Review

The Applied Biology & Chemistry Journal
https://www.theabcjournal.com
eISSN: 2582-8789

Bio-genesis and deregulation of circular ribonucleic acid and their role in human cancer

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Received December 03, 2020
Revised December 20, 2020
Accepted December 23, 2020
Published December 26, 2020

Abstract: RiboNucleic Acid (RNA) occupies the center position in the central dogma of molecular biology. These are the nucleotide with a ribose sugar and are found either in linear or circular form. The linear RNAs are of different types and include ribosomal RNA (rRNA), messenger RNA (mRNA), transfer RNA (t-RNA), small nuclear (snRNA) RNA, and very small/micro RNA (microRNAs). The circular (circRNA) RNA is a group of noncoding RNA, stable molecules, established recently and linked with the regulation of different genes, RNAs including microRNAs. The current understanding of these molecules suggests that these circRNAs are fairly conserved and show tissue-specific expression patterns. These molecules are connected with different pathogenic conditions and associated with verities of diseases, including cancer. CircRNAs are thus contributing to tumorigenesis, and these molecules show the potential to become future predictive biomarkers for diagnosis, prognosis and even can be targeted in personalized therapy. Hence, these bio-molecules will get exposed frequently, and their new cellular role will emerge, soon. This review outlines the current trend, limitations, and future potential of circRNA in cancer research.

Keywords: cancer; cancer hallmarks; circRNA; circRNA biogenesis; circRNA function; circular RNA

1. Introduction

Circular RNAs (circRNAs) were initially reported nearly forty-five years ago [1]. Originally, circRNAs were considered as errors of the regular RNA splicing process with uncertain biological importance. Electron microscopy revealed the presence of circRNAs in the cytoplasmic compartment of eukaryotic cells [2]. Of late thousands of genes are reported to produce these highly conserved, stable, and closed RNA circles. These new cellular roles for these circRNA molecules and these bio-molecules are recognized for their active role in gene expression and regulation [3]. These molecules are also found essential for normal cellular differentiation and tissue homeostasis. Often their deregulations are correlated with various disease pathogenesis [4-6].

CircRNAs are single-strand RNA molecules, and these do not get translated. As evident from literature, these circRNAs are not directly expressed via transcription, from cellular genes. But these are highly stable molecules with a long half-life in comparison to many other RNAs. These circRNAs are also lacked their open ends (5' and 3') and thus protected against exonucleolytic degradation.

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Furthermore, circRNAs are steady-state byproducts of mRNA (Fig. 1A) splicing [7] and are generated through defective and/or regulated alternative splicing. Evidence from other studies suggests that circRNAs are functionally important and well conserved. Many of the circRNAs found in humans were also detected as circularised orthologous exons in mice. These were found to be conserved in the codons (third position), in comparison to the exons that are not located in the circRNAs [5]. Biogenesis of circRNA begins with the base (nucleotide) pairing of 2 introns complementary to one another. Since the splice sites from these exon(s) approach close and facilitate the back splicing and biogenesis of the circRNAs (Fig. 1B), millions of circular noncoding RNAs can be produced from thousands of coding (protein) genes with non-canonical splicing. It is the splicing machinery that determines whether to generate a circRNA or a linear mRNA. Alteration of cis-regulatory (DNA/ RNA) elements (like the protein-interactive motifs or the inverted repeats), a small number of trans-acting RNA-interacting factors such as Adenosine Deaminase RNA Specific (ADAR), quaking, RNA binding protein (FUS), Heterogeneous nuclear ribonucleoprotein L (HNRNPL), and DExH-Box Helicase9 (DHX9) can influence circRNA regulation and expression and has been reported in various cancer types [8]. Chemical modifications of RNA (i.e. N6-methyladenosine, N1-methyladenosine, 5-methylcytosine, 5-hydroxymethylcytosine, pseudo-uridine, and inosine-to-adenine editing) are central in the control of non/coding RNA stability/ activity and frequently altered in cancer.

