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OPINION REVIEW

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OPINION REVIEW

Circular RNA: The evolving potential in the disease world

Aarti Sharma, Cherry Bansal, Kiran Lata Sharma, Ashok Kumar

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Abstract

Circular RNAs (circRNAs), a new star of noncoding RNAs, are a group of endogenous RNAs that form a covalently closed circle and occur widely in the mammalian genome. Most circRNAs are conserved throughout species and frequently show stage-specific expression during various stages of tissue development. CircRNAs were a mystery discovery, as they were initially believed to be a product of splicing errors; however, subsequent research has shown that circRNAs can perform various functions and help in the regulation of splicing and transcription, including playing a role as microRNA (miRNA) sponges. With the application of high throughput next-generation technologies, circRNA hotspots were discovered. There are emerging indications that explain the association of circRNAs with human diseases, like cancers, developmental disorders, and inflammation, and circRNAs may be a new potential biomarker for the diagnosis and treatment outcome of various diseases, including cancer. After the discoveries of miRNAs and long noncoding RNAs, circRNAs are now acting as a novel research entity of interest in the field of RNA disease biology. In this review, we aim to focus on major updates on the biogeny and metabolism of circRNAs, along with their possible/established roles in major human diseases.

Key Words: Circular RNAs; Cancer; MicroRNA sponges; Biomarkers; Long noncoding RNA; RNA biology

Core Tip: This opinion review covers the biogenesis and metabolism of circular RNAs (circRNAs) as well as their functions and potential roles in major human diseases. We review major peer-reviewed articles published in the field of cirRNAs and the involvement of this class of noncoding RNAs in major human diseases. The role of circRNAs as molecular markers or potential targets will provide promising application perspectives, such as in early diagnoses, better treatment plans, therapeutic evaluations, prognosis predictions, and even gene therapy for human diseases.

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INTRODUCTION

The human genome is defined as "blueprint" for human life and is composed of DNA. The intermediate molecules arising from the genome, known as RNA, help manufacture crucial biomolecules such as proteins, which perform cellular processes. After sequencing the human genome, researchers surprisingly found that approximately 95% of the genome does not code for proteins. Since this is noncoding DNA, it originally appeared to have an unknown biological function, and many scientists referred to it as junk DNA or garbage of the human genome. However, there are multiple molecular milestones after the discovery of the function of the noncoding DNA, especially the regions of genome, which eventually get transcribed to RNA. Hence, these RNAs have been randomly designated as "intergenic RNA", "long non-coding RNAs" *etc.*, which initially led to their underrepresentation in molecular biology. Circular RNAs (circRNAs) are one of the great surprise discoveries that include a huge group of non-coding RNAs that are produced by an unconventional splicing method, also known as a non-canonical splicing event. Non-canonical splicing is called backsplicing, through which a downstream splice-donor site is covalently linked to an upstream splice-acceptor site. Previously mysterious circRNAs have been noted to impact gene expression by acting as microRNA (miRNA) sponges. Some circRNA molecules serve as molecular "sponges," binding to and deactivating gene modulators called miRNAs to influence gene expression[1]. These findings reveal an unseen world of previously unmapped RNA molecules, and remind us that there are many more RNA types than merely mDNA and its respective encoded protein. Over the past 40 years, researchers have uncovered a string of surprising forms of RNA, from uncommonly short RNA and extraordinarily long noncoding RNA (lnRNA) that prevent other RNA strands from being translated. However, due to the absence of a poly(A) tail, circRNAs, went unnoticed with conventional RNA sequencing methods as their ends are joined together to from a loop. Recently, the advancement of technologies has confirmed the presence of circRNAs in many species, including humans. It is a matter of curiosity to follow the lead of circRNA surprises, just like the *Junk DNA* previously known as garbage DNA now so-called remote control of the human genome. The present review outlines the remarkable potential of circRNA surprises in the disease world. We will focus on major updates on the biogeny and metabolism of circRNAs, along with their potential/established roles in major human diseases.

TYPES OF NON-CODING RNAS

The noncoding RNAs (ncRNAs) can be characterized into two subdivisions, the housekeeper ncRNAs (rRNA, tRNA, snRNA, and snoRNA) and regulatory ncRNAs[2-4]. The regulatory ncRNAs are classified by length of transcript which comprises small ncRNAs < 200 bp (siRNA and miRNAs) and lnRNAs (transcript > 200 bp). CircRNAs are part of lnRNAs that emerged as a new class of endogenous RNAs and exist extensively in mammalian cells, which are emerging as crucial elements of cellular homeostasis. Figure 1 shows the circRNA biogenesis through various mechanisms.

DISCOVERY

CircRNAs are different from linear RNAs as the 3' and 5' ends typically present in an RNA molecule are merged. This characteristic feature has laid the foundation of various newly discovered functions of circRNAs. Many circRNAs evolve from protein-coding genes which do not code for any proteins themselves. Instead, they act as potential regulators of gene expression by various known and unknown biological processes. The first human circRNA was discovered around 32 years ago by Nigro *et al*[5] in 1991 from spliced transcripts of a candidate tumor suppressor gene, *DCC*[5]. This novel discovered RNA product had been considered to be a result of splicing errors during transcription[6]. Since advances in high throughput sequencing techniques, many circRNAs have been discovered, though there are still a lot to be discovered[7]. Furthermore, circRNAs are more stable than linked mRNAs *in vivo* and are resistant to RNase activity[7,8]. CircRNAs form more than 14% of actively transcribed genes in human fibroblasts and in some cases, the abundance of circRNA molecules surpassed that of associated linear mRNA by greater than 10-fold[7-9].

