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Review

Roles of Circular RNAs And Their Interactions With MicroRNAs in Human Disorders

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Abstract

Circular RNAs (circRNAs) are a class of non-coding RNAs (ncRNAs) that are involved in transcriptional and posttranscriptional gene expression regulation by sponging microRNAs (miRNAs). As miRNAs control a large set of biological processes, circRNA sponge activity also affects these pathways and thereby participates in human disease initiation and development. A growing number of works have confirmed that circRNAs may play critical roles in normal human tissues and organ functions and in the pathogenesis of human diseases, mainly by interacting with miRNAs. Herein, we review the expressions and functions of circRNAs in diverse disorders, including those of the nervous system and cardiovascular system, cancer, and other common diseases. As circRNAs are easily detected in many clinical samples, they present great potential as biomarkers for disease diagnosis and prognostic evaluation; thus, the prospect of using circRNAs as biomarkers for clinical decision-making is also discussed.

Keywords: circular RNAs; miRNAs; neurological disorders; cancer; cardiovascular diseases; biomarker

INTRODUCTION

Circular RNAs (circRNAs) have recently been identified as a novel class of non-coding RNAs (ncRNAs) that are more stable than linear RNAs because of their unique closed loop structure, with no 5′ to 3′ polarity or polyadenylated tail [1]. They are generated from either exons or introns via alternative back-splicing, with an upstream splice acceptor joined to a downstream splice donor [2]. Reverse complementary sequences or RNA-binding proteins are necessary for circRNA biogenesis. Emerging evidence reveals that the majority of circRNAs are evolutionarily conserved across species and specifically expressed in distinctive tissues and developmental stages [3]. The dysregulation and abnormal expression of circRNAs have been implicated in disease development and progression [4], implying their potential role in pathogenesis.

MicroRNAs (miRNAs) are another type of ncRNAs that negatively regulate gene expression at the post-transcription level by binding to the 3′ UTR of their target mRNAs to participate in multiple biological processes. However, competitive endogenous RNAs (ceRNAs) of miRNAs, such as the long non-coding RNAs (lncRNAs), devote themselves to binding with miRNAs and thus relieving their inhibitory effects on their target genes[5]. Similarly to other ceRNAs, circRNAs also serve as miRNA sponges and cause miRNA deregulation that affects cell function[6]. It has been widely validated that endogenous circRNAs work as miRNA sponges to rescue their target genes, forming a circRNA-miRNA-mRNA axis to modulate numerous signaling pathways. Considering the enormous number of miRNAs and their target mRNAs encoded in human genome, their interactions and the regulation mediated by circRNAs have attracted extensive attention in human disorders. Therefore, the roles that circRNAs play in human disorders by interacting with miRNAs are reviewed in this article. CircRNAs' potential as biomarkers for clinical diagnosis and prognosis is also emphasized.

CIRCRNAS IN NEUROLOGICAL DISORDERS

CircRNAs are pivotal in neurodevelopment and are reported to be highly enriched in the nervous system and notably upregulated during neuronal differentiation [7,8], hinting at their potential neural function. The much-studied circRNA cerebellar degeneration-related protein 1 antisense (CDR1as) is a well-known miR-7 sponge that has over 60 binding sites for miR-7 (also called ciRS-7) [9] (Figure 1) and has been linked to nervous system diseases. Through

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glioblastoma multiforme (GBM) biopsies, CDR1as was found to manifest as a downstream miR-671-5p target in human GBM, an aggressive cancer originating from the central nervous system. The expression of CDR1as was also found to be negatively correlated with that of miR-671-5p [10]. In the sporadic Alzheimer's disease (AD) hippocampal CAI region, a dysregulated miR-7-ciRS-7 system has been noted [11]. Deficits in ciRS-7 and ciRS-7 sponging activities were expected to elevate ambient miR-7 levels in brain cells affected by AD, contributing to the downregulation of the mRNA targets of miR-7, such as the ubiquitin protein ligase A (UBE2A).

CDR1as has also been proven to be expressed mostly in the brain and has been associated with the neurological disorder Parkinson's disease, which results from the degeneration of dopamine-generating cells in the midbrain [12]. Recently, a major breakthrough was made in demonstrating an in vivo loss-of-function circRNA phenotype in mice [13]. When the CDR1as locus was knocked out from the mouse genome, the animals displayed sensorimotor gating deficits and a behavioral phenotype involving failure to filter out unnecessary information, manifesting as neuropsychiatric disorders. This was the first time the function of a circRNA was verified in vivo, highlighting the roles of circRNAs in normal brain function.