Citation: Mishra R (2020). Bio-genesis and deregulation of circular ribonucleic acid and their role in human cancer. *T Appl. Biol. Chem. J;* 1(2):83-94. https://doi.org/10.52679/tabcj.2020.0010

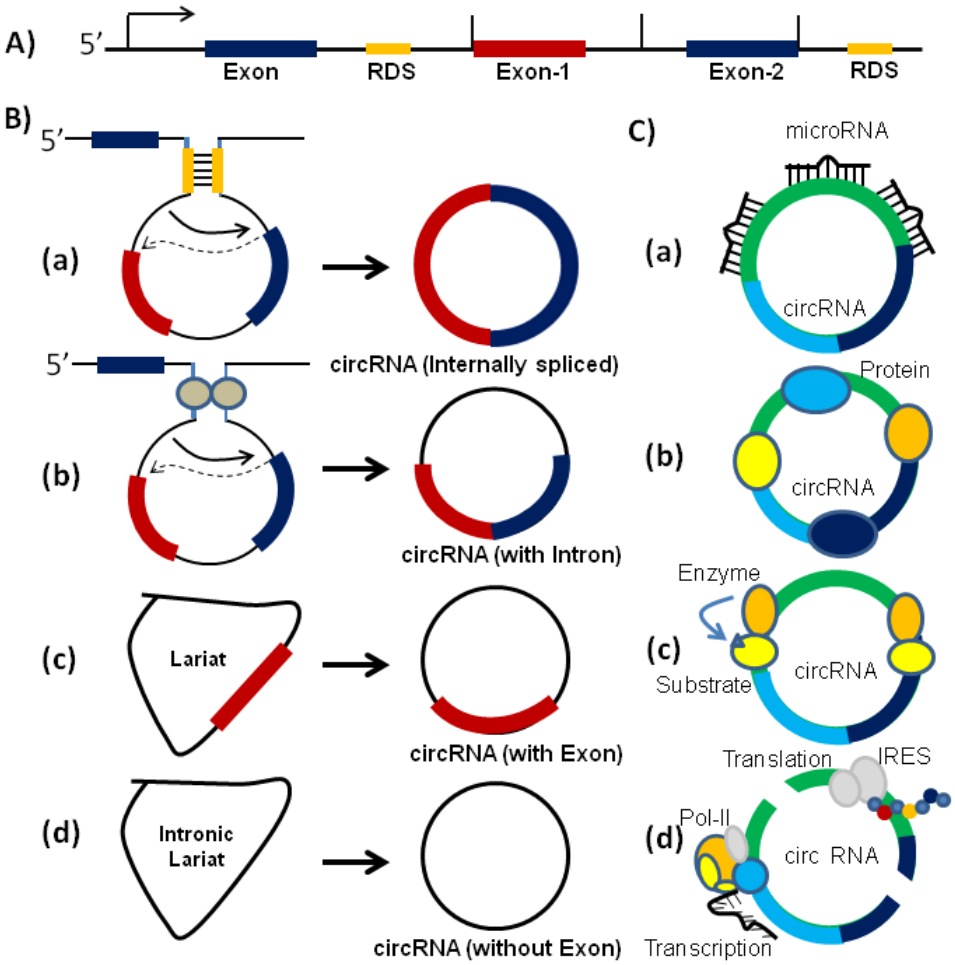

Figure 1: The biogenesis and function of circRNAs. (A) Hetero nuclear (hnRNA) RNA of most human genes with distinct exons, introns (equipped with long flanking sequences), inverted repeat elements (IRE), repetitive DNA sequences (RDS) and often found with trans-acting RBPs (RNA Binding Proteins). **(B)** Biogenesis of different types of circRNAs occur through back-splicing, and the long flanking introns with inverted repeat elements (IRE; like Alu-elements) and trans-acting RBPs enhance this process. During back-splicing, an upstream branch point (towards 5'end) attacks a downstream site, which then attacks an upstream site resulting in the formation of (a) exonic circRNAs and (b) an exon-intron circRNAs (as shown). Besides, circRNAs can be generated from splicing intermediates aka lariat precursors. The exon-skipping event during linear splicing produce (c) a circRNA with a functional exon; or from intronic lariat precursors (escape from the debranching step) (d) a circRNA without functional exon. **(C)** CircRNA can act as (a) microRNA decoys/ sponges, and that trap different miRNA/ alter mRNA stability, (b) can bind to RBP and thus act as protein-decoys/sponges, (c) as protein scaffolds, facilitating the co-localization of enzymes and their substrates, and/or (d) participate in gene regulation program, binding to ribosomes (affecting translation; circRNAs with IRES elements and AUG sites can be translated), RNA polymerase-II complex with U1-snRNP (affecting transcription), recruit specific proteins (to certain loci/sub-cellular compartments/ promoter region) for host gene regulation.