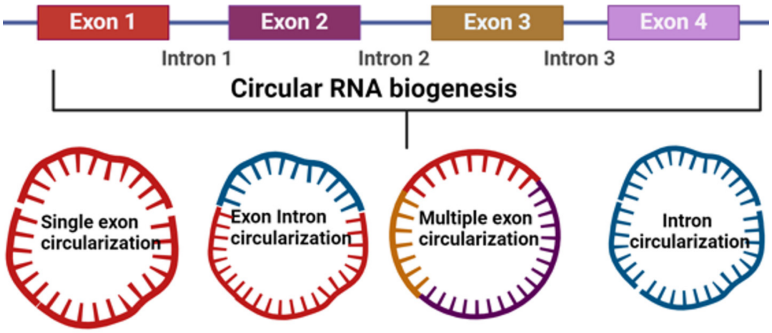

Figure 1 Formation of circular RNAs (created with BioRender.com).

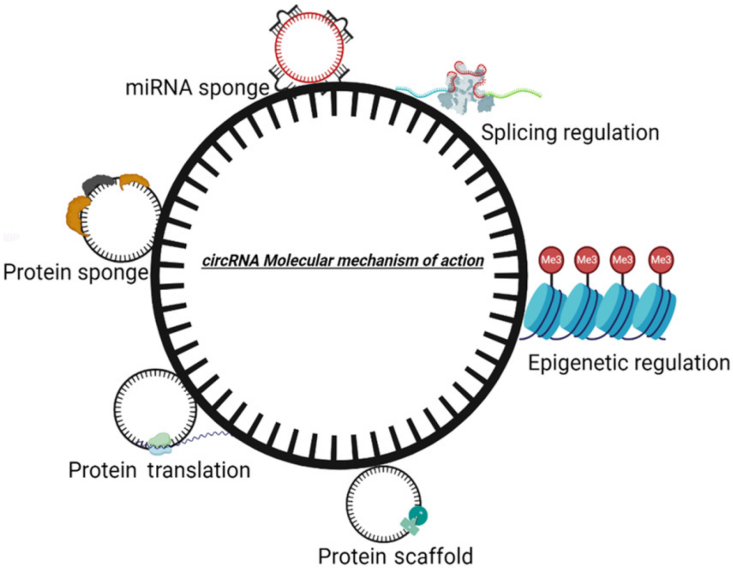

Figure 2 Molecular mechanisms of gene regulation *via* circular RNAs (created with BioRender.com). circRNA: Circular RNAs.

CIRCULAR RNAS AND THE UNDERLYING MECHANISM FOR GENE REGULATION

CircRNAs have remarkable potential in regulating the function of a gene. The various mechanism by which circRNAs are involved in controlling genetic events are sponging miRNA, interacting with RNA-binding protein (RBP), regulating transcription, regulating splicing, getting translated into proteins, and epigenetic regulation (Figure 2).

The major role of circRNAs as strong posttranscriptional regulators of gene expression is *via* acting as miRNAs sponges. They might also possibly sponge RBPs. CircRNAs throw genetics for a loop as they not only can act as sponges for miRNAs originating outside the cell but also have various other surprising functions including possible binding sites for viral miRNAs[10]. The combined analysis of high throughput transcriptome data coupled with deeper bioinformatic analyses characterizes a powerful approach to illuminate likely biological functions of ribonucleoprotein complexes. By examining circRNAs predominantly expressed in the brains of humans and mice, researchers at Aarhus University in Denmark, found that some circRNA molecules were blocking miR-7 (a type of miRNA) that usually inhibits expression of certain mRNAs. Therefore, the circRNA was controlling the activity of the blocker, increasing the expression of miR-7's target genes[11]. A research article studied the expression profile of circRNAs using advanced microarray technology and demonstrated the changing expression profiles of 24 circRNAs and 37 miRNAs often altered at each stage of osteoclast differentiation during osteoclastogenesis[12]. This shows a great involvement of circRNAs in developmental biology. Nevertheless, the universal properties of circRNAs are not recognized yet. Because circRNAs do not have 5' or 3' end, they are resistant to exonuclease-mediated degradation and are presumably more stable than most linear RNAs in cells [13].

PUTATIVE FUNCTIONS OF CIRCULAR RNAS

CircRNAs are mainly known to function as molecular sponges or decoys for miRNAs and controlling gene expression. CircRNAs can impact protein function either by sequestering the proteins and hence modifying their functional potential or *via* acting as a scaffold for protein-protein interaction. CircRNAs can interact with other RNA molecules and act as