In addition to CDR1as, circRNAs are abundant in the brains of mammals, and their ability to transverse the blood-brain barrier makes them good candidate regulators in central nervous system disorders. In mouse and human brain samples, the 15849 and 65731 circRNA candidates have been respectively determined, with distinct spatio-temporal expression patterns[8]. In spared nerve injury-induced neuropathic pain, 188 circRNAs were found to be markedly up- or downregulated 14 days after spared nerve injury surgery, facilitating the development of promising neuropathic pain therapeutics targeting circRNAs[14] JIn cerebral ischemia-reperfusion injuries (IRI) induced by oxygen-glucose deprivation/reoxygenation (OGD/R), the significant upregulation of mmu-circRNA-015947 and its interaction with five miRNA targets were verified, showing that this circRNA plays a crucial role in OGD/R-induced neuron injury by binding with miRNAs[15]. A recently identified circRNA, hsa_circ_0021001, was confirmed to be significantly decreased in the peripheral blood of intracranial aneurysm patients as compared to that of controls, demonstrating its great effectiveness in the diagnosis of intracranial aneurysms [16]. The circRNAs involved in neurological disorders and their up- or downstream targets are presented in Table 1. The functions in vivo of these circRNAs require further confirmation, and more decisive identifications of the circRNAs involved in neurological disorders are expected in the future.

CIRCRNAS IN CANCERS

The detection of increased circRNAs in the peripheral blood, sera, and tissues of cancer patients have been widely reported (Table 2). A circular, testis-specific sense transcript of the sex-determining region Y (SRY) gene, also named SRY, acts to control the biological effects of miR-138 by binding to its 16 conserved binding sites [17]. In cholangiocarcinoma, SRY suppresses the expression of miR-138, leading to decreased mRNA and protein levels for the Ras homolog gene family member C (RhoC). This finally promotes the proliferation, migration, and invasion of cholangiocarcinoma cells [18]. CDR1as was shown to be upregulated in hepatocellular carcinoma (HCC) tissues, and the knockdown of CDR1as was shown to repress HCC cell proliferation and invasion by targeting miR-7 [19], suggesting that CDR1as has an oncogenic effect in HCC [20,21]. Through targeting miR-7, CDR1as also influences the progression of colorectal cancer, and it was found to be positively related to tumor size, T stage, lymph node metastasis, and poor overall patient

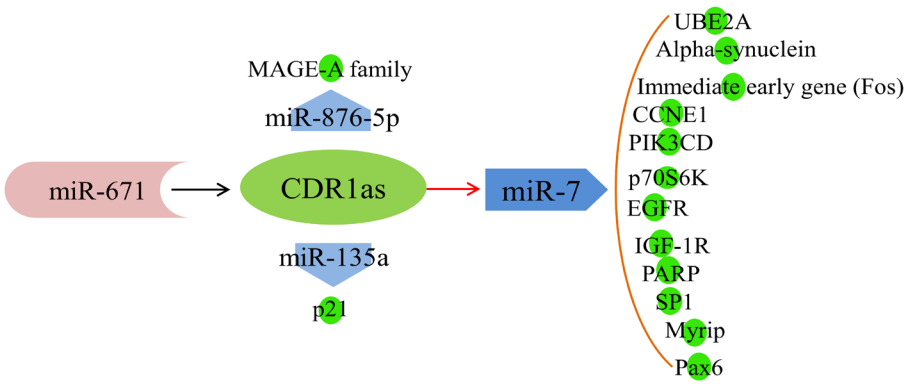

Figure 1. CircRNA CDR1as and its interaction with miRNAs.

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Table 1. CircRNAs identified in neurological disorders.

Disorders	Sites or samples	CircRNAs	MiRNAs	Potential targets	References
GBM	Biopsies	CDR1as	miR-671-5p1	——	[10]
AD	Hippocampal CAI region	CDR1as	miR-7	UBE2A	[11]
Parkinson's disease	Midbrain	CDR1as	miR-7	Alpha-synuclein	[12]
Neuropsychiatric disorder	In vivo	CDR1as	miR-7	Immediate early gene (Fos)	[13]
OGD/R-induced neuron injury	HT22 cells	mmu-circRNA-015947	2miR-188-3p, miR-329-5p, miR-3057-3p, miR-5098, miR-683	PSMG3	[15]
Intracranial aneurysms	Peripheral blood	hsa_circ_0021001	——	——	[16]

1CDR1as is the downstream target of miR-671-5p. 2These refer to miRNAs in mice.