The gene-regulatory functions of many of the circRNA are lately open up with clarity. The uniqueness and role of individual circRNAs for the regulation of RNA dynamics were well recognized after the "microRNA sponge" function [9]. For example, ciRS-7 contains more than seventy conserved binding sites for miR-7. Hence these are considered as circRNA sponge [10, 11]. Several circRNAs reported with miRNA (microRNA) sponging properties, while the majority circRNAs show diverse functions. Bio-genesis of circRNA and their regulation appears to be complex. A lot of circRNAs are synthesized because of a back-splicing reaction that covalently joins the 3′-end of an exon to an upstream 5′-end [12]. The bio-genesis of many circRNAs become possible with reverse complementary *Alu* repeats edging the circularized exons [13].

Furthermore, circRNA biogenesis is promoted by the deregulation of splicing factors recruitment to *cis*-acting splicing-regulatory elements (Fig. 1). These splicing factors recruitment promote the back-splicing reaction to occur. Furthermore, an exon with lariat precursor can be formed by an exon-skipping event also reported for the bio-genesis of circRNA. The internal splicing (removal of intronic sequence) of the lariat can produce a circRNA [14]. The circRNAs can be synthesized from the transcription of many fusion genes that are produced by the chromosomal translocations, including in promyelocytic leukemia and acute myeloid leukemia. All these were named fusion-circRNAs [15]. All the above-mentioned information highlights the biogenesis of circRNAs.

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To date, several circRNAs are observed in different types of human cancer [16]. Those include but not limited to hepatocellular carcinoma (HCC) [17], lung cancer [18], colorectal carcinoma [19], breast cancer [20], prostate cancer [21], bladder [22], ovarian [23], kidney cancer [24], gastric cancer [25], head and neck cancer/ oral cancer (HNSCC/ OSCC) [26, 27], hematological malignancies [28] and tumors of the central nervous system [29]. All this evidence underscores the importance of cirRNA in cancer pathogenesis and treatment. Here the roles of different circRNAs in cancer have been discussed. This review gathers information on circRNAs and their role in the origin and progression of cancer besides their potential as diagnostic, prognostic, and therapeutic biomarkers.

2. Circular-RNA and their cellular function

As mentioned earlier, these circRNAs are single-strand and do not get translated. However, some circRNAs possess AUG sites and Internal ribosome entry site (IRES) elements, for ribosome entry and initiation of translation. Only a few circRNAs found translated in different cell types are known, to date [30]. These circRNAs can have a completely different role and they might be free from their parental genes. Recently, a web-based tool has been reported for circRNA interactome study and known as 'CircInteractome'. This was developed for mapping the miRNA-interaction sites and/ or the RNA-binding proteins binding sites located on circRNAs [31]. The longer half-life of circRNAs in comparison with other linear RNA molecules proposes its regulatory function. Several pieces of evidence found a correlation between circRNAs and numerous cellular processes, including miRNA decoys, protein decoys, protein scaffolding, splicing, and transcription process.

CircRNAs are well appraised for their stability feature since these molecules lack free ends and thus offers protection against exonucleolytic degradation. However, many circRNAs were observed with specific endonuclease sites, and those could be cut open to performing other functions. For example, a well-conserved site to miR-671 promotes precise cleavage of ciRS-7 (circRNA) by the endonuclease enzyme Ago2 [32]. The elevated expression of ciRS-7 with stability has been reported in different human tissues. CiRS-7 can act as a miR-7 sponge and prevent its activity. Like this, many miRNAs/ circRNAs balance may affect several oncogenes/ tumor suppressors gene expression/ stabilities involved in different human cancers. The following section deals with many of the silent features of circRNA.