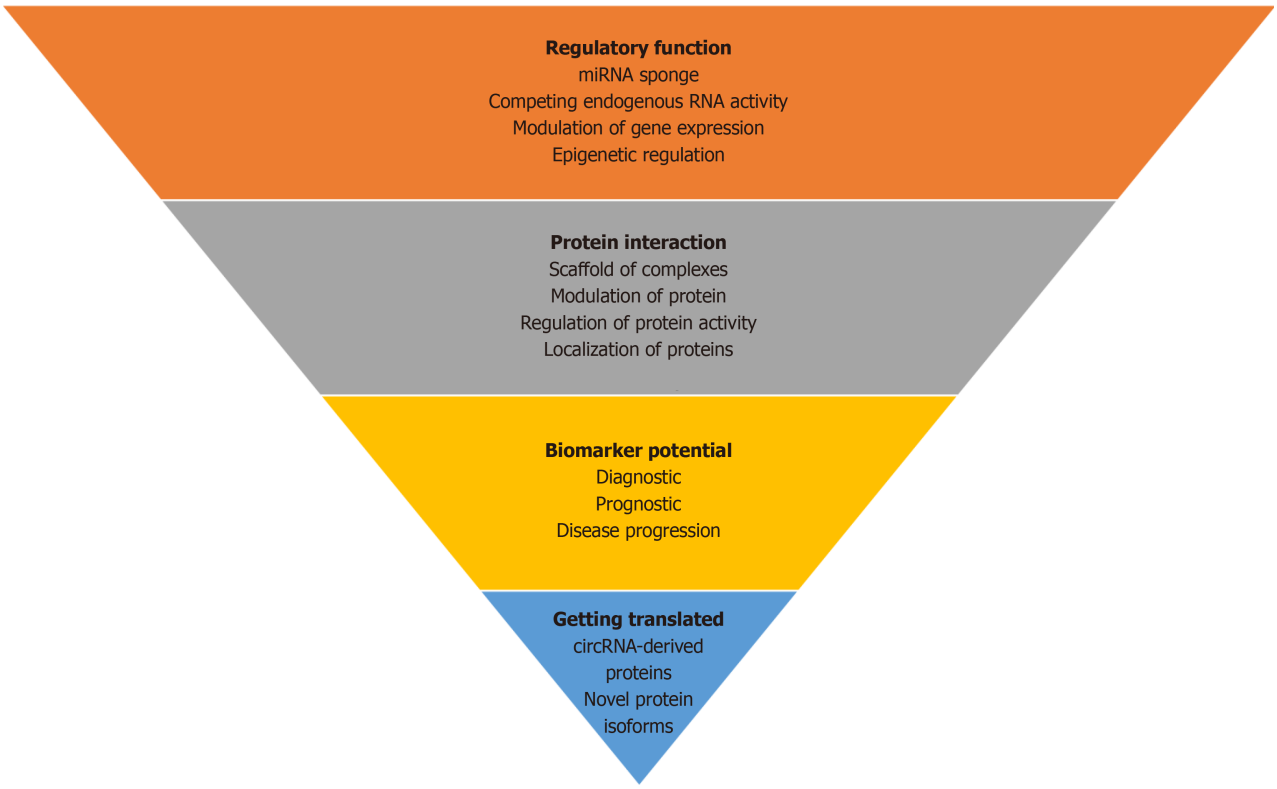

Figure 3 Functions of circular RNAs in descending order of abundance. circRNA: Circular RNAs.

regulators of gene expression by interacting with RNA-binding proteins and modulating their functions. CircRNAs are also translated into proteins known as circRNA-derived proteins. Moreover, circRNAs have shown potential as diagnostic or prognostic biomarkers for various diseases, including but not limited to cancer, cardiovascular diseases, and neurological, respiratory, and endocrine disorders (Tables 1 and 2). Their stability, tissue-specific expression patterns, and presence in bodily fluids make them attractive candidates for disease detection and monitoring. The field of circRNAs research is still evolving, and further studies are needed to fully understand their biological functions and significance. The putative roles mentioned above represent current hypotheses and areas of ongoing investigation. Figure 3 shows the functions of circRNAs in descending order of abundance.

GENOME-WIDE CATEGORIZATION OF CIRCULAR RNAS

Genome-wide investigations have found many circRNAs are conserved during evolution and enormous in number. CircRNAs have been categorized through extensive collections of the RNA sequencing data[14-16]. As circRNAs lack a poly(A) tail, the possible circRNA isoforms were identified *via* search for sequencing reads indicating a junction between two "scrambled" exons. A published landmark research article revealed that the junction sites of many circRNAs in rice (*Oryza sativa*) are flanked by diverse non-GT/AG splicing signals whereas most human exonic circRNAs are flanked by canonical GT/AG splicing signals[17]. This research provided a method for genome-wide identification of full-length circRNAs and increased the understanding of splicing signals of circRNAs. Most of the circRNAs functionally remains indefinable with only few exceptions. Table 3 summarizes the preliminary attempts of genome-wide circRNA identification in the human genome[18-20].

CIRCULAR RNAS AND THEIR INVOLVEMENT IN VARIOUS HUMAN DISEASES

Circular RNAs and cancer

CircRNAs are extensively studied in cancers and there is huge data available showing their tissue-specific and cancer-specific expression patterns. Cancer-based studies revealed the clinical relevance of circRNAs like cancer-associated biomarkers, prognosis indicators, and formulation of treatment options. CircRNAs have been detected in liquid biopsies such as in various body fluids like plasma, blood, saliva, and urine making it an excellent choice as a non-invasive diagnosis for cancer[21]. There are many circRNAs identified in various cancers, which have diverse functions such as maintaining growth signaling, escaping growth inhibitors, resisting apoptosis, uncontrolled replicative immortality, promoting angiogenesis, and activating invasion and metastasis. The malignant cell must have one or more of these characteristics to gain immortality. CircRNAs are highly dysregulated in various human cancers and contribute to dif-

