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Review: Research status of cardiovascular and cerebrovascular diseases and non-coding RNA

Xiaofeng Hu [1#] , Jun Jiang [2,3,*]

1 Department of Cardiology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China
2 School of Life Sciences, Fudan university, Shanghai, China
3 Endoscopy Center, Minhang Hospital, Fudan University, Shanghai, China

[#] This author contributed equally to this work
* Address for Correspondences:
Jun Jiang
School of Life Sciences, Fudan University, Shanghai, China
Endoscopy Center, Minhang Hospital, Fudan University, Shanghai, China
E-mail: jun_jiang@fudan.edu.cn

Abstract

Cardiovascular and cerebrovascular diseases (CVD) encompass a range of conditions affecting the heart, brain, and blood vessels, including coronary heart disease, hypertension, and stroke. In recent years, there has been growing evidence highlighting the significant role of non-coding RNAs (ncRNAs) in the development and progression of cardiovascular diseases. Among the various types of ncRNAs, long-stranded non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) have emerged as prominent players in cardiovascular research. Advancements in technology and in-depth research have revealed that ncRNAs and circRNAs exert regulatory effects on the biological functions of the cardiovascular system through various pathways. For instance, they can modulate the proliferation, migration, and apoptosis of vascular endothelial cells, as well as regulate cardiac muscle contraction and cardiomyocyte apoptosis. Additionally, ncRNAs and circRNAs can influence downstream targets and pathways involved in cardiovascular diseases. The exploration of ncRNAs and circRNAs in cardiovascular research has opened up new avenues for the diagnosis and treatment of CVDs. By understanding the intricate regulatory mechanisms mediated by these non-coding RNAs, researchers have gained valuable insights into the pathogenesis of cardiovascular diseases and identified potential therapeutic targets. Consequently, these studies have provided novel ideas and approaches for the diagnosis, prevention, and management of CVDs.

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KEYWORDS

Cardiovascular and cerebrovascular diseases; LncRNA; CircRNA; Clinical implications; Review

Introduction

Cardiovascular and cerebrovascular diseases (CVD) are prevalent conditions caused by atherosclerosis and a combination of risk factors, including high blood pressure, blood viscosity, smoking, diabetes, alcoholism, obesity, and genetic predisposition. These diseases pose a significant threat to human health and are characterized by their high prevalence, mortality, and death rates[1, 2]. Globally, CVD accounts for the highest number of deaths, with approximately 15 million fatalities reported each year[3]. Common CVD conditions include hypertension, coronary heart disease, atrial fibrillation, heart failure, atherosclerosis, and stroke[4]. Other conditions such as aneurysms, cardiomyopathy, and pericarditis are also encompassed within the scope of CVD[5]. Among these, coronary heart disease and stroke are particularly common and pose greater risks[6]. With advancements in technology and medical techniques, the prevention and treatment of CVD have seen improvements and updates. Strategies such as exercise, dietary modifications, and drug therapies have been developed to address these conditions[7, 8]. Additionally, interventions targeting high-risk groups have gained attention and recognition.

Overview of lncRNAs and circRNAs

Non-coding RNA (ncRNA) refers to a group of endogenous small RNA molecules that do not encode proteins but play important regulatory roles in post-transcriptional processes[9, 10]. This category includes long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and other types of ncRNAs, all of which are closely associated with the regulation of various cardiovascular pathophysiological functions and the development of diseases[11]. LncRNAs, in particular, represent 80%-90% of all ncRNAs and are found widely in animals, plants, yeast, and even viruses[12, 13]. Figure 1 illustrates the diverse functions of lncRNAs. One of the key roles of lncRNAs is acting as a microRNA (miRNA) sponge, regulating the expression of target genes by sequestering miRNAs[14, 15]. Additionally, lncRNAs can interact with proteins, influencing their activities. They can serve as structural components, forming nucleic acid-protein complexes that bind to gene promoter regions, thereby controlling gene transcription and repressing the expression of adjacent protein-coding genes[16]. LncRNAs can also modulate gene expression by inhibiting RNA polymerase II or mediating chromatin remodeling and histone modifications[17]. Moreover, lncRNAs can generate complementary double strands with transcripts of protein-coding genes, interfering with mRNA splicing and producing various splicing variants[18]. Another mechanism by which lncRNAs regulate gene expression is by forming complementary double strands with transcripts of protein-coding genes and generating endogenous small interfering RNAs (siRNAs) under the action of the Dicer enzyme[19]. Furthermore, lncRNAs may interact with specific proteins and modify their subcellular localization[20]. The advancement of sequencing technology has facilitated numerous studies that have demonstrated the potential of targeting lncRNA expression to improve various diseases, including coronary heart disease, heart failure, and hypertension. LncRNAs may also serve as biomarkers for the diagnosis and prognosis of cardiovascular diseases[21, 22].

