**Role of Circular-RNAs in Cancer Diagnosis**

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**Abstract**

Circular RNA (circRNA) belongs to a class of endogenous single-stranded, non-coding closed circular RNA. CircRNAs are formed from pre-mRNAs, and biogenesis is regulated by protein-coding genes, RNA polymerase II (RNA pol II), and spliceosomal machinery. CircRNAs are stable molecules and serve as effective microRNAs and protein sponges respectively and play significant roles in regulating transcription and splicing. Despite their remarkable conservation and tissue-specific expression patterns, they often exhibit poor correlations with host gene expression. CircRNAs play a role in many physiological functions in cell cycle regulation, angiogenesis in tumors, haematological malignancies, and tumor-promoting Inflammation, and various important roles. Though the majority of endogenous circRNAs associated with cancer remain poorly understood, their numbers are steadily growing. In this chapter, we discuss biogenesis, its function in cancer, and its potential use as therapeutic targets, prognostic indicators, and diagnostic biomarkers in oncology.

**Keywords**: Circular RNA, stable molecules, microRNA sponges, cancer biomarkers, diagnosis.

1. **INTRODUCTION**

Circular RNAs (circRNAs) are a class of endogenous single-stranded closed circular RNA molecules that are created when hundreds of genes in eukaryotes undergo a covalently closed continuous loop by backsplicing or skipping events in their precursor mRNA. They lack 3' poly(A) tails and 5' end caps at ends, resistant to exonuclease RNase R and more durable than their corresponding linear RNA isoforms [21, 28]. Through the use of bioinformatics and high-throughput sequencing, it has become possible to identify the expression of circRNAs between species. They have important functions in controlling transcription and splicing and function as efficient microRNAs and protein sponges, respectively. Their remarkable stability, abundance, and evolutionary conservation across species are indicative of their distinct characteristics and wide range of physiological roles. The expression levels and functions of circular RNA are distinct from those of linear RNA isoforms. CircRNA expression, thus, may provide information about a condition that is not detectable through conventional RNA analysis. CircRNAs have a very low production efficiency, but because they are resistant to RNA exonucleases, they have a long half-life and can remain at stable levels in the body under normal circumstances. However, since endonucleases can break open circular RNA, RNA interference can be used to decrease the amount of circular RNA produced. During the development of cancer, abnormal expression of certain circRNAs is seen in specific tissues.

1. **Genesis of circRNAs**

circRNAs are formed from pre-mRNAs, and biogenesis is regulated by protein-coding genes, RNA polymerase II (RNA pol II), and spliceosomal machinery. Currently, two models explain how circRNAs form: the direct back-splicing model and the exon skipping or lariat intermediate model [10In the exon skipping or lariat intermediate model, canonical splicing takes place initially, resulting in a linear RNA that has exons skipped. By using backsplicing to determine the creation of circRNA, the lengthy intron lariat containing these skipped exons is created. According to the direct back-splicing paradigm, processing begins with back-splicing to identify a circRNA and an exon-intron (s)-exon intermediate. These can then be processed to create a linear RNA with exons skipped[10, 21, 28]. The biogenesis of circRNAs is also regulated by splicing factors and RNA-binding proteins [2]. The splicing factor muscleblind (MBL) can be involved. MBL promotes the circularization of the circular RNA circMBL, binding to the introns flanking the circRNA generated from the second exon of its RNA [2]. CircRNA biogenesis's mechanisms of action, however, are not entirely understood. CircRNAs can be formed from introns, intergenic regions, antisense RNAs, 3' UTRs, 5' UTRs, and the exons of coding areas [11]. Exonic circRNAs (ecircRNAs), which make up more than 80% of all known circRNAs, are among them. Using this technique, high-throughput sequencing has discovered three more types of circular RNAs: tRNA intronic circRNAs (tricRNAs), which can splice into stable circRNA through pre-tRNA splicing; circular intronic RNAs (ciRNAs), which only contain introns; and exon-intron cirRNAs (EIciRNAs), which contain both introns and exons.