Table 1 Circular RNAs as potential biomarkers in major human diseases

Body system	Disease	circRNA	Expression	Ref.
Cardiovascular	Myocardial infarction	circRNA_081881	Down	[43]
		MICRA	Up	
	Cardiac fibrosis	circRNA_010567	Up	[44]
	Congenital heart disease	hsa_circ_004183	Down	[45]
		hsa_circ_079265		
		hsa_circ_105039		
	Hypertension	hsa_circ_0037911	Up	[46]
	Cardiomyopathy	circDNAJC6	Down	[47]
		circTMEM56		
		circMBOAT2		
	Heart failure	hsa_circ_0062960	Up	[48]
	Coronary artery disease	hsa_circ_0124644	Down	[49]
		hsa_circ_0001879	Down	[50]
		hsa_circ_0004104	Down	[51]
		hsa_circ_0001445	Up	
	Atrial fibrillation	hsa_circ_025016	Up	[52]
Central nervous system	Moyamoya disease	hsa_circRNA_089761	Down	[53]
		hsa_circRNA_100914		
		hsa_circRNA_089763		
	Temporal lobe epilepsy	circ-EFCAB2	Up	[54]
		circ-DROSHA	Down	[55]
		circRNA-0067835	Down	
	Alzheimer's disease	CDR1as/ciRS-7	Down	[56,57]
		circPVT1	Up	[58]
	Parkinson's disease	CDR1as/ciRS-7	Up	[59]
		circzip-2		
	Multiple sclerosis	circ_0005402	Down	[60]
		circ_0035560		[61]
	Prion disease	CDR1as/ciR-7	Up	[56,62]
Psychiatry	Schizophrenia	hsa_circRNA_104597	Down	[63]
Respiratory	Tuberculosis	hsa_circRNA_001937	Up	[64]
		hsa_circRNA_005086	Up	[35]
		hsa_circRNA_009024	Up	
		hsa_circRNA_104964	Down	
		hsa_circRNA_102101	Down	
		hsa_circRNA_104296	Down	
	Siliocosis	hsa_circ_0058493	Up	[65]
		circRNA-012091	Down	[66]
	Pulmonary hypertension	circ-GSAP	Down	[67]
		circ_0068481	Up	[68]
	Acute respiratory distress syndrome	hsa_circRNA_101952	Up	[69]

		hsa_circRNA_101523	Up	
		hsa_circRNA_102927	Down	
		hsa_circRNA_100562	Down	
		hsa_circRNA_102034	Down	
Endocrine	Diabetes mellitus	CiRS-7	Up	[70]
		hsa_circ_0068087		[71]
		hsa_circ_0124636		[71]
		hsa_circ_0139110		
		hsa_circ_0054633		
	Diabetes/glucose	CDR1as/cirRS-7	Up	[70,72]
	Homeostasis/CVD	circRNA-HIPK3	Up	[73]
		circRNA-WDR77	Up	
		circANKRD36	Up	
	Diabetic cardiomyopathy	circRNA_000203	Up	[74]
		circRNA_010567	Up	[44]
		hsa-circ-0076631	Up	[75]
	Diabetic nephropathy	circRNA_15698	Up	[59,75,76]
	Gestational diabetes	circ_5824	Down	[75]
		circ_3636	Down	
		circ_0395	Down	
	Diabetic retinopathy	circRNA-0005015	Up	[75]
		circRNA-HIPK3	Up	[77]
		cZNF609	Up	[78]
		circRNA-cPWWP2A	Up	[79]

ferent phenotypes.

The most intriguing circRNAs that have drawn the focus of scientists are the fusion-circRNAs (f-circRNA) which can arise from tumor-associated chromosomal translocations. F-circRNAs are capable of stimulating cellular transformation, therapeutic resistance, and tumor cell survival[22]. Previous studies identified circRNAs derived from cancer-associated chromosomal translocations and showed their tumor-promoting properties. These studies further found that tumor-associated chromosomal rearrangements lead to formation of f-circRNAs that are produced from transcribed exons of distinct genes affected by the translocations[23,24]. F-circRNAs participate in a variety of functions including cellular transformation and stimulating cell viability and/or resistance upon therapy[23,24]. Their work demonstrated the existence of f-circRNAs and their relevance to human disease and the findings lead to a milestone on f-circRNA and its link with the progression of cancer. These studies are very exciting leads, but further research on clinical samples is needed to fully establish their role. Table 2 shows only those articles that have sufficient evidence of circRNAs as potential biomarkers in various human cancers.

Circular RNAs in neurological disorders

CircRNAs levels are dynamically altered in neuronal cells throughout differentiation and many of them are enhanced in synapses. Moreover, there is evidence showing that circRNAs also accumulate with age, which is still a less explored area of biology[25]. Collectively, existing data indicate that circRNAs have crucial functions in synaptic plasticity and neuronal function. CircRNAs in the mammalian brain are highly abundant, conserved, and dynamically expressed[26]. Numerous studies have shown that circRNAs are more enriched in neuronal tissues and are often originated from genes specific for neuronal and synaptic function. In addition, their expression is regulated during neuronal development by synaptic plasticity, indicating their potential in specific neuronal functions[27].

Circular RNAs and endocrine diseases

The involvement of circRNAs in various endocrine disorders like gynecological disease, Graves' disease, age-related macular degeneration, and diabetes has been studied widely. However, this review only focuses on the landmark discoveries made regarding circRNAs; therefore, it covers the major articles only. There is evidence about the involvement of various circRNAs in diabetes. Studies have shown that circRNAs might be potential promising diagnostic biomarkers and valuable clinical treatment targets for diabetes and diabetic nephropathy[28].