2.1 CircRNAs regulates miRNA: circRNAs are acknowledged as the key regulators of different miRNAs. The single-nucleotide polymorphisms (SNPs) are exceptionally uncommon, at the circRNA-miRNA interaction sites. This suggests a strong selection pressure to conserve these circRNA-miRNA binding regions in evolution. Different circRNAs harbor one or many miRNA-binding sites. Other circRNAs offer interaction sites for many different miRNAs or even control the entire family of miRNA/s. Since the miRNAs are well-recognized gene/mRNA regulators, the regulation and sponging activity of circRNAs are thus vital. Recent reports find only a limited number of circRNAs exist with several complementary sites for a particular miRNA. The presence of circRNAs in many organisms; those lack RNA interference pathways has also been observed [33]. All this evidence suggests that circRNAs may have some other cellular role (than regulating just miRNAs, pseudogenes, and linear long noncoding RNAs or functioning as miRNA decoy). miRNAs found associated with the regulation of numerous oncogenes/ tumor suppressor genes (TSGs) in various human cancers. For example, a circRNA originated from the CCDC66 gene found with different miRNAs binding/ complementary sites that target oncogenes/ TSGs [34]. Further, circFoxo3 offers several miRNA-binding sites and traps the miRNAs, and prevent them from degrading the linear host transcript [35]. Additionally, circHIPK3 is linked with miRNA decay function [36], and circPVT1 is found with sponging activity of several tumor-suppressor miRNAs, including let-7b [37]. All these pieces of evidence strongly suggest much circRNAs play a role as miRNA decoy in cancer.

2.2 CircRNAs regulate RNA interacting protein function

Some circRNAs possesses binding sites so that one or many RBPs (RNA-binding proteins). This characteristic makes them qualify as protein decoys too. The *mbl* locus /sites in a circRNA offer the MBL (homolog of muscleblind-like protein 1) protein binding. The circRNA that bind to MBL get prevented from other targets [38, 39]. Further, the MBL protein can attach to the introns flanking the circularized exon and promote its own (circRNA) bio-genesis [40]. It has also been reported that HuR binds to circPABPN1 (a PABPN1 gene-derived circRNA). The binding of HuR to circPABPN1 sequester out HuR from its binding to PABPN1 mRNA and impede its translation [41]. HuR also regulates different miRNAs, including the tumor-suppressor miRNA *i.e.*, miR-7 [41]. The circANRIL plays as a protein sponge or decoy for PES-1 (Pescadillo homologue-1). CircANRIL binds to PES-1, a crucial 60S pre-ribosomal assembly factor and prevent exonuclease driven pre-rRNA processing. This leads to the ribosome and subsequent activation of p53 [42]. Similarly, circ-Foxo3 acts as a protein sponge for (mouse double minute 2 homolog) MDM2 and p53 (to prevent ubiquitylation of FOXO3) and thus regulates apoptosis in cancer cells [43]. Hence, the circRNAs can act like protein decoy and contributes to the tumorigenesis process (Fig. 1C).

2.3 CircRNAs and their effect on splicing and transcription

The majority of circRNAs are located in the cytoplasmic compartments, and many of these molecules are also located in the nucleus [38]. These nuclear circRNAs may affect nuclear events like transcription and splicing. Recently, the exon-intron circRNAs were found interacting with RNA polymerase-II and with U1 snRNP, which regulates the transcription of respective parental genes [44]. Many circRNAs communicate via specific RNA-RNA interaction (between U1 snRNA and exon-intron circRNAs) and actively participate in the gene expression/ transcription program [45]. These circRNAs may promote alternative splicing and direct modulation of transcription, and by interfering with splicing mechanisms [46]. Besides,

Figure 2: Circular RNAs and their link with diverse cancer hallmarks. Here, few examples provided which suggest each of the cancer hallmarks like **(A)** Sustaining proliferative signaling [35, 49, 50]; **(B)** Evading growth suppressors [51, 52]; **(C)** Activating invasion and metastasis [53, 54]; **(D)** Enabling replicative immortality [43, 56]; **(E)** Inducing angiogenesis [57, 58]; **(F)** Resisting cell death [43, 55]; **(G)** Evading immune-destruction [59, 60]; **(H)** Genomic instabilities and mutation [61]; **(I)** Reprogramming cellular Energetics [62]; **(J)** Tumor promoting inflammation [63] are driven by several circ-RNA, as discussed in the text.

the circular intronic RNAs (ciRNAs) ci-ankrd52, found accumulates near transcription site, and associates with RNA Polymerase-II mediated regulation of gene transcription. This suggests how parent coding genes can be regulated with the help of noncoding intronic cis-regulatory transcripts [47].

