Review Article

Circulating circular RNAs as biomarkers of cancer

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Abstract: Circular RNA (circRNA) is a kind of novel non-coding RNA, which is widely present in eukaryotes and has a special circular structure formed by 3'- and 5'-ends linking covalently. CircRNA has many features, including high stability, conservation, etc. Since the discovery of circRNA, it has been considered a "by-product" of gene expression. In recent years, many studies have confirmed that circRNAs play an essential role in the pathogenesis of many diseases. CircRNA is involved in various cancer processes including the regulation of cell growth, proliferation, invasion, metastasis, etc., and is differentially expressed in tumor tissues and even in the circulation of patients. Because of these characteristics, circRNA has become a competitive candidate in being a novel biomarker of cancer. This article reviews the role of circulating circRNA in cancer and its diagnostic significance.

Keywords: Circular RNA; circulation; biomarker; cancer

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Introduction

According to the human genomic data, approximately 75% of genes are transcribed into RNAs, of which more than 20,000 are protein-coding genes. About 2% of the total genomic sequences can be translated into proteins for multiple biological functions (1-3). Non-coding RNA (ncRNA), known as the major component of human transcriptome, participates in the pathological processes of various diseases by interfering directly or indirectly with target gene expression (4-7). In addition to the well-known classical ncRNA such as transfer RNA (tRNA) and ribosomal RNA (rRNA), ncRNA also includes long non-coding RNA (lncRNA, ≥200 nucleotides) and small non-coding RNA (sncRNA, ≤200 nucleotides), according to the length of RNA (8).

Another type of ncRNA, circular RNA (circRNA), is novel and endogenous (9). Unlike the chain structure of linear RNAs, circRNA has a circular structure such that the 3'- and 5'- ends are covalently linked based on the "back-splicing" reaction (10,11). Recent studies report that circRNA is a kind of closed-loop singled-stranded structural RNA with neither 5'-3' polarities nor polyadenylated tails. Due to this special structure, circRNA is regarded as a promising biomarker. Indeed, since the rapid expansion of RNA sequencing technology, circRNA has garnered considerable research intensity both in China and the international sphere.

History of circular RNA

In 1976, a single-chain covalent closed-loop molecule in plant-infected viroids was identified by electron microscopy; this was the first circRNA found in the world (12). With the discovery of pre-mRNA splicing in 1977, the presence of exon and introns was also soon realized (13,14). In 1987, an RNA loop was observed which was thought to be the

splicing of the 5' splice site downstream of the 3' splice site in the splicing substrate of group I (15). The expression of this kind of RNA loop is expressed in *E. coli* and yeast (16). In addition, circRNAs have been reported to be more stable *in vivo* than linear RNAs because of the resistance to end-dependent degradation (17).

Despite these discoveries, circRNAs were misunderstood as an "unexpected product" in the splicing of pre-mRNA in the nucleus for a long time—so-called "transcriptional noise" or "transcriptional trash". Thus, circRNAs did not receive much attention at that time (18,19). In recent years, with the technological surge in RNA sequencing, a large amount of RNA sequence data have been generated. Based on these "unexpected products", a large number of circRNAs were discovered in various organisms, such as humans, mice, nematodes, zebrafish, and yeast (20-22).

Sources and characteristics of circular RNA

CircRNAs are derived from protein-coding genes, and the pre-mRNA is linked in a "head-to-tail" manner by linear RNA, which is generated by non-classical selective cleavage. It is commonly understood that the splicing of pre-mRNA includes three of the following ligation forms (23): (I) the 5'-splice site being ligated to the downstream 3'- splice site; (II) the 5'- splice site being ligated to the upstream 3'- splicing site; (III) the downstream 5'- splice site being ligated to the upstream 3'- splice site head to tail, i.e., RNA cyclization. Therefore, some believe that during the transcription of pre-mRNA, the RNA is partially folded, and thus the distance between non-adjacent exons is narrowed and exon skipping occurs. These two exons form a circular intermediate, which subsequently turns into circRNA (18,24-28).

Although most circRNAs are derived from exons, circRNAs are mainly classified into five classes according to the different sources of circRNA (29,30): (I) exon-derived circRNAs (ecircRNAs) which are the largest type of circRNAs, accounting for more than 80% of the discovered circRNA; (II) intron-derived circRNAs (EIciRNAs); (III) intergenomic circRNA which includes viroid and hepatitis D virus; (IV) circRNA intermediates during RNA processing which includes circRNA intermediates in tRNA or human RNA processing; (V) circRNA with housekeeping gene function (ciRNAs) which includes RnaseP or some snoRNAs.

