

Circular RNAs

Subjects: **Genetics & Heredity**

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in adults in developed countries. CVD encompass many diseased states including hypertension, coronary artery disease and atherosclerosis. Studies in animal models and human studies have elucidated the contribution of many genetic factors, including non-coding RNAs. Non-coding RNAs are RNAs not translated into protein, involved in gene expression regulation post-transcriptionally and implicated in CVD. These include long non-coding RNAs. Of these, circular RNAs (circRNAs) and micro RNAs. CircRNAs are created by the back-splicing of pre-messenger RNA and have been underexplored as contributors to CVD. These circRNAs may also act as biomarkers of human disease as they can be extracted from whole blood, plasma, saliva and seminal fluid. CircRNAs have recently been implicated in various disease processes, including hypertension and other cardiovascular disease. This review article will explore the promising and emerging roles of circRNAs as potential biomarkers and therapeutic targets in CVD, in particular hypertension.

long non-coding RNA

circular RNA

micro RNA

hypertension

coronary artery disease

atherosclerosis

cardiovascular disease

heart disease

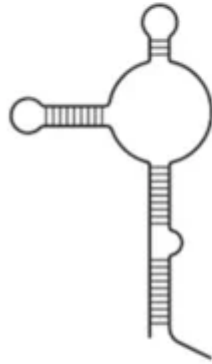
1. Introduction

CircRNAs are abundant, underexplored ncRNAs. Recent studies revealed that large numbers of circRNAs are endogenous, highly conserved and stable in mammalian cells and prevalent in disease states (Figure 1)^[1]. Although mRNA and circRNAs both originate from precursor-mRNAs, they are formed differently, giving them unique characteristics. mRNAs are formed by RNA splicing where introns are removed, and certain exons are included or excluded to create alternative coding mature mRNAs. This process creates linear mRNAs with exposed poly(A) tails. This characteristic leaves them prone to degradation by RNases^[2]. Meanwhile, circRNAs are formed by back-splicing, promoting the circularization process where exons and/or introns converge onto each other, potentially protecting them from degradation and conferring a half-life of approximately 48 h, around five times more stable than linear mRNAs (Figure 2)^[3].



Micro RNAs

- around 22 bp long
- tissue specific
- high conservation



Long non-coding RNAs

- over 200 bp long
- tissue specific
- low conservation



Circular RNAs

- from 32 bp to several thousand
- tissue specific
- high conservation
- more resistant to degradation

Figure 1. Brief characteristics of non-coding RNAs. Legend: bp, base pairs.