3. CircRNA and acquisition of cancer hallmark properties

Over the years, several circRNAs have been associated with cancer [46, 48]. Till date, nearly ten important cancer hallmarks have been proposed (Fig. 2A-J) and circRNAs are involved in each one of these hallmarks. Cancer cells receive mitogenic signal and active their proliferation agenda aka 'sustaining proliferative signaling'. The circFoxo3 recruits p21 (a cell cycle inhibitor) and CDK2 (Cyclin-Dependent Kinase-2), thus prevent CDK2 activity and halt the cell cycle [35]. On the other hand, circITCH and circMTO1 have been linked with cell cycle and cell proliferation program [49, 50]. 'Evading growth suppressors' is another cancer hallmark. CircRNA, circZNF292, has been found to halts cell cycle progression/cellular transformation and acts like a tumor-suppressor [51]. ciRS-7 inhibits miR-7 causing cell proliferation and rapid cell division by enhancing the epidermal growth factor receptor (EGFR), mitogen-activated protein kinase (MAPK) pathway [52].

Cancer cells activate invasion and metastasis property. Many circRNAs are linked with the Wnt/β-Catenin pathway [53] that promote epithelial-to-mesenchymal transition (EMT) and cell migration. Recently, many circRNAs including, circCCDC66, circKCNH1, circHIAT1, and circZKSCAN1 have been identified, with tumor metastases [54]. Furthermore, various cancer cells achieve immortality with the help of some circRNAs. For example, a circRNAs recruit both MDM2 and p53 and establish a functional interaction, that leads to p53 ubiquitination and degradation [43]. Besides this increased circFoxo3 recruits more MDM2 and hence decreased their (MDM2-Foxo3) interaction and degradation of Foxo3 [43, 55]. The Foxo3 also controls Puma and Bax expression and control cell death agenda. Furthermore, circRNAs originated from TTBK2 (circTTBK2) and UBAP2 (circUBAP2) have been exposed to inhibit apoptosis and achieve immortalization [56].

Cancerous tumors form new blood vessels and thus induce angiogenesis. CircZNF292 and circMYLK have also been linked with hypoxia/ vascular endothelial growth factor A (VEGFA) and VEGFR2 signaling pathways that promote angiogenesis [57, 58]. Cancerous cells impair their cell death and survive longer. circFoxo3 has been linked with an anti-apoptosis program [43]. The increased circFoxo3 recruits more MDM2 and hence decreased their (MDM2-Foxo3) interaction and degradation of Foxo3 [43, 55].

Furthermore, many cancer cells escape from host immunity (Evading immune destruction). circRNA do also play an important role in tumor immunity and are recently considered for tumor immunotherapy [59, 60]. The cancerous cells are prone to genomic instabilities and mutation. 'Alu' elements are also found to be mutagenic, acts as splice acceptor promoting genomic instability. These Alu elements and their associated molecules like DHX9 alters many circular-RNA-producing genes and the number of circRNAs [61]. The reprogramming cellular energetics is another cancer hallmark. Recently the circACC1 found causing 5'AMP-activated protein kinase (AMPK) activation and thus qualify for cancer cells metabolic reprogramming [62]. Tumor promoting inflammation is commonly observed in tumors. Cancer-related inflammation is an essential hallmark, and recent works support the role of several circRNAs (like circ-NT5C2 and circRNA-002178 and hsa_circ_0005519) in cancer [63]. Though this small list of examples described above found the association of circRNA with each type of cancer hallmarks (Fig. 2); with discoveries in the near future, this list will grow and may cover more areas.

4. Aberrant expression of circRNA in different human tumor

CircRNAs are differentially expressed in a variety of human tumors, including solid tumors and hematological malignancies. Here, some of the important findings have been presented in table 1.