Table 2 Circular RNAs as potential biomarkers in major human cancers

Cancer	circRNA	Expression	Function/target	Ref.
Lung cancer	hsa_circ_0005962	Up	Promotes proliferation; non-invasive diagnostic biomarker	[80]
	hsa_circ_0086414	Down	Cancer progression; non-invasive diagnostic biomarker	[80]
	hsa_circ_0102537	Down	Biomarker for diagnosis; fluid shear stress and PI3K-Akt signaling pathway	[81]
	hsa_circ_0000190	Up	Tumorigenesis and immune evasion; facilitates tumorigenesis and immune evasion by upregulating the Expression of soluble PD-L1 in non-small-cell lung cancer	[82]
	CDR1as	Up	Enduring growth signaling; regulating miR-219a-5p/SOX5 axis	[83]
	hsa_circ_0001715	Up	Distant metastasis; potential diagnostic and prognostic Biomarker	[84]
	circPTK2	Down	Activating invasion and metastasis; inhibits TGF-β-induced epithelial-mesenchymal transition and metastasis by controlling TIF1γ	[85]
	circ_0067934	Up	Activating invasion and metastasis; regulating miR-1182/KLF8 axis and activating Wnt/β-catenin pathway	[86]
	hsa_circ_0012673	Up	Cancer cell proliferation and invasion; *via* miR-320a/LIMK18521 axis	[87]
	F-circEA-2a	Up	Promotes cell migration and invasion	[88]
	F-circEA	Up	Promotes cell migration and invasion; potential diagnostic value	[89]
	circRNA_100876	Up	Distant metastasis; potential prognostic biomarker and therapeutic target	[90]
	circRNA_ZEB1/hsa_circ_0023404	Up	Promotes proliferation, migration, and invasion; regulating miR-217/ZEB1 axis	[91]
	CiRS-7	Up	Increased proliferation, migration, and invasion, yet reduced apoptosis; targets NF-κB signaling	[92]
HCC	has_circ_0001445	Up	Regulates proliferation and migration; targets miR-942-5p/ALX4 axis	[93]
	has_circ_0027089	Up	Biomarker for diagnosis of hepatitis-related HCC	[94]
	has_circ_0016788	Up	Evading growth inhibitors; targets miR-486/CDK4 pathway	[95]
	circ-SMARCA5	Down	Inhibits cell proliferation and promotes apoptosis; potential prediction and monitoring biomarker for HCC	[96]
	circSMAD2	Down	Activating invasion and metastasis; inhibits epithelial-mesenchymal transition by targeting miR-629	[97]
	has_circ_0064428	Down	Immune-associated prognostic biomarker for HCC patients	[98]
	has_circ_0009582; circ_0037120	Up	Biomarker for diagnosis	[99]
	has_circ_0140117	Up	Potential biomarkers for predicting occurrence of HCC	[99]
	CDR1as	Up	Cell proliferation and migration; enduring growth signaling	[100]
Gastric cancer	has_circ_0010882	Up	Role in proliferation, migration, and invasive phenotypes; regulation of PI3K/Akt/mTOR signaling	[101]
	has_circ_0001017	Down	Cell proliferation, migration, and invasion; sponge of miR-197	[102]
	has_circ_0061276; hsa_circ_0001017	Down	Potential prognostic tumor biomarkers	[103]
	has_circ_0000745	Down	Regulating GC growth and migration; promising diagnostic biomarker	[104]
	circ-Rangap1	Up	Cancer invasion and metastasis; targeting miR-877-3p	[105]
	has_circ_0000181	Up	Distant metastasis and TNM stage; diagnostic biomarker	[106]
	circ-PSMC3	Down	Cell proliferation and metastasis	[107]
	circ-LMTK2	Down		
	circ-DLST	Up		
	circ-KIAA1244	Down	TNM stage and lymphatic metastasis	[108]