CircRNAs have the following characteristics: (I) high stability; since circRNA is a covalently closed-loop singled-stranded structural RNA without 3'-end cap and 5'-end polyadenylated tails, circRNAs cannot be degraded by debranched enzyme and endonuclease, and so circRNAs can avoid normal RNA conversion pathways. Thus, circRNA is more stable than the homologous linear RNA. It has been reported that the average half-life of circRNAs can exceed 48 h, while the average half-life of linear RNA is about 10 h in most species (23). (II) High abundance; due to the high stability of circRNA, circRNA is more abundant and widely distributed than linear RNA. (III) High conservation; among different species, the mutation rate of circRNA is relatively low (20). (IV) Prevalence in cytoplasm; most circRNAs are present in the cytoplasm and regulate the expression of the target genes (9,24,31,32).

Biological functions of circular RNA

Views concerning the function of circRNA have gradually changed from "unexpected product of the pro-mRNA splicing" to "important regulatory non-coding RNA".

Circular RNA acts as a miRNA sponge

CircRNAs with an miRNA binding site competitively bind to miRNAs and reduce the effect of the miRNA on target genes, thereby indirectly regulating the expression of target genes (32,33).

In 2013, circRNA was firstly reported to function as an miRNA sponge in mammals. The natural antisense transcript of cerebellar degeneration-associated protein 1 (CDR1as), also known as ciRS-7, was found to tightly bind to the effector complex of miR-7 and inhibit its function, similarly to miR-7 knockdown (9). Following this discovery, the testis-specific circRNA, sex determining region Y (Sry) was found to act as a miR-138 sponge (32). Interestingly, CDR1as was found to be able to be degraded by miR-671 in some special situations, indicating that miR-671 indirectly regulates miR-7 expression via CDR1as (34). Moreover, the itchy E3 ubiquitin ligand (ITCH) is the parental gene of circ-ITCH, and the 3'-end of ITCH contains a miRNA binding site. circ-ITCH can also act as a miRNA sponge through the interaction with miR-7, miR-17, and miR-124 and ultimately regulate the expression of ITCH (35).

Circular RNA is involved in regulation of alternative splicing and transcription

Several studies have shown that circRNA is involved in

the regulation of alternative splicing and transcription. Mannose-binding lectin (MBL) was found to be an RNA splicing factor that bound to its parental gene exon 2 and promoted its cyclization to form circMBL (10). CircMBL and its intron sequences contain a conserved binding site for MBL, which promotes circMBL production when MBL is increased. At the same time, circMBL combines with excess MBL and clears it to ensure a relatively stable level of MBL. It was also reported that there were many single exon-derived circRNAs in human fibroblasts, and each contains translation initiation sites (36). This means that these circRNAs can regulate the transcription process of target genes by translational isolation.

Circular RNA regulates the expression of parental genes

In addition to the aforementioned circ-ITCH which can regulate the expression of the parental gene ITCH through the interaction with some miRNAs, there is also a part of circRNA which regulates the expression of its parental genes by other means. Intron-derived EIciRNAs are mainly found in the nucleus and interact with U1 small nuclear RNA protein particles (U1 snRNP) and RNA polymerase II (Pol II) to regulate the expression of parental genes (31,37,38).

Circular RNA participates in protein translation

Recently, circRNA was found to be capable of encoding proteins as mRNA. A translation initiation site was found in circRNA sequence, which means that circRNA is capable of translation (36). The circRNA in the hepatitis D virus (HDV) is the first naturally occurring circRNA that can encode protein found in eukaryotic cells (39). The initiation process of circRNA encoding protein was also found to be enhanced by the basic modification of RNA by N^6 methyladenosine (m^6A) (16).

CircRNA and cancer

CircRNAs have a variety of biological functions, particularly in regulating gene expression. Through these biological functions, circRNAs are also involved in the occurrence and development of various diseases (40). The role of circRNA in the development of different cancers has also been investigated. Previous studies have shown that circRNA can widely regulate the function of cancer cells, and the expression of circRNAs changes in tumor tissues and/or circulating blood. Moreover, circRNA is closely related to the pathogenesis of neoplastic diseases. Most studies have reported that circRNAs acted as an miRNA sponge influencing cancer cell proliferation, epithelial-mesenchymal transition (EMT), and angiogenesis. circRNA may affect cancer cell apoptosis as well.

