, targeted techniques to use RNA sequencing data in 2017 to identify and quantify circRNA expression throughout the genome [6].

Cell cycle regulation, proliferation, and apoptosis are just a few of the functional functions that circRNAs play. These activities are ultimately shaped by their unique features, which include wide distribution, stability, and expression specific to specific cell types and tissues [7], [8]. Posttranscriptional regulation is achieved via the function of the microRNA (miRNA) sponge [9], [10], round translation of pseudogenes produced from RNA [11], [12] and interaction with aberrantly expressed proteins roundRNAs have tumor-suppressive or oncogenic properties that affect the onset, progression, and spread of cancer as well as therapy resistance [13]. These substances are already proving to be an intriguing new area of research and a promising molecular target for cancer detection and therapy.

## 2. Discussion

### *2.1. All about circular RNAs*

A sizable Circular RNAs (circRNAs) are a class of RNAs. forms continuous loops that are covalently closed. In 1976, an RNA virus contained the first known circular RNA [14], [15]. Soon after, Hsu MT et al. discovered via electron microscopy that monkey renal CV-1 cells' cytoplasm included a circular shape of RNA [5]. In 1996, it was discovered that exons from RNA transcripts in human cells made up circRNAs [16]. Recent advances in sequencing technology, like as the RNA-seq method of next-generation sequencing, have led to the discovery of a growing number of circRNAs. Up to 30,000 different circRNAs have been discovered so far by scientists.

According to recent study, circRNAs—which were previously believed to be the unintentional consequence of transcriptional processing errors—now play a vital function in a wide range of biological processes [17]. CircRNAs perform a wide range of roles, including those of regulators of RNA binding protein (RBP) and miRNA sponges [18], which aid in regulating the expression of genes that code for proteins [19]. Peptides are even encoded by some circRNAs [20]. Therefore, circRNA abnormalities ought to have an impact on the emergence of numerous human illnesses, such as cancer [21]. Ribonucleases cannot cut circRNAs due to their unusual structures. This means that circRNA molecules can be found in the blood, urine, and tissues, in contrast to linear RNAs. The great promise of circRNAs as biomarkers for the detection of human cancer has been demonstrated by this feature.

### 2.2. The production for circular RNAs

Three types exist for RNAs; CircRNAs with retained-intron, exonic, and intrinsic sequences. Back splicing links upstream and downstream sequences in the opposite direction whereas certain sequences are conserved during the development of circRNAs, ultimately resulting in mature circRNA [22]. CircRNAs are highly abundant inside cells despite having a considerably lower back splicing efficiency than linear RNAs [17], which can be attributed to their stability and extended half-life [23]. Complementary intron matches are necessary for the first back splicing mechanism [24], and they are commonly seen during the exonic circRNA creation process. Special repeating sequences, like Alu and other short sequences, are present on both sides of CircRNAs constructed by this method [25], [26]. Following RNA precursor transcription, a circular pattern will be formed when repeating sequences, like Alu, are encouraged, since the exon sequences on either side of the cycling region complementarily match with each other. After that, U6 and U2 cause the spliceosome to attach to the cyclic RNA precursor. After that, it interacts with the protein complex and the U5 core to specifically remove the exon in the cycle area [27], [28]. Mature circRNA is formed at the same time that the connections between exon sequences are reversely severed.

An other process than that used to produce exonic circRNA is used to produce intronic circRNA. A 5′ splice site with GU-rich sequences and a branch point with C-rich sequences are necessary for intraonic circRNA production. The joining of the two pieces results in a back splice.

### 2.3. Development of circular RNAs

Many different mechanisms can lead to the formation of circRNAs, the majority of which are dependent on the origin of the donor transcript. Intergenic regions, exons, introns, or a combination of the two are potential origins of circRNAs [29], [30], [31]. Circular RNAs that are placed inside the nucleus are known as intronic circRNAs, and those that are located outside the nucleus are known as exon circRNAs [32].

### 2.4. Circular RNAs' biological roles

Discoveries of several circRNAs in various model species with diverse cell types have been made possible by RNA-seq research. Furthermore, it was demonstrated that many naturally occurring circRNAs included components of both AUG sites and internal ribosome entrance sites. Still, the time has come when although their biological functions are mostly unknown tiny percentage of circRNAs have been shown to translate in vivo. In 2019, researchers found that circRNAs function as microRNA (miRNA) sponges and can control transcription [33].

### 2.5. The roles of circular RNAs in cancer

It is well-established that cRNAs have several functions in the cancer, including growth suppression, initiation of invasion and metastasis, promotion of angiogenesis, and maintenance of proliferative signalling. Furthermore, abnormal cell cycle activity is a hallmark of malignancy [34], [35], [36]. Several examples below show that circRNAs are essential for cancer signalling pathway regulation, including phosphoinositide 3-kinase (PI3K) and Wnt/beta-catenin.

### 2.6. Circular RNAs' function in medication resistance

In contemporary oncology, medication therapy is a very successful and effective approach. Recent advancements in conventional procedures and the development of anticancer agents—which are essentially novel in terms of their mode of action—have allowed

it to become more capable. Targeted treatment, chemotherapy, and immunotherapy are now the three types of pharmacological therapy for cancers [37].

### *2.7. Circular RNAs in the metabolism of cancer*

The loss of oncosuppressor gene function and the enhanced function of oncogenes in tumour cells have been the primary goals of tumour formation research in the last several decades. Even while this paradigm predominates in tumour biology, it is increasingly clear that other factors contribute to carcinogenesis as well. It is now well-established that cancers resulting from genetic instability in 2020 are characterised by reprogramming of energy metabolism [38].

### *2.8. Circular RNAs' potential as cancer prognostic and diagnostic tools*

Numerous research teams have reported that cRNAs could serve as biomarkers for cancer detection and prognosis. cRNAs are preserved against exonuclease dissolution by their circular form, which also gives them a much longer half-life (approximately 48 hours compared to 10 hours for the parent mRNA) [39]. Moreover, they are reliably found in physiological fluids such as blood and saliva, or "liquid biopsies," which are samples of the body that can be taken non-invasively in order to perform diagnostics [39].

### *2.9. Targeting circular RNAs for treatment in cancer*

Cancer therapies may target both circRNAs that are carcinogenic and those that prevent tumor growth. Some circRNAs have a special reverse splicing junction sequence that allows them to be targeted without impacting the parental mRNA. Consequently, Ago2-mediated degradation of carcinogenic circRNAs may occur when small interfering RNAs (siRNAs) target those circRNAs. On the other hand, long-tail expression vectors can be used to ectopically create tumor-suppressive circRNAs [40].

## 3. Conclusion

Thousands of extremely conserved endogenous circRNAs have been discovered among mammals cells, despite the fact that circRNAs were earlier considered to be RNA splicing "mistakes". CircRNAs possess the potential to yield stable and effective miRNA inhibitors. Nevertheless, many questions regarding the role of circRNAs remain to be resolved. Firstly, circular RNAs has the same capacity to stop the growth of tumors as long noncoding RNAs.

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