	circ-ZFR	Down	Evading growth inhibitors; sponging miR-130a/miR-107 and modulating PTEN	[109]
	CDR1as	Down	Evading growth inhibitors; targeting miR-876-5p/GNG7 axis	[110]
	circRNA-000425	Down	Evading growth inhibitors; proliferation, apoptosis, and cell drug sensitivity *via* YAP1-induced tumorigenesis	[111]
	circRNA_0023642	Up	Activating invasion and metastasis; regulating epithelial-mesenchymal transition	[112]
	has_circ_0001178	Up	Invasion and metastasis; *via* sponging multiple miRNAs	[113]
	has_circ_0005927	Down	Cell colony-forming ability, migration, and invasion; regulating miR-942-5p/BATF2 axis	[114]
	has_circ_0082182	Up	Drug resistance and cancer progression; sponging miR-326	[115]
	hsa_circ_0082182, hsa_circ_0000370	Up	Inhibit apoptosis; potential diagnostic markers	[116]
	has_circ_0035445	Up	Promotes proliferation and migration but suppresses apoptosis; potential diagnostic marker	[116]
	has_circ_0006990	Up	Cancer progression; *via* mediation of hsa_circ_0006990/miR-132-3p/MUC13 axis	[117]
	CDR1as	Up	Enduring growth signaling; regulating microRNA-7	[118]
	circHIPK3	Up	Enduring growth signaling; sponging miR-7	[119]
	hsa_circ_0007534	Up	Blocking apoptosis	[120]
	hsa_circRNA_103809	Down	Cell proliferation and migration; *via* miR-532-3p/FOXO4 axis	[121]
	hsa-circ-0020397	Up	Regulates CRC cell viability, apoptosis, and invasion by promoting the expression of miR-138 target genes	[121]
Breast cancer	hsa_circ_0001785	Up	Proliferation, migration, and invasion; potential diagnostic value	[122]
	hsa_circ_0008673	Up	Prognostic predictor of OS and DSS	[122]
	circ-ITCH	Down	Evading growth inhibitors; targets Wnt/β-catenin pathway	[123]
	hsa_circ_0104824	Down	Cell migration, cell-cell adhesion, and proliferation; promising predictive biomarker and therapeutic target	[124]
Esophageal cancer	circ-TTC17	Up	Promotes proliferation and migration; novel biomarker for diagnosis, treatment, and prognosis	[125]
	hsa_circ_0007203 (circ-DLG1)	Up	Promotes cell proliferation	[126]
	hsa_circ_0004771	Up	Diagnostic biomarker; targets *via* miR-339-5p/CDC25A axis	[127]
	circGSK3β	Up	Promoting metastasis; augmenting β-catenin signaling	[128]
	circ-SLC7A5	Up	Regulator of tumorigenesis and metastasis	[129]
Pancreatic cancer	circ-LDLRAD3	Up	Proliferation, migration and invasion; *via* miR-137-3p/PTN axis	[130, 131]
	circNFIB1, hsa_circ_0086375	Down	Lymphangiogenesis and lymphatic metastasis; *via* miR-486-5p/PIK3R1/VEGF-C axis	[132]
Thyroid cancer	has_circ_0124055	Up	Regulates proliferation and apoptosis: Prognostic and diagnostic indicator	[133]
	has_circ_0101622	Up	Regulates proliferation and apoptosis: Prognostic and diagnostic indicator	[133]
Gallbladder cancer	circ-MTO1	Up	Early diagnostic and prognostic marker	[134]
	circHIPK3	Up	Evading growth inhibitors; sponging miR-124	[135]
Ovarian/endometrial cancer	has_circ_0078607	Up	Adverse prognostic indicator for ovarian cancer; regulating miR-32-5p/SIK1 network	[136]
	has_circ_0061140	Up	Activating invasion and metastasis; targeting miR-197/high mobility group protein A1 axis in endometrial cancer	[137]
Glioma/glioblastoma	hsa_circ_0046701	Up	Enduring growth signaling; critical regulatory roles *via* hsa_circ_0046701/miR-142-3p/ITGB8 axis	[138]
	circ-FBXW7	Down	Enduring growth signaling; potential prognostic implications	[139]

	circNFIX	Up	Blocking apoptosis; regulating miR-378e/RPN2 axis	[140]
	cZNF292	Up	Promoting angiogenesis; Wnt/β-catenin signaling	[141]

HCC: Hepatocellular carcinoma; OS: Overall survival; DSS: Disease-specific survival; TGF-β: Transforming growth factor-β; GC: Gastric cancer; circRNA: Circular RNAs.

Table 3 Genome-wide identification of circular RNAs: How it began

Ref.	Genome-wide identification of circRNAs
Salzman *et al*[18], 2012	Aimed to distinguish cancer-specific exon scrambling events
	Identified 2748 scrambled isoforms in Hela and H9 embryonic stem cells
	Conclusion: 98% of scrambled isoforms represent circRNAs
Jeck *et al*[8], 2013	Classified circular transcripts based on their levels of abundance using three stringencies categories (low, medium, high)
	Conclusion: circRNAs are conserved, stable, and nonrandom products of RNA splicing that could be involved in the control of gene expression
Memczak *et al*[7], 2013	Developed a computational method to detect circRNAs
	Conclusion: circRNAs form a significant class of post-transcriptional regulators
Guo *et al*[19], 2014	Identified and quantified human circRNAs from ENCODE Ribozero RNA-seq data
	Conclusion: Most circRNAs are nonsignificant side-products of splicing error
Zhang *et al*[20], 2014	Developed CIRCexplorer to distinguish thousands of circRNAs in humans with p(A)-wloRNase R RNA-seq data
	Conclusion: Alternative circularization paired with alternative splicing can generate additional circRNAs from one gene, which is suggestive of the new line of complexity in gene regulation

circRNA: Circular RNAs.

A previous study observed that elevated glucose levels might modify circRNA expression in endothelial cells. This connection between endothelial cells and diabetic associated complications is mediated by circRNAs, which are the center of the events causing the pathogenesis of hyperglycemic endothelial injury[29]. Moreover, the ciRS-7–miR-7 axis is deeply linked to diabetes[30]. In support of the above statement, previous research data has shown that pancreatic islet cells highly express miR-7 that ultimately blocks beta-cell proliferation, leading to disrupted rapamycin (mTOR) signaling pathway[31]. However, circRNAs and their link to diabetes mellitus are a comparatively new discovery and additional research required. Table 1 outlines the various research articles and their findings in more detail.

Circular RNAs and cardiovascular disorders

CircRNAs are broadly expressed in mammalian cells, and it they have a crucial role in cardiogenesis. The literature shows that 1702 circRNAs are expressed during cardiogenesis[32], which contribute to cell specification and differentiation[33, 34]. Further evidence suggests that circRNAs have a crucial role in the pathogenesis of cardiac disorders[35]. Hence, these can act as potential biomarkers in cardiovascular diseases.