Table 1: Aberrant expression of different circRNA in diverse cancer types

Sl. No.	circRNA/s	Tumor Type	Characteristics/ role in different types of cancer with References
1	hsa-circ-0022383, hsa-circ-0022392	**Basal cell carcinoma (BCC)**	A total of 23 and 48 circRNAs with elevated and reduced expression were observed. These circRNAs showed sponging with 354 miRNA in BCC miRNome [64]. In another study, the expression of 2 most decreased circRNAs hsa-circ-0022383 and hsa-circ-0022392 (derived from the FADS2 gene) and 2 most elevated circRNAs derived from LINC00340 found [65].
2	circRNA derived TCF25, MYLK	**Bladder cancer**	A circRNA generated from TCF25 gene induces proliferation and migration program by sponging miR-103a-3p and miR-107 [66]. A circRNA generated from MYLK gene bind to miR-29a and eliminate the suppressive effect on VEGFA gene, and thus promote angiogenesis, metastasis, and EMT [58].
3	circFOXO3, circABCB10	**Breast cancer (BC)**	A total of 256 circRNA in triple-negative breast cancer (TN BC), 288 in estrogen receptor-positive (ER+) BC, and 411 in HER2-positive BC subtypes was reported [67]. A tumor suppressor circRNAs (i.e., circFOXO3) down-regulated in BC [43]. A circRNA from ABCB10 up-regulated in BC that induce cell proliferation and suppress apoptosis through sponging miR-1271 [68].
4	ciRS-7, circMETTL3, circITCH	**Colorectal carcinoma (CRC)**	Higher expression of ciRS-7 was observed in CRC [69]. A circRNA synthesized from the METTL3 gene (m6A methyltransferase gene) found in CRC and its reduced expression reported [70]. Several circRNAs biogenesis from the CCDC66 (oncogenic decoy by binding miRNAs), STIL, BANP, PTK2, and ITCH gene were reported CRC [71].
5	circLARP1B, circFADS2	**Cutaneous squamous cell carcinoma (CSCC)**	A total of 143 and 179 circRNAs in CSCC, observed with increased and decreased expression respectively [72]. The two circRNAs expressions those were found elevated, and reduced were from the LARP1B gene and FADS2 gene respectively [64].
6	circPRKCI, circRNA_001059, circRNA_000167	**Esophageal squamous cell carcinoma (ESCC)**	A circRNA produced from PRKCI gene found up-regulated in ESCC; correlated with higher stage (TNM stage) disease [73]. In the human radio-resistant ESCC cell line, KYSE-150R 3752 and 57 circRNAs were found up-regulated and down-regulated compared with the parental cell line i.e., KYSE-150 [74]. More than 400 target genes were observed from the Wnt signaling pathway alone. The CircRNA_001059 and circRNA_000167 were the two largest nodes in the circRNA/ microRNA co-expression network [74].
7	circPVT1 circRNAs from CNIH4, HIAT1, KIAA0907	**Gastric cancer (GC)**	circRNA circPVT1 was found up-regulated in GC. circPVT1 associated with better overall survival (OS) and disease-free survival (DFS) [75]. Three different circRNAs derived from the *CNIH4*, *HIAT1*& *KIAA0907* genes were found down-regulated in GC [76].