In *Table 1*, we listed the latest studies of some circRNAs in different cancers, including the circRNA function and mechanism of action during tumorigenesis and development.

Circulating circRNA and cancer

circRNAs have covalent circular structure in the absence of 3'-end and 5'-end. circRNAs exist stably and abundantly in circulating blood, especially in serum exosomes (67). As a result, circulating circRNAs are considered to be promising biomarkers in different cancers.

Studies based on a large number of serum samples from gastric cancer patients have shown that the serum level of circ-SFMBT2 (68) is up-regulated, while some circRNAs are down-regulated, including hsa_circ_0000745 (69), hsa_circ_0000181 (70), hsa_circ_0001649 (71), hsa_circ_0000190 (72), and hsa_circ_002059 (73). These circRNAs are expected to become the potential biomarkers of gastric cancer. Apart from gastric cancer, hsa_circ_0001649 was also negatively correlated with the degree of pathological differentiation of colorectal cancer patients (74). In the tumor tissues and serum samples of hepatocellular carcinoma patients, the level of circSMARCA5 (hsa_circ_0001445) is reduced; meanwhile, when combined with AFP, it can diagnose hepatocellular carcinoma more sensitively (75). Some circulating circRNAs were also changed in patients with pancreatic tumors. The elevation of serum circ-PDE8A suggests cancer progression and poor prognosis of PDAC patients (76). Serum circ-LDLRAD3 (77) is associated with venous invasion, lymphatic invasion, and metastasis of pancreatic cancer, while serum circ-IARS (78) is also closely related to liver metastasis, vascular invasion, and tumor-node-metastasis (TNM) stage. In addition to cancer progression, circulating circRNAs are associated with cancer phenotypes and can guide clinical treatment interventions. F-circEA has been reported to elevate in EML4-ALK fusion gene positive NSCLC patients' serum (79). Overwhelming evidence has indicated that increasing serum circBA9.3 in

Table 1 CircRNAs involved in the pathogenesis of different cancers

Change in cancer	Cancer	Name of circRNAs	Function	Related molecules, signaling pathways and mechanism	Ref.
Up-regulated	Breast cancer	FECR1	Promotes metastasis	TET1, DNMT1, FLI1	(41)
		CircANKS1B/hsa_circ_0007294	Promotes EMT, invasion and metastasis	miR-148a-3p, miR-152-3p, USF1, TGF-β1/Smad pathway	(42)
		Circ-DNMT1	Promotes cell growth and proliferation; inhibits cell senescence	p53, AUF1, autophagy	(43)
		CircAGFG1，hsa_circ_0058514	Promotes cell proliferation, migration and invasion; promotes tumorigenesis, angiogenesis and metastasis; inhibits cell apoptosis	miR-195-5p, CCNE1 (triple-negative breast cancer)	(44)
		CircEPSTI1，hsa_circ_000479	Promotes cell proliferation; inhibits cell apoptosis	miR-4753, miR-6809, BCL11A (triple-negative breast cancer)	(45)
	Hepatocellular carcinoma	CircHIPK3	Promotes cell growth and proliferation	miR-124, IL6R, DLX2	(46)
		Cul2 circular RNA, circ-10720	Promotes EMT and metastasis; positively correlates with tumor malignancy	Twist1, vimentin (EMT related protein)	(47)
		CircFBLIM1	Promotes cell proliferation and invasion; inhibits cell apoptosis	miR-346, FBLIM1	(48)
	Glioma	Circ-DICER1	Promotes cell viability, migration and angiogenesis	RNA-binding protein MOV10, miR-103a-3p, miR-382-5p, ZIC4, Hsp90β, PI3K/Akt pathway	(49)
	Bladder epithelial carcinoma	CircPRMT5	Promotes EMT and invasion	miR-30c, SNAIL1	(50)
	Glioblastoma	CircNT5E, hsa_circ_0077232	Promotes cell proliferation, migration and invasion; inhibits cell apoptosis	RNA editing enzyme ADAR2, miR-422a	(51)
	Glioblastoma multiforme	CircMMP9	Promotes cell proliferation, migration and invasion	miR-124, cyclin-dependent kinase 4 (CDK4), aurora kinase A (AURKA), eukaryotic initiation factor 4A3 (eIF4A3)	(52)
	Non-small cell lung cancer (NSCLC)	CircPTK2, hsa_circ_0008305	Promotes EMT and invasion	miR-429, miR-200b-3p, TIF1γ, TGF-β	(53)
	Osteosarcoma	CircFAT1	Promotes cell growth, migration, invasion and tumorigenesis	miR-375, Yes-associated protein 1 (YAP1)	(54)
	Pancreatic ductal adenocarcinoma (PDAC)	hsa_circ_0000977	Promotes PDAC progression	miR-874-3P, PLK1	(55)
	Multiple cancer cell lines	Circ-CTNNB1	Promotes cell migration, invasion and tumor growth	DEAD-box polypeptide 3 (DDX3), Yin Yang 1 (YY1), β-catenin	(56)