GBM, glioblastoma multiforme; AD, Alzheimer's disease; OGD/R, oxygen-glucose deprivation/reoxygenation; CDR1as, cerebellar degeneration-related protein 1 antisense; UBE2A, ubiquitin protein ligase A; PSMG3, Proteasome assembly chaperon 3

survival [22].

By acting as a miR-876-5p sponge to boost the melanoma-antigen family A (MAGE-A) expression, CDR1as also accelerates esophageal squamous cell carcinoma progression [23]. This effect is distinct from the inhibitory effect of circ-IICH on this cancer[24]. In addition, one recent study proclaimed that CDR1as exhibited anti-oncogenic functions in bladder cancer by sponging miR-135a. In this study, a downregulation of CDR1as was observed, and the overexpression of CDR1as suppressed the proliferation, invasion, and migration of bladder cancer cells in vitro and retarded tumor growth in vivo [25]. In cholangiocarcinoma, the expression of CDR1as was notably higher than that in adjacent normal tissues, and it was closely associated with lymph node invasion, advanced tumor node metastasis (TNM) stage, and postoperative recurrence, implying its involvement in the oncogenesis and metastasis of cholangiocarcinoma [26].

In osteosarcoma cell lines, tissues, and plasma, circ-HIPK3 was found to be stably downregulated, and this downregulation was associated with poor prognosis. In addition, circ-HIPK3 overexpression notably inhibited the proliferation, invasion, and migration of osteosarcoma cells [27]. Screening differential circRNA expression profiles also revealed the regulatory role of circTCF25 in bladder carcinoma [28]. Analyses of gastric cancer tissues from gastric cancer surgery patients and plasma samples from preoperative and postoperative gastric cancer patients revealed remarkably low expressions of hsa_circ_002059. Low hsa_circ_002059 expression was significantly associated with advanced TNM stage, distal metastasis, male, and age [29]. CircRNA_100269 was also verified as being downregulated in gastric cancer and as suppressing tumor cell growth by targeting miR-630 [30]. In human oral squamous cell carcinomas, circRNA_100290 was shown to function as a competing endogenous RNA to modulate CDK6 expression via the sponging of miR-29b family members [31]. Similarly to CDR1as, circ_001569 was also shown to be upregulated in colorectal cancer and correlated with its aggressive characteristics [32], while its interaction with miRNAs warrants future clarification.

CIRCRNAS IN CARDIOVASCULAR DISEASES

Cardiovascular diseases related to stroke and coronary heart disease are increasingly recognized as leading causes of premature mortality. Hence, therapeutic intervention and early prevention are urgently needed to address this issue [33]. In the diabetic mouse myocardium, 45 circRNAs were found to be increased, while 31 were decreased. Among these, circRNA_000203 was shown to be remarkably upregulated and to contribute to myocardial fibrosis by restraining the function of miR-26b-5p [34]. By controlling the miR-141/TGF-β1 signaling axis, circRNA_010567 presented a similar impact on myocardial fibrosis progression [35]. In the peripheral blood of patients with acute myocardial infarction, 1670 circRNAs and 13 miRNAs showed differential expressions, and multiple circRNA-miRNA interactions were implicated in the occurrence of acute myocardial infarction [36]. An in silico approach identified decreased expression of a myocardial infarction-associated circRNA (MICRA) in the peripheral blood of patients with myocardial infarction. Low MICRA expression predicted left ventricular dysfunction [37], and MICRA also improved risk classification after myocardial infarction [38]. The CDR1as/miR-7 pathway also plays a role in inducing cardiomyocyte apoptosis to promote

Table 2. Roles of circRNAs in diverse cancers.

	Sites or samples	CircRNAs	Target miRNAs	Potential targets	References
Cholangiocarcinoma	Cells	SRY	miR-138	RhoC	[18]
Hepatocellular carcinoma	Tissues and cells	CDR1as	miR-7	CCNE1, PIK3CD	[19]
				p70S6K	[20]
				EGFR	[21]
Colorectal cancer	Tissues and cells	CDR1as	miR-7	EGFR, IGF-1R	[22]
	Tissues and cells	Circ_001569	miR-145	E2F5, BAG4, FMNL2	[32]
Cholangiocarcinoma	Tissues	CDR1as	——	——	[26]
Esophageal squamous cell carcinoma	Tissues	CDR1as	miR-876-5p	MAGE-A family	[23]
	Tissues	circ-ITCH	miR-7	Wnt/β-catenin	[24]
Bladder cancer	Tissues and cells	CDR1as	miR-135a	P21	[25]
	Tissues and cells	circTCF25	miR-103a-3p, miR-107	CDK6	[28]
Osteosarcoma	cell lines, tissues and plasmas	circ-HIPK3	——	——	[27]
Gastric cancer	Tissues and plasma	hsa_circ_002059	——	——	[29]
	Tissues and cell lines	CircRNA_100269	miR-630	——	[30]
Oral squamous cell carcinomas	Tissues	CircRNA_100290	miR-29b family	CDK6	[31]