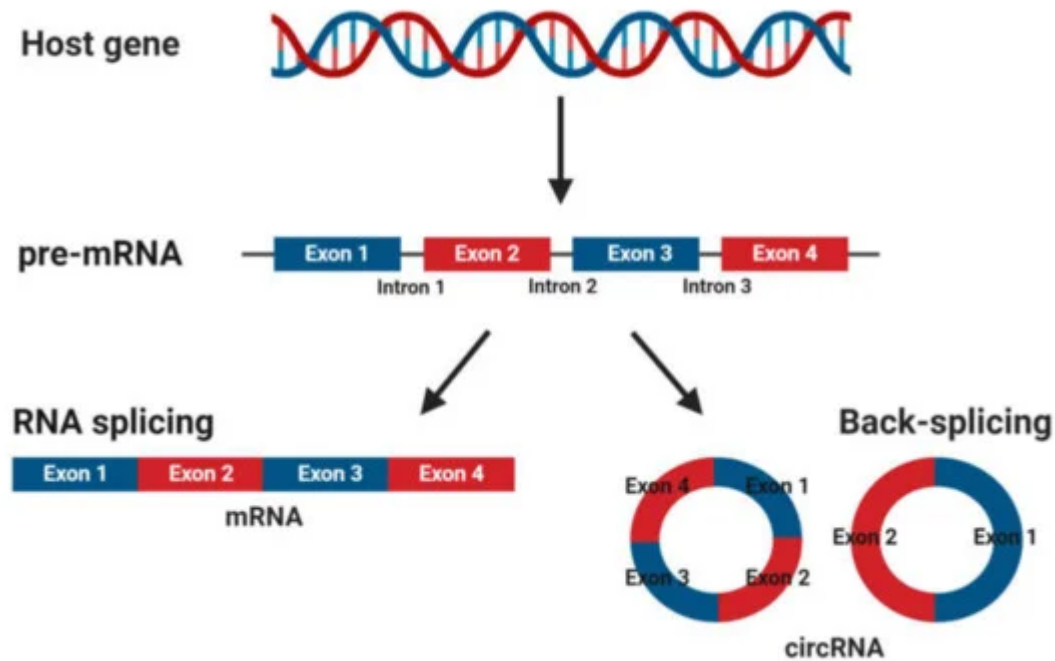


Figure 2. Biogenesis of mature messenger RNA (mRNA) and circular RNA (circRNA) from precursor mRNA (pre-mRNA). Pre-mRNA undergoes RNA splicing to form a mature mRNA or back-splicing to form circRNAs.

2. Function

The definitive function of circRNAs still remains unclear. It has been proposed that circRNAs regulate the expression of linear mRNA transcripts both directly, via the competition with the splicing machinery^[4]; and indirectly, acting as sponges to miRNAs due to the presence of multiple binding sites, allowing them to interact with and sequester cellular miRNAs preventing the performance of their roles on post-transcriptional regulation (Figure 3)^{[5][6]}.

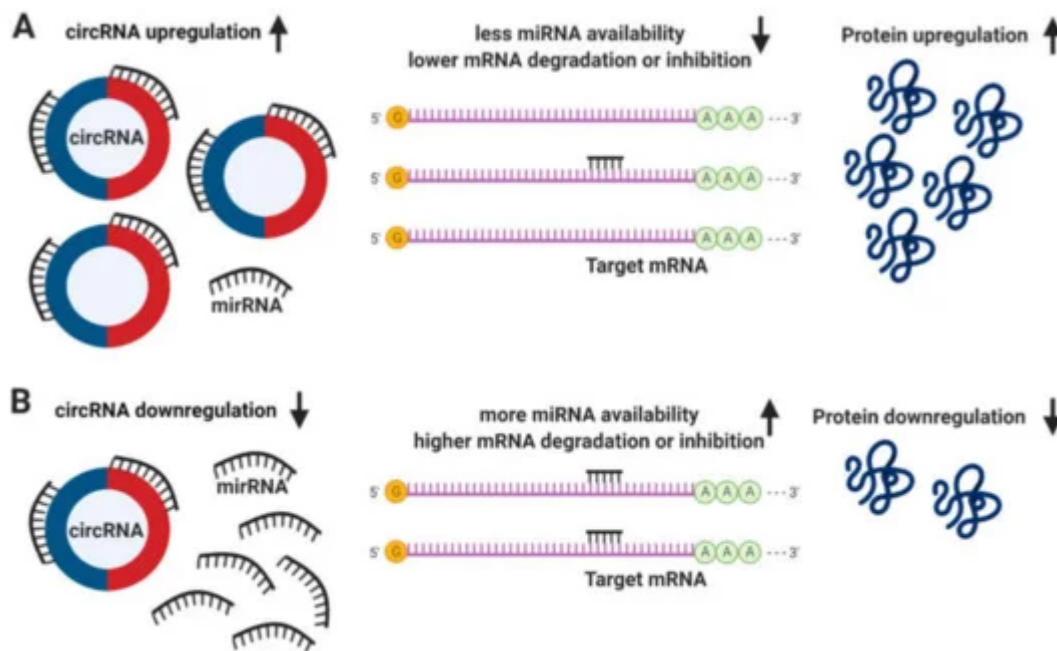


Figure 3. Circular RNA (circRNA) functions. **(A)** The upregulation of circRNAs leads to a decrease in microRNA (miRNA) availability, messenger RNA (mRNA) degradation or inhibition, resulting in an increase of protein translation. **(B)** Conversely, the downregulation of circRNAs leads to more miRNA available and higher levels of mRNA degradation or inhibition, leading to a downregulation in protein translation.

Importantly, circRNAs make up 1% of total RNA being expressed widely in various cell types and may have a regulatory function in human disease, with a pivotal role in the initiation and progression of various types of biological processes^[5], potentially acting as a biomarker for the discovery and investigation on the progression of disease. However promising, research to identify and characterize circRNAs has mostly been performed using bioinformatics and in silico approaches and a limited number of studies have investigated their function in situ or in vivo to establish their involvement in disease.