Table 1 *(continued)*

Table 1 *(continued)*

Change in cancer	Cancer	Name of circRNAs	Function	Related molecules, signaling pathways and mechanism	Ref.
Down-regulated	Glioma	CircPINTexon2	Inhibits cell proliferation	PINT87aa, PAF1 complex, Pol II	(57)
	Hepatocellular Carcinoma	cSMARCA5	Inhibits cell growth and migration	miR-17-3p, miR-181b-5p, TIMP3	(58)
		CircMTO1, hsa_circ_0007874, hsa_circ_104135	Inhibits cell proliferation and invasion	miR-9, cyclin-dependent kinase inhibitor 1 (p21)	(59)
	Gastric carcinoma	CircYAP1	Inhibits cell growth and invasion	miR-367-5p, p27 Kip1	(60)
		CircFAT1 (e2)，hsa_circ_0001461	Inhibits cell proliferation, migration and invasion	miR-548g, RUNX1, Y-box binding protein-1 (YBX1)	(61)
	Bladder cancer	BCRC-3	Inhibits cell proliferation	miR-182-5p, p27	(62)
		CircFNDC3B	Inhibits cell proliferation, migration and invasion	miR-1178-3p, G3BP2, RC/FAK pathway	(63)
		Circ-ITCH	Inhibits cell proliferation, migration, invasion and metastasis	miR-17, miR-224, p21, PTEN	(64)
	Renal clear cell carcinoma	CircATP2B1，hsa_circ_000826	Inhibits invasion and metastasis	ERβ, miR-204-3p, FN1	(65)
	Multiple cancer cell lines	CircFoxo3	Inhibits cell cycle progression	cyclin-dependent kinase 2/ cell division protein kinase 2 (CDK2), p21	(66)

chronic myeloid leukemia patients leads to tyrosine kinase inhibitor resistance (80). Furthermore, nasopharyngeal carcinoma patients with increased serum hsa_circ_0000285 showed lower sensitivity to radiotherapy and five-year survival rate (81).

FECR is an exon circRNA of Friend leukemia virus integration 1 (FLI1), which inactivates the tumor suppressor miR-584-3p, subsequently resulting in the activation of Rho-associated coiled-coil containing protein kinase 1 gene (ROCK1) (82). Clinically, tracking serum FECR level can monitor small cell lung cancer (SCLC) progression (82). Hsa_circ_0109046 and hsa_circ_0002577 were found to be differentially expressed in endometrial cancer patient serum, indicating that these two circRNAs may be potential biomarkers for predicting the progression and prognosis of endometrial cancer (83). The serum circPTK2 (84) (hsa_circ_0003221) increased in bladder cancer patients and the postoperative serum hsa_circ_0001785 (85) decreased in breast cancer patients, which confirmed the diagnostic value of serum circRNA in neoplastic diseases. The circulating circRNAs in cancers are summarized in *Table 2*.

Conclusions

This review summarized the characteristics and biological functions of circRNAs, and the relevant studies concerning circulating circRNAs acting as cancer biomarkers. The high stability and conservation of circRNAs make them promising biomarkers. However, standard protocol should be fixed so that studies from different groups can be compared. In addition, the source and function of circulating circRNAs should be investigated. Moreover, studies based on multiple centers should also be conducted.