SRY, sex-determining region Y; RhoC, Ras homolog gene family member C; CCNE1, Cyclin E1; PIK3CD, phosphoinositide 3-kinase catalytic subunit delta; p70S6K, p70S6 kinase; EGFR, Epidermal growth factor receptor; IGF-1R, Insulin-like growth factor 1 receptor; E2F5, E2F Transcription Factor 5 Protein; BAG-4, BCL2-associated athanogene 4; FMNL2, Formin-like 2; MAGE-A family, melanoma-antigen family A; CDK6, cyclin-dependent kinase 6.

myocardial infarction [39].

A circRNA termed "heart-related circRNA" (HRCR) has been proven to function as an endogenous miR-223 sponge to inhibit cardiac hypertrophy and heart failure, providing an attractive target for the diagnosis and treatment of these disorders [40]. The circular antisense non-coding RNA in the INK4 locus (circANRIL) is located at a position of atherosclerotic cardiovascular disease on chromosome 9p21, conferring atheroprotection by binding to pescadillo homolog 1 (PES1), an essential 60S-preribosomal assembly factor, thereby impairing exonuclease-mediated pre-rRNA processing and ribosome biogenesis in vascular smooth muscle cells and macrophages [41]. CircRNAs related to cardiovascular diseases and their potential targets are displayed in Table 3.

CIRCRNAS AND OTHER COMMON DISORDERS

Apart from these cancers and disorders of the nervous and cardiovascular systems, many other common diseases have been shown to be associated with circRNAs (Table 4). A strong interaction pair, CDR1as/miR-7, was identified in islet cells, and the overexpression of CDR1as was shown to enhance insulin content and secretion, contributing to the improvement of β cell function in diabetes [42]. In the peripheral blood of type 2 diabetes mellitus patients, 489 circRNAs were discovered to be differentially expressed, including 78 upregulated and 411 downregulated. Among them, hsa_circ_0054633 showed the highest value as a therapeutic target in pre-diabetes and type 2 diabetes mellitus [43]. Through the study of sera from diabetic retinopathy patients via circular microarray, 30 circRNAs were observed to be markedly upregulated [44]. Subsequently, circ_0005015 was verified as being upregulated in the plasma, vitreous samples, and fibrovascular membranes of diabetic retinopathy patients and to facilitate retinal endothelial angiogenic function by targeting miR-519d-3p [45]. These findings suggest the potential function of circRNAs in the pathogenesis of diabetic retinopathy through interaction with miRNAs.

The function of the chondrocyte extracellular matrix (ECM)-related circRNA (circRNA-CER) in osteoarthritis has also been unraveled. It competes for miR-136 with MMP13 to participate in the process of chondrocyte ECM degradation [46]. Hsa_circ_0005105 also promotes chondrocyte ECM degradation by sponging miR-26a and regulating nicotinamide phosphoribosyltransferase (NAMPT) [47]. Their involvement in pathogenesis earns these two circRNAs the biological marker property in osteoarthritis and other orthopedic diseases.

In the livers of nonalcoholic steatohepatitis model mice, 69 upregulated and 63 downregulated circRNAs have been authenticated, and four circRNA-miRNA-mRNA pathways have been constructed (Table 4), providing candidate targets for nonalcoholic steatohepatitis treatment [48]. Finally, given the roles of circRNAs in sponging miRNAs and the implication of miRNAs

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Table 3: CircRNAs involved in cardiovascular diseases.

	Sites or samples	CircRNAs	MiRNAs	Potential targets	References
Myocardial fibrosis	Myocardium	circRNA_000203	miR-26b-5p	Col1a2 and CTGF	[34]
	Myocardium	circRNA_010567	miR-141	TGF-β1	[35]
Myocardial infarction	Peripheral blood	MICRA	——	——	[37, 38]
	Mouse model, cardiomyocytes	CDR1as	miR-7	PARP and SP1	[39]
Cardiac hypertrophy	Mouse heart	HRCR	miR-223	ARC	[40]
Atherosclerosis	Tissues	circANRIL	——	PES1	[41]

MICRA, myocardial infarction-associated circRNA; HRCR, heart-related circRNA; Col1a2, Collagen, type I, alpha 2; CTGF, Connective tissue growth factor; PARP, Poly(ADP-Ribose) polymerases; SP1, specificity protein 1; ARC, Apoptosis repressor with caspase recruitment domain; PES1, pescadillo homologue 1.

in the initiation and progression of systemic lupus erythematosus (SLE), circRNAs have been conjectured to play a role in SLE [49], and this must be examined closely in future studies.