1. **Different Roles of circRNAs**
2. **Function of CircRNAs as miRNA Sponges:** MiRNAs are known to be important in several biological and pathological processes, including cancer. Through direct base-pairing to specific locations within mRNAs, circRNA influence gene expression [ 3, 4, 5]. The majority of circRNAs may function as competitive endogenous RNAs and modulators of miRNA activity by competing for these regions because they are mainly located in the cytoplasm. According to Li et al. [24], cirRNA itchy E3 ubiquitin protein ligase (cir-ITCH) functions as a miRNA sponge to increase ITCH levels and prevent tumor growth. According to Chen et al. [8] by acting as a sponge for the miR-125 family, circPVT1 might promote cell division. Significantly, other studies have indicated that ciRS-7 has, by functioning as a designated miR-7 inhibitor or sponge and increasing the quantities of miR-7-targeted transcripts while decreasing miR-7 activity, has conceptually changed our view of the mechanisms of miRNA networks.
3. **Role of CircRNAs From Translocations Have Carcinogenic Function:** Guarnerio et al. state that transcription of fusion genes produced by chromosomal translocations can result in CircRNAs. [13]. Fusion-circRNAs (f-circRNAs) are circular RNAs derived from several tumor-associated translocations, including mixed lineage leukemia (MLL)-AF9 in acute myeloid leukemia (AML) and promyelocytic leukemia-retinoic acid receptor-alpha (PML-RARA) in promyelocytic leukemia. According to the f-circRNAs (f-circPR and f-circM9), these f-circRNAs have pro-proliferative and pro-oncogenic effects and are physiologically active. Guarnerio et al. [13]. They may enhance cell survival, aid in cellular transformation, and facilitate resistance to therapy. The suppression of f-circRNAs generated from MLL-AF9 resulted in an increase in p27 and p21 expression as well as the induction of apoptosis in THP1 cells, indicating that f-circRNAs may also be essential for cell viability [1].
4. **Role in the Hallmarks of Cancer Sustaining Proliferative Signaling:** CircRNAs may play a significant function in regulating long-term proliferative signals and the progression of cancer. Circ-FOXO3, which has decreased expression in tumors and may have an effect on the expression of FOXO3, p53, and PUMA, is one of the most successful experimental instances. Although endogenous circ-FOXO3 suppression can have the opposite impact as ectopic circ-FOXO3, it decreased the growth of tumors and increased mouse survival. The reduced formation of blood vessels may have contributed to the smaller tumors created by cells expressing circ-FOXO3, FOXO3, and FOXO3P in comparison to control cells. Alternatively, CDK2 (cyclin-dependent kinase 2) may be inhibited by the development of the ternary complex of circ-FOXO3-p21-CDK2, thereby stopping the cell cycle. Finding a proto-oncogenic circRNA (circ-PRKCI) in lung adenocarcinoma (LAC) required Qiu et al. [26] to merge bioinformatics analysis of altered circRNAs with localized copy-number changes.
5. **Role of circRNA from Evasion of Growth Suppressors:** Even though the majority of tumor suppressor genes encode proteins that help slow the growth of tumors, some cancers may grow more quickly if one or more of these "brakes" are absent. CircRNAs can support tumor suppressors by halting the growth of cancer cells in addition to these additional advantages. Hepatocellular carcinomas (HCC) ability to proliferate, migrate, and invade was strongly suppressed when circC3P1 was overexpressed. Through sponging miR-4641 in HCC cells, CircC3P1 may also promote PCK1 synthesis. The formation of tumors and the division of cells may be aided by the inhibition of the circZKSCAN1 and zinc finger with KRAB and SCAN domain 1 (ZKSCAN1) gene activities [33].