Table 2 Circulating circRNAs change in cancers

Cancer type	Name of circRNAs	Change in cancer	Diagnostic significance	ROC curve	Ref.
Gastric cancer	Circ-SFMBT2	Up	Associated with TNM stage	–	(68)
	hsa_circ_0000745	Down	Associated with pathological differentiation not tumor size, lymphatic metastasis, and TNM stage	(I) Serum circRNA; AUC value: 0.683; Sensitivity: 0.855; Specificity: 0.45 (II) Combined with CEA; AUC value: 0.775; Sensitivity: 0.800; Specificity: 0.633	(69)
	hsa_circ_0000181	Down	Associated with tumor size, distal metastasis and lymphatic metastasis	AUC value: 0.582; Specificity: 0.206; Sensitivity: 0.990	(70)
	hsa_circ_0001649	Down	Associated with pathological differentiation	AUC value: 0.834; Sensitivity: 0.711; Specificity: 0.816	(71)
	hsa_circ_0000190	Down	Associated with distant metastasis and advanced cancer	(I) Serum circRNA; AUC value: 0.60; Sensitivity: 0.414; Specificity: 0.875 (II) Combined with tissue circRNA; AUC value: 0.78; Sensitivity: 0.712; Specificity: 0.750	(72)
	hsa_circ_002059	Down	Associated with TNM stage and distant metastasis	AUC value: 0.73; Sensitivity: 0.81; Specificity: 0.62	(73)
Colorectal cancer	hsa_circ_0001649	Down	Associated with colorectal cancer pathological differentiation	AUC value: 0.857; Sensitivity: 0.828; Specificity: 0.781	(74)
Hepatocellular carcinoma	CircSMARCA5, hsa_circ_0001445	Down	Associated with intrahepatic metastasis; differential diagnosis of hepatocellular carcinoma, cirrhosis, and hepatitis B	(I) Serum circRNA; A. with health control, AUC value: 0.862, Sensitivity 0.942, Specificity 0.712 B. with liver cirrhosis, AUC value: 0.672; C. with hepatitis B, AUC value: 0.764 (II) Combined with AFP; A. with health control, AUC value: 0.970; B. with liver cirrhosis, AUC value: 0.743; C. with hepatitis B, AUC value: 0.877	(75)

Table 2 *(continued)*

Table 2 *(continued)*

Cancer type	Name of circRNAs	Change in cancer	Diagnostic significance	ROC curve	Ref.
Pancreatic tumor	Circ-PDE8A	Up	Associated with tumor progression and prognosis of PDAC	–	(76)
	Circ-LDLRAD3	Up	Associated with venous invasion, lymphatic invasion, and metastasis of pancreatic cancer	(I) Serum circRNA; AUC value: 0.67; Sensitivity: 0.5738; Specificity: 0.7049 (II) Combined with CA199; AUC value: 0.87; Sensitivity 0.8033; Specificity 0.9355	(77)
	Circ-IARS	Up	Associated with liver metastasis, vascular invasion, TNM stage, and postoperative survival time of pancreatic cancer	–	(78)
Lung cancer	F-circEA	Up (EML4-ALK $^{(+)}$ NSCLC)	Detection of EML4-ALK fusion gene in EML4-ALK positive NSCLC	–	(79)
	FECR	Up	Associated with disease progression and lymphatic metastasis in SCLC	–	(82)
Leukemia	CircBA9.3	Up	Associated with prognosis and tyrosine kinase inhibitor (TKI) resistance in patients with chronic myeloid leukemia	–	(80)
Endometrial cancer	hsa_circ_0109046	Up	Associated with the occurrence, metastasis, and prognosis of endometrial cancer	–	(83)
	hsa_circ_0002577	Up	Associated with the occurrence, metastasis, and prognosis of endometrial cancer	–	(83)
Bladder cancer	CircPTK2，hsa_circ_0003221	Up	Associated with pathological differentiation, lymphatic metastasis, and TNM stage	–	(84)
Breast cancer	hsa_circ_0001785	Down (Postoperative)	Associated with pathological differentiation, TNM stage, and distant metastasis	(I) Serum circRNA; AUC value: 0.784; Sensitivity: 0.764; Specificity: 0.699 (II) Combined with CEA and CA153; AUC value: 0.839; Sensitivity: 0.758; Specificity: 0.904	(85)
Nasopharyngeal carcinoma	hsa_circ_0000285	Up	Associated with radiosensitivity and five-year survival rate of patients	–	(81)

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ncri.2019.02.01). The authors have no conflicts of interest to declare.

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