The properties described above and promising research in the field of cancer genomics using circRNAs as biomarkers is encouraging and should be explored and translated into cardiovascular genomics research. This is extremely relevant, as conventional methods for controlling risk factors and initiating early treatment in CVD intervention have often led to poor prognosis. Current biomarkers usually detect the disease at later stages of development, increasing the need for the discovery of new biomarkers for prevention or at early onset of disease. This further highlights the benefits of using circRNAs as potential biomarkers in CVD (Table 1).

Emerging evidence of circular RNAs in cardiovascular disorders has demonstrated differential expression in both healthy and diseased hearts^{[7][8][9][10]}. However, the relevance of circular RNAs to the cardiovascular system remains poorly characterised, and an improvement in understanding of circRNA involvement in CVD will form a basis for the development of these RNAs as biomarkers for discovery, prediction and therapeutic agents. Importantly, the combination of genetic sequencing and bioinformatics discovery has enabled the identification of many novel circRNAs.

Table 1. Summary of circRNAs implicated in cardiovascular diseases, including species and sample types studied and differential expression direction.

Disease	Circular RNA	Species	Sample	Expression	References
Hypertension	hsa_circ_0005870	Human	Blood	Down	[11]
	hsa_circ_0037909	Human	Blood	Up	[12]
	hsa_circ_0037911	Human	Blood	Up	[13]
	hsa_circ_0126991	Human	Blood	Up	[14]
	hsa_circ_0014243	Human	Blood	Up	[15]
Myocardial infarction	mmu_circ_0001878	Mouse	Cardiomyocytes	Up	[16]
	circTtc3	Rats	Cardiomyocytes	Up	[17]
	MICRA	Human	Blood	Down	[18]
	circNfix	Mouse	Cardiomyocytes	Up	[19]

Atherosclerosis	circFndc3b	Mouse Human	Cardiomyocytes	Down	[20]
	circRNA-0044073	Human	Blood	Up	[21]
	ocu-ciR-novel-18038	Rabbit	Blood	Down	
	ocu-ciR-novel-18298	Rabbit	Blood	Up	
	ocu-ciR-novel-15993	Rabbit	Blood	Up	
	ocu-ciR-novel-17934	Rabbit	Blood	Down	[22]
	ocu-ciR-novel-17879	Rabbit	Blood	Up	
	ocu-ciR-novel-18036	Rabbit	Blood	Up	
	ocu-ciR-novel-14389	Rabbit	Blood	Up	
	circANRIL	Human	Blood	Up	[23]
	circCHFR	Human	VSMC	Up	[24]
	circRNA-0003575	Mouse	Endothelial cells	Up	[25]

Coronary artery disease	hsa_circ_0001879	Human	Blood	Up	[26]
	hsa_circ_0004104	Human	Blood	Up	
	hsa_circ_0124644	Human	Blood	Up	[27]
	hsa_circ_0098964	Human	Blood	Up	
	hsa_circ_0030769	Human	Blood	Up	[28]
	hsa_circ_0079828	Human	Blood	Up	
	hsa_circ_15486-161	Human	Blood	Up	
	hsa_circ_0122274	Human	Blood	Up	
	hsa_circ_16316-13	Human	Blood	Up	
	hsa_circ_0140538	Human	Blood	Up	
Cardiomyopathy	mmu_circ_0000254	Mouse	Cardiomyocytes	Down	[29]
	hsa_circ_0076631	Human	Cardiomyocytes and Serum	Up	[30]
	circRNA_000203	Mouse	Ventricular Cardiomyocytes	Up	[31]

circSlc8a1	Mouse	Cardiomyocytes	Up	[32]
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Legend: ciR, circular; circ, circular; circANRIL, circular antisense non-coding RNA in the INK4 locus; circCHFR, circular checkpoint with fork-head associated and ring finger; circFndc3b, circular fibronectin type III domain containing 3B; circNfix, circular nuclear factor I X; circSlc8a1, circular solute carrier family 8 member a1; circTtc3, circular tetratricopeptide repeat domain 3; hsa, Homo sapiens; MICRA, myocardial infarction-associated circular RNA; mmu, Mus musculus; ocu, Oryctolagus cuniculus; VSMC, vascular smooth muscle cells.

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