6. **Role in Enabling Replicative Immortality:** Tumor cells are known to be far more capable of multiplying than normal cells. circRNAs assembled in the nucleus to link with the genomic DNA's opposing strand. Circular RNA produces a DNA-RNA triple helix that prevents DNA replication. But as of right now, neither this theory nor this hallmark has any trustworthy outcomes.
7. **Role of circRNAs in** **tumor-promoting Inflammation:** Non-coding RNAs (ncRNAs) have been discovered to have significant functions in a range of cancer cells. These include miRNAs, lncRNAs, and circRNAs. Bioinformatics investigations by Bahn et al. led to the discovery of 422 circRNAs in human saliva after they ran a gene ontology analysis of the genes overlapping putative circRNAs in human chronic fatigue syndrome. Salivary circRNAs play a role in inflammatory responses and intercellular signaling as they were discovered to be considerably enriched in several closely related categories, including chemotaxis, the formation of T cell polarity, and integrin-mediated signaling pathways [36]. Alternatively, the proteolytic activation of inflammatory cytokines by caspase-1, such as IL-18 and IL-1b, may also play a role in the establishment of an inflammatory state [19]. Furthermore, compared to non-tumor tissues, osteosarcoma (OS) tissues express caspase-1 more significantly [19]. Taken together, the results of Jin et al. point to the possibility that caspase1/miR-214/circ-0016347, via pathways related to inflammation, maybe a major player in the development of OS.
8. **Role in the Activation of Invasion and Metastasis:** Human circRNAs have been found to aid in the invasion and development of cancer. Metastatic tumor cells express several circRNAs with preference. Using matched tumor colorectal and healthy tissue samples, Hsiao et al. [47] looked into several circRNAs that were particularly increased in cancer cells. In animal experiments, circCCDC66 knockdown lowered tumor development and malignant invasion, per a report by Xu et al. hsa\_circ\_000984 can function as a competing endogenous RNA (ceRNA) by competitively binding miR-106b, upregulating the expression of cyclin-dependent kinase 6 (CDK6), and promoting a malignant phenotype in tumor cells [31].
9. **Role in Induction of Angiogenesis**: Numerous research groups have looked at the impact of hypoxia on endothelial cells and the expression of circRNA since it is thought to play a major role in the beginning of angiogenesis. Hypoxia greatly alters several circRNAs, as shown by Boeckel et al. [6]. circRNA cZNF292 was one of these; in vitro, it was shown to exhibit proangiogenic properties and to be involved in the control of endothelial cell growth. Additionally, Li et al.[25] found that hsa\_circ\_0003575 silencing loss-of-function studies might encourage the growth and angiogenesis of human umbilical endothelial cells. According to Zhong et al. [42], upregulating circRNA-MYLK may have an impact on the signaling pathways of vascular endothelial growth factor A (VEGFA) and VEGF receptor 2 (VEGFR2). This could promote angiogenesis, metastasis, and growth in breast cancer models. According to Zhong et al. [42], upregulating circRNA-MYLK may have an impact on the signaling pathways of vascular endothelial growth factor A (VEGFA) and VEGF receptor 2 (VEGFR2). This could promote angiogenesis, metastasis, and growth in breast cancer models.
10. **CircRNAs as cancer biomarkers:**