8	476 circRNAs were differentially expressed, circVCAN, circTTBK2, ciRS-7, circZNF292	**Glioma**	A total of 476 circRNAs were differentially expressed among thousands of different circRNAs in glioma [77]. CircRNAs derived from the VCAN [78], and TTBK2 gene [56] found up-regulated; whereas ciRS-7 and circZNF292 found down-regulated [57].
9	circRNAs derived from genes (JAK2, PAX5, IKZF1, ETV6 and EBF1) circRNA derived from WDR37	**Hematological malignancies**	CircRNAs generated from B-cell differentiation genes/ acute myeloid leukemia (ALL) such as EBF1, ETV6, IKZF1, JAK2, and PAX5 found elevated in ALL w.r.t. normal leukocytes [79]. CircRNA produced from WDR37 expression found deregulated in ALL [80]. CircRNA synthesized from the MLL-AF9 fusion offered drug resistance (against cytarabine) in ALL [15].
10	ciRS-7 circRNA derived from SHPRH, ZKSCAN1, SMYD4 and FAM53B HIPK3	**Hepatocellular carcinoma (HCC)**	Overexpression of ciRS-7 inversely correlated with miR-7 expression and hepatic microvascular invasion [81]. Respective circRNA/s generated from the SHPRH, *ZKSCAN*, *SMYD4* , and *FAM53B* gene found down-regulated in HCC wrt tumor-adjacent tissues [75, 82, 83]. CircRNA produced from exon 2 of *HIPK3* was differentially expressed in HCC [84].
11	circITCH circRNA from ACP6	**Lung cancer**	CircRNA derived from the ITCH gene downregulated in lung cancer tissues wrt adjacent noncancerous tissues [85]. CircRNA from ACP6 found up-regulated in adenocarcinoma and associated with TNM stage and lymphatic metastasis [86].
12	circUHRF1, circPVT1; has_circ_0004491, circ_0001162, circ_0055538, circRNA_102459, circRNA_043621,	**Oral squamous cell carcinomas (OSCC), Head and Neck SCC (HNSCC)**	CircUHRF1 (hsa_circ_0002185) overexpressed in OSCC. Functionally, circUHRF1 acted as miR-526b-5p sponge, thereby it regulates c-Myc and fuel the cell proliferation, invasion, migration, EMT and associated with poor prognosis [87]. Decreased Hsa_circ_0004491 expression reported in OSCC. This circRNA found associated with lymph node metastasis, cell migration, invasion, and protein expression, and overall progression of OSCC [88]. A circRNA produced from matrix metalloproteinase-9 (hsa_circ_0001162 sponging effect on AUF1 and miR-149), found elevated in OSCC and positively associated with MMP9 expression. That fuel metastasis and advanced TNM stage [89, 90]. Another hsa_circ_0055538 with altered expression levels, can alter Bcl-2/ p53/ caspase signaling pathway and involved with the development of OSCC [91, 92]. The down/ upregulation of Hsa_circRNA_102459 and hsa_circRNA_043621 were reported respectively, in OSCC. Targeting these circRNAs can affect MAPK, PI3K/Akt, Bcl-2 signaling axis and alter cell proliferation, and apoptosis program in TSCC1 cells [93-95]. CircPVT1 expression was elevated by the mut-p53/YAP/TEAD complex in HNSCC/ OSCC. CircPVT1 acts as an oncogene act as miR-497-5p sponge and genes involved in the control of cell proliferation [27, 96].

13	**CircUBAP2,** circ-0016347, circ-0002052, circTADA2A	**Osteosarcoma**	CircUBAP2 overexpression detected in osteosarcoma (OS) and promote cell growth and inhibit apoptosis [97]. A circRNA (hsa_circ_0002052) expression got reduced in OS, and this was found associated with reduced cell proliferation, invasion/ migration, and cell survival *in vitro*. This circRNA found a connection with miR-1205, APC2, and Wnt/β-catenin signaling pathway [98]. Circ-0016347 synthesized from KCNH1 oncogene was overexpressed in osteosarcoma, and it promotes cell proliferation, invasion/ metastasis [99]. CircTADA2A found with sponging effect on miR-203a-3p and regulate CREB3 expression thus fuel OS progression and metastasis [100].
14	circ-ITCH, circ_0078607, Circ-ABCB10	**Ovarian Cancer**	A tumor suppressor ciecRNA, Circ-ITCH reported in OC, and it acts as a ceRNA and alter the expression of miR-145, RASA1, and thus impede the oncogenesis of OC [101]. Circ_0078607 expression reduced in ovarian cancer. Induced expression of circ_0078607 alter miR-518a-5p/ Fas pathway in OC cells with reduced cell division and cell survival [102]. An oncogenic circ-ABCB10 correlated with unfavorable survival of OC patients. It acts as a negative regulator of miR-1271, miR-1252, and miR-203 and promotes cell division, reduces cell death and in epithelial ovarian cancer [103].
15	circRNA-DLEU2, Circ-Foxo3, Circ_0009910, Hsa_circ_0080145	**Hematological malignancy (AML)**	CircRNA-DLEU2 hastens human acute myeloid leukemia (AML) by suppressing miR-496 and promoting PRKACB expression. Further, circRNA-DLEU2 reduced miR-496 expression and enhanced PRKACB expression, and alter cell proliferation and apoptosis program in AML [104]. Circ-Foxo3correlated positively with Foxo3 gene expression and better disease outcome of AML patients [105]. Another cirRNA observed in CML (chronic myeloid leukemia), i.e., Circ_0009910 which target miR-34a-5p and promoted imatinib-resistance by altering ULK1-induces autophagy [106]. Hsa_circ_0080145 with miR-29b sponging property promotes CML cell proliferation [107].