BIOMARKER ROLES OF CIRCRNAS IN EARLY DIAGNOSIS, TARGETED THERAPY, AND PROGNOSIS

Biomarkers are officially defined as characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [50]. Due to their indicative role in various biological and pathogenic processes, biomarkers are widely identified in many human diseases for their value in early diagnosis, personalized treatment, pharmaceutical research, and prognosis [51-54] The ncRNAs, such as the common lncRNAs and miRNAs, are a large class of macromolecular biomarkers that have attracted much attention. Recently, circRNAs have become potential new biomarkers for the processes of various disorders because of their abundance, conservation, and stage-specific and tissue-specific expression [6]. CircRNAs are usually observed to be up- or downregulated in various specimens from diseased patients, such as tissue, plasma, peripheral blood, and saliva, which are easy and suitable to obtain for quantification via painless and minimally invasive methods [55].

The clearest case is the circRNA CDR1as, which can become a biomarker for neurodegenerative disorders [11], hepatocellular carcinoma [19], and myocardial infarction [39]. In addition, a prognostic value analysis and a correlation analysis between CDR1as level and overall patient survival demonstrated that CDR1as expression could be considered an independent prognostic biomarker for cholangiocarcinoma [26]. The circRNA MICRA improved risk classification after myocardial infarction, supporting its value as a novel biomarker in future prognostication strategies [38]. The inhibitory effect of circ-HIPK3 overexpression on the proliferation, invasion, and migration of osteosarcoma cells makes it a promising diagnostic biomarker and treatment target in osteosarcoma [27]. In gastric cancer, a low expression level of hsa_circ_002059 was noted and significantly associated with advanced TNM stage, distal metastasis, male, and age, suggesting that this circRNA offers great potential as a stable biomarker for the diagnosis of gastric carcinoma [29]. Finally, circRNAs are enriched and stable in exosomes, thus presenting a promising biomarker for cancer diagnosis [56].

We have demonstrated that circRNAs play critical roles in human disease pathogenesis by interacting with miRNAs. We have also shown that the abnormal expression of circRNAs in pathological conditions

Table 4: CircRNAs and other common diseases.

	Sites or samples	CircRNAs	MiRNAs	Potential targets	References
Diabetes	Islet cells	CDR1as	miR-7	Myrip, Pax6	[42]
	peripheral blood	hsa_circ_0054633	——	——	[43]
Diabetic retinopathy	Plasma and tissues	circ_0005015	miR-519d-3p	MMP-2, XIAP, and STAT3	[45]
Osteoarthritis	Cartilage	circRNA-CER	miR-136	MMP13	[46]
	Chondrocytes	hsa_circ_0005105	miR-26a	NAMPT	[47]
Nonalcoholic steatohepatitis	Liver tissues	circRNA_002581	miR-122	Slc1a5, Plp2, and Cpeb1	[48]
		circRNA_007585	miR-326	UCP2	[48]

Pax6, Paired box 6; MMP-2, Matrix metalloproteinase-2; XIAP, X-linked inhibitor of apoptosis; STAT3, signal transducers and activator of transcription 3; MMP13, Matrix metalloproteinase 13; NAMPT, nicotinamide phosphoribosyltransferase; Slc1a5, solute carrier family A1 member 5; Plp2, proteolipid protein 2; Cpeb1, cytoplasmic polyadenylation element binding protein 1; UCP2, uncoupling protein 2.

makes them optimal clinical therapeutic targets and biomarkers for disease diagnosis and therapeutic and prognostic evaluation. As future sequencing techniques and data analysis methods evolve, we can expect more circRNAs to be exploited in various tissues and organs. Although the sponge activities and biomarker prospects of circRNAs have been fully discussed, some issues must urgently be resolved before their formal utility. Firstly, the nomenclature for circRNAs has not been standardized, and the current databases are awaiting integration. Secondly, additional bioinformatics methods must be developed for data processing. Finally, the biogenesis of circRNAs and their pathological pathways have not yet been thoroughly elucidated. With the prompt resolution of the above problems, we may anticipate the wide application of circRNAs as therapeutic targets and diagnostic biomarkers, which may lead to breakthroughs from evidence-based to precision medicine.

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