CircRNAs' versatility, conservatism, tissue/cell specificity, and stability in expression patterns make them great choices for application as biomarkers [48, 49]. CircRNAs have been detected in human blood, saliva, and stomach fluids, suggesting that they could be utilized as disease biomarkers [50, 51]. Memczak et al. discovered that blood contains significant amounts of circRNA compared to linear RNA [50]. CircRNAs are expressed in high quantities in blood, in contrast to medium or low abundances of linear RNAs. Blood circRNA may therefore provide information on illness diagnosis that traditional RNA analysis is unable to provide. It has been shown that exosomes have at least twice as much circRNA as generating cells do. Bahn and colleagues found 422 circRNAs in human cell-free saliva by employing bioinformatics analysis, and they demonstrated that these circRNAs are involved in inflammatory responses and intercellular signaling [51]. Numerous studies that have recently examined the clinical application of circRNAs in cancer have shown that certain circRNAs not only outperform their corresponding mRNA in terms of stability and diagnostic value but also reflect the features of tumorigenesis at different stages, offering enormous potential for cancer diagnosis.

1. **CircRNAs biomarkers in cancer**

The expression, mechanism and function of different CircRNA in various tissues are discussed in below tables( file: Table 1, 2, 3,4).

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| **Table 1** |
| **Cancer**  | **Circular RNA** | **Expression** | **Function**  | **Mechanism**  | **Ref** |
| **Hepatocellular Carcinoma (HCC)** | circC3P1 | Down | tumor suppressor | stimulates phosphoenolpyruvate carboxykinase 1 expression through sponging of miR-4641 in HCC cells & significantly suppresses the proliferation of HCC cells | 37 |
| hsa\_circ\_0067531 | Down | - |  | 34 |
| hsa\_circ\_0004018 | Down | - | correlates with serum alpha-fetoprotein (AFP) level, tumor diameter, and differentiation | 12 |
| circRNA\_100338 | Up | - | functions as an endogenous sponge for miR-141-3pin HCG and high expression of circRNA\_100338 is closely associatedwith metastasis progression in HCC patients | 17 |
| circ\_000839 | Up | - | inversely correlates with miR-200b |  |
| circMTO1 | Down | tumor suppressor | suppresses HCC progression by acting as the sponge of oncogenic miR-9 to enhance p21 expression and serves as a prognostic factor for poor survival of patient | 46 |
| circZKSCAN1 | Down | tumor suppressor | mediates several cancer-related signaling pathways and inhibits cell proliferation, migration, and invasion | 33 |
| ciRS-7 | Down | - | High expression of ciRS-7 is significantly correlated with hepatic microvascular invasion, and AFP level, and thus partly related to the deterioration of HC | 30 |

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| **Table 2** |
| **Lung Adenocarcinoma (LAC)** | **Circular RNA** | **Expression** | **Function**  | **Mechanism**  | **Ref.** |
| circRNA\_102231 | up  | Oncogene | associated with advanced tumor, metastases (TNM), stage, lymph node metastasis, and poor overall survival of lung cancer patients and Induces lung cancer cell proliferation and invasion ability in vitro | 41 |
| circPRKCI | Up | Oncogene | functions as a sponge for both miR-545 and miR-589 and abrogates their suppression of the pro-tumorigenic transcription factor E2F7 51 promotes proliferation and tumorigenesis of LAC | 26 |
| hsa\_circ\_0013958 | Up | Oncogene | promotes cell proliferation and invasion, and suppresses cell apoptosis of LAC and functions as a sponge of miR-134, thus upregulating oncogenic cyclin D1 | 40 |

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| Table 3 |
| Bladder Cancer | Circular RNA | Expression | Function  | Mechanism  | Ref. |
|  | circRNA-MYLK | Down | Oncogene | function as ceRNA for miR-29a, which can contribute to EMT and the development of bladder cancer by activating the VEGFA/VEGFR2 pathway | 38 |
|  | circHIPK3 | Down | tumor suppressor | can abundantly sponge up miR-558 to suppress the expression of heparinase and may suppress angiogenesis and migration of bladdercancer cells | 23 |
|  | circTCF25 | Up | Oncogene | can downregulate miR-103-3p and miR-107, increase CDK6 expression, and promote proliferation in vitro and in vivo | 39 |
|  | circ-ITCH | Down | tumor suppressor | acts as tumor suppressor by a novel circ-ITCH/miR-17, miR-224/p21, and phosphatase and tensin homolog axis | 32 |

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| **Table 4** |
| **Gastric Cancer (GC)** | **Circular RNA** | **Expression** | **Function**  | **Mechanism**  | **Ref.** |
| hsa\_circ\_0000520 | Down | Oncogene | negatively associated with the TNM stage in GC plasma | 28 |
| hsa\_circ\_0047905 | Up | Oncogene | acts as a tumor promoter in the pathogenesis of GC | 21 |
| hsa\_circ\_0000745 | Down | - | associated with tumor differentiation and the expression level in plasma correlates with the TNM stage | 16 |

**VII. Conclusions**

CircRNAs are great targets for cancer and play a significant impact in human tumors as either promoters or suppressors of tumor growth. They don't prevent linear mRNA from being expressed. For clinical usage, the majority of circRNA indicators are currently too sensitive or specific. Though research on CircRNAs is still in its early stages, though they play a major impact. Larger sample numbers should be used in future studies, and long-term follow-up clinical data is needed for circRNA-based therapeutic and diagnostic techniques in cancer management.

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