5. Prospect of circRNA in neoplastic diseases

Current developments suggest the presence of circRNAs can affect different gene regulation, cell signaling, and thus participate in cellular transformation. Evidence has been accumulated supporting the circRNAs connection with cell proliferation, EMT, tumor angiogenesis, apoptosis, and even drug resistance. The understanding of circRNAs biology in neoplastic diseases is still at a primitive state [3, 33]. There is a lack of evidence (pre/ clinical) that support the benefit of targeting these oncogenic circRNAs. However, oncogenic circRNA appear to be smart targets for cancer treatment though some bottlenecks need to be addressed.

Foremost, the targeting of these tumor-specific circRNAs should be cautiously performed, so that other transcripts inside the cell will not be affected. The knockdown of onco-circRNA can be possible with the help of various molecular tools [108]. siRNA/ shRNA approach can be utilized to target the exceptional back-splice junction of oncogenic circRNAs [108, 109]. Antisense oligonucleotides (AS-ON) that are complementary to back-splice signals of the pre-mRNA can interfere with the back splicing junction [110]. With the help of these abovementioned tools (i.e. siRNA/ AS-ON), the flanking intronic *Alu* repeats/ trans-acting splicing factors binding sites the back splicing can be prevented [111].

Further, the induced expression of tumor-suppressor circRNA in cancer cells can be beneficial. This tumor-suppressor circRNA and artificial circRNAs can be designed and introduced in cancer cells with the help of the gene therapy method [112]. Care should be taken for this because the introduction of foreign circRNA can stimulate interferon driven chaos [113].

Further, circRNAs transcriptional program can be rewired with the design of the RNA Polymerase-II driven cell-specific promoters [114]. More understanding of circRNA in gene regulation can be beneficial for cancer therapy. CircRNA can be used as a molecular tool for the controlled regulation of different biomolecules like miRNA, RNA, and proteins. These molecules can be used to rectify the signaling network in cancer and may bring back regular cell functioning or may support cell death. CirRNA is quite stable and thus, can be exploited as a vector for cancer therapy [115]. With their assistance, different therapeutics can be delivered to target cancer-causing pathways.

The alterations of circRNAs are reported, but the exact mechanism is elusive in cancer. Alternative splicing and miRNA expression are regulated by spliceosomes [116]. Mutations in many of these genes like U2AF1, SF3B1, and SRSF2 have also been reported in cancer [117], those need to be identified. Similarly, mutations of spliceosome genes and other trans-acting factors, like Quaking (QKI), can control the biogenesis of different circRNAs [118] should be identified for therapeutic purposes. Current evidence suggests an abnormal expression of QKI on diverse human cancers, including lung cancer. Hence, the altered expression/ regulation of circRNAs observed in cancer may be due to genetic or/and

epigenetic changes of numerous upstream regulatory genes, and those need to be thoroughly checked before designing personalized cancer therapy.

The regulation of circRNA turnover is also not well understood. Some of the circRNAs are observed in several body fluids and thus have great potential to become a biomarker for disease monitoring. The functional role of circRNAs can be further analyzed in different types of body fluids, such as serum/blood and saliva, which is important if they are to be used as non-invasive biomarkers. Finally, recently, there are some excellent reviews in this field and maybe referenced for more information [71, 119-121]. In conclusion, circRNA investigation is still at a primitive stage, and their role in cancer is just beginning. The circRNAs show potential not only as a precious cancer biomarker but also can be served as possible targets for cancer therapy in the future.

Declarations

Acknowledgement: The author wants to acknowledge his teachers and mentors for what he learns from them in his career.

Funding: Not Applicable

Conflict of Interest: None

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