Heart-related circRNA (HRCR) was the first circRNA found to be inhibited in hypertrophic hearts. Researchers noticed that HRCR binds and impedes the miRNA miR-223, which was associated with cardiac hypertrophy[36]. Additionally, it has also been found that the circRNA CDR1AS binds to miR-7 and miR-7a and exacerbates myocardial infarction-mediated cardiomyocytes loss[37]. CircRNA_081881 expression levels drop by 10-times in myocardial infarction patients' blood, which makes this circRNA a potential biomarker for cardiac diseases[38]. Although the evidence present in the literature are intriguing and exciting, additional research on circRNAs using advanced technologies can enlighten this relatively less explored area of research.

Circular RNAs in respiratory disorders

CircRNAs are implicated in malignant and non-malignant respiratory disorders. Many research articles are suggestive of their prospective as biomarkers for respiratory disorders. To date, circRNAs have been identified in lung cancer as well as in non-cancerous respiratory diseases like pulmonary hypertension, pulmonary tuberculosis (TB), acute respiratory distress syndrome, and silicosis, but they may not be limited to just these entries mentioned here[39]. One of the exciting roles of circRNAs which made a headline previously is the diagnosis of TB. A study by Fu *et al*[40] confirmed that blood samples could be used to diagnose TB. They examined circRNAs in peripheral blood mononuclear cells in healthy individuals and TB patients regarding the diagnosis of TB using circRNAs[40]. Hence, circRNAs can act as biomarkers to diagnose TB. In a nutshell, circRNA expression signatures could be probable biomarkers in the diagnosis and prognosis of various respiratory disorders.

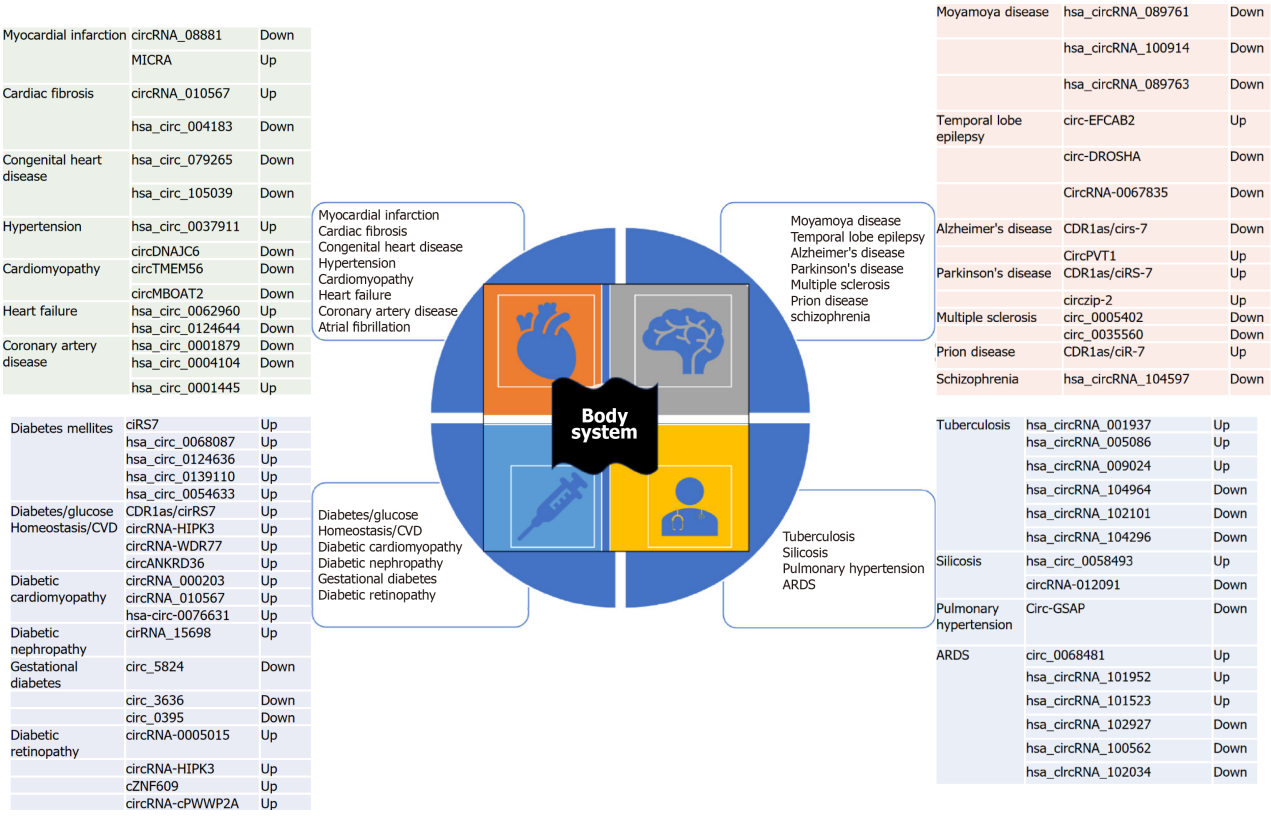

Figure 4 Role of circular RNAs in various non-malignant human diseases. ARDS: Acute respiratory distress syndrome; CVD: Cardiovascular disease; circRNA: Circular RNAs.

Figure 4 shows important roles of circRNAs in various non-malignant human diseases. Figure 5 shows summarized view of circRNAs as potential biomarkers in major human cancers classification based on cancer hallmark signatures[41, 42].

LIMITATIONS

The emerging evidence from experimental settings has shown the crucial role of circRNAs in various human diseases. A single circRNA can perform multiple functions including but not limited to miRNA sponging, protein sponging, translation, spliceosome regulation, and epigenetic regulation. Therefore, targeting circRNAs to manipulate the effect of its downstream targets like miRNAs and genes can prove to be a new powerful treatment-oriented approach for multiple diseases. The covalently closed loop like structure of circRNAs is highly stable compared to other RNAs and can be detected in body fluids like saliva, blood, and urine. These characteristics make circRNAs an favorable choice for biomarkers. Multiple patient-based studies have also validated the correlation of circRNA expression levels with clinical data.

However, circRNAs are still underrepresented targets in molecular biology because of the lack of enough functional studies. A few challenges associated with circRNAs are that they are not detected in RNA sequencing data because of the lack of poly(A) tail and hence easily ignored from most of RNA sequencing studies. Moreover, circRNAs perform a diverse range of complex functions that require a high level of computational skills to decode. The current methods of circRNA detection in body fluids have limitations and are associated with high cost. These challenges can be solved with further advancement of research by future studies. Although circRNAs are favorable disease biomarkers, there are yet various key problems to be addressed for the application of circRNAs in disease settings and further evidence is needed to support the clinical significance of circRNAs in specific diseases.

CONCLUSION

CircRNAs play critical roles in numerous diseases. Once thought to be functionless, circRNAs have now become a major research agenda. Most of the research articles enlisted in this review are related to the relationship between the expression of circRNAs and patient clinical characteristics. Moreover, circRNAs play a vital role in many aspects of disease-related phenotypes, including cell cycle, apoptosis, vascularization, invasion, and metastasis. Additional studies are required to further understand the mechanism of interactions between circRNAs and tumors. Moreover, the abundance

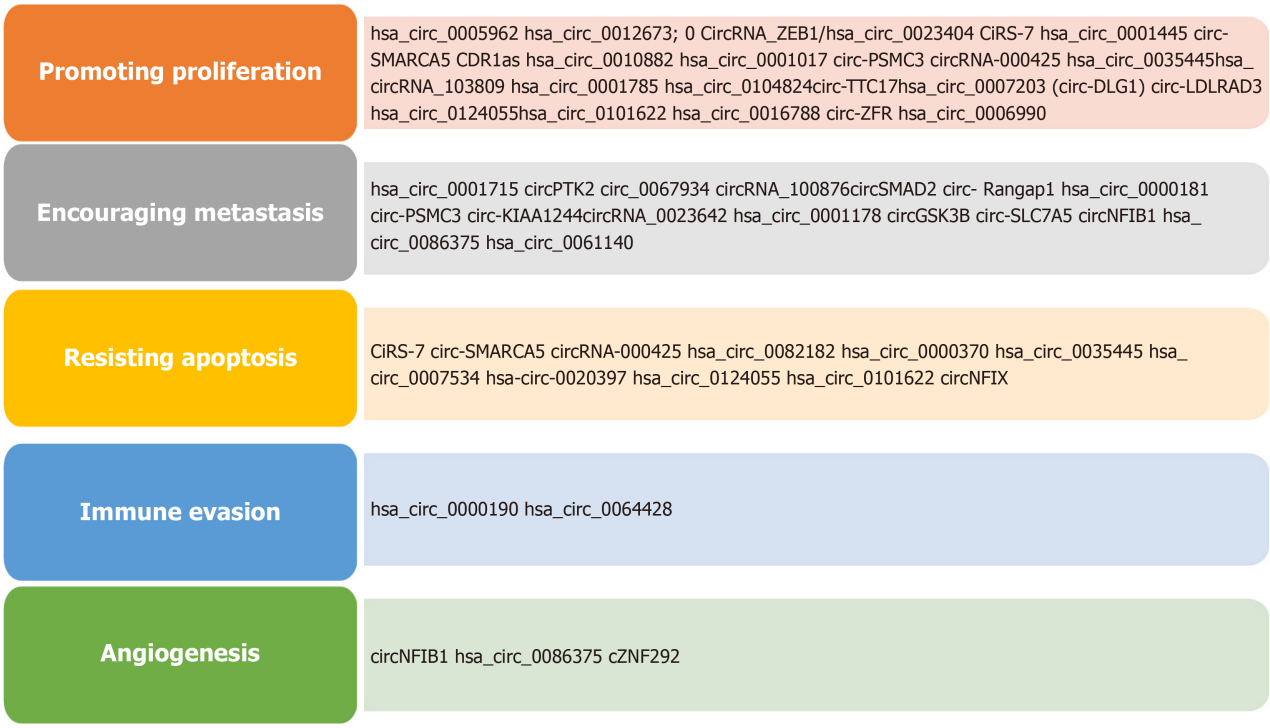

Figure 5 Circular RNAs as potential biomarkers in major human cancers (classification based on cancer hallmark signatures).

of circRNAs in other human diseases like cardiovascular, endocrine, and respiratory disorders has also opened doors for potential identification of new circRNA-based therapeutic and prognostic markers in major human diseases. The functions of circRNAs as potential molecular markers and potential targets still need to be studied more extensively. In conclusion, there are potential application perspectives of circRNAs in healthcare science including but not limited to early diagnosis, better treatment formulation, prognosis prediction, and even gene therapy for human diseases.

FOOTNOTES

Author contributions: Sharma A designed and wrote the manuscript; Sharma KL and Bansal C performed the literature search and designed the tables and figures; Kumar A is the senior author and supervised all the work. All authors have proofread and finalized the manuscript.

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