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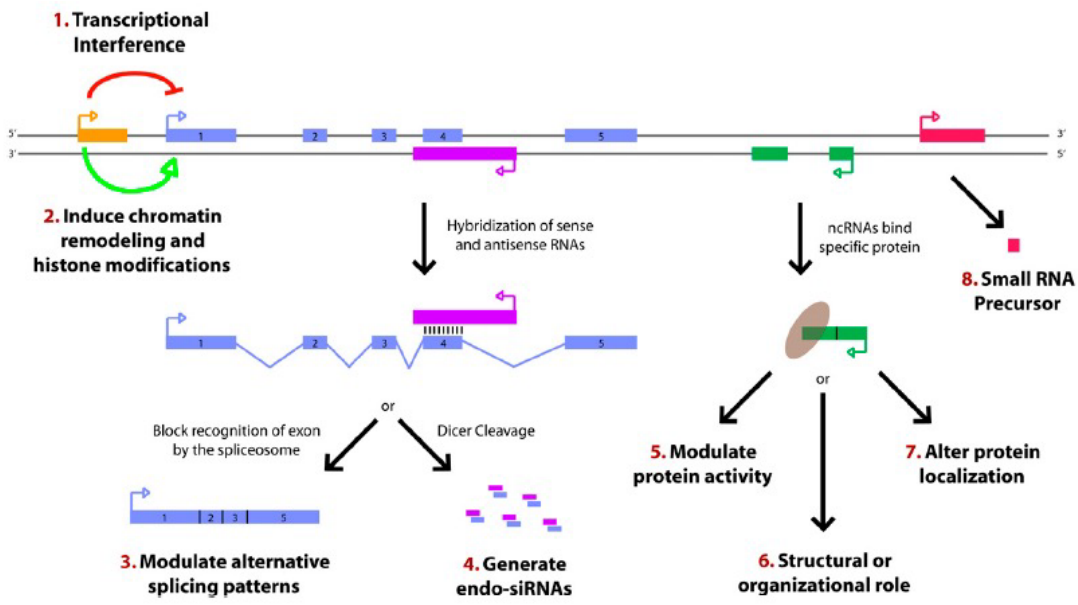

FIGURE 1

Mechanism of lncRNA functions.

Circular RNA (circRNA) is a type of non-coding RNA that forms a closed circular structure without a 5' cap and a 3' poly(A) structure[23] (Figure 2). CircRNAs are primarily located in the cytoplasm, with some also present in the nucleus, and they exhibit characteristics such as tissue specificity and stability[24, 25]. These molecules possess various biological activities, including acting as miRNA sponges to competitively bind and sequester miRNAs, thereby indirectly regulating the expression of downstream target genes (Figure 3a)[26]. CircRNAs can also interact with RNA-binding proteins (RBPs) to influence mRNA splicing patterns or mRNA stability (Figure 3b)[27]. Furthermore, circRNAs and ElcircRNAs can bind to small ribonucleoproteins, influencing transcription by interacting with RNA polymerase II (Figure 3c)[28]. Certain circRNAs have been found to be capable of translation by ribosomes, leading to the production of functional polypeptides involved in regulatory processes (Figure 3d)[29]. Numerous studies have demonstrated that dysregulated expression of circRNAs plays a significant role in the development of cardiovascular diseases[30, 31]. For instance, circEsyt2 was found to be highly expressed in mouse atherosclerotic plaques and neointima during vascular remodeling. Knockdown of circEsyt2 resulted in inhibited proliferation and migration of vascular smooth muscle cells (VSMCs), as well as increased cell apoptosis[32]. Additionally, circRNAs have been implicated in various pathological processes of cardiovascular diseases, including cardiac apoptosis, cardiac hypertrophy, and myocardial fibrosis[33, 34]. In cerebrovascular diseases, circRNAs can regulate vascular endothelial cell function and impact cerebrovascular permeability and stability[35, 36]. Moreover, circRNAs have been implicated in the development and progression of hematological diseases, as well as in cell proliferation, migration, and apoptosis in the vascular wall[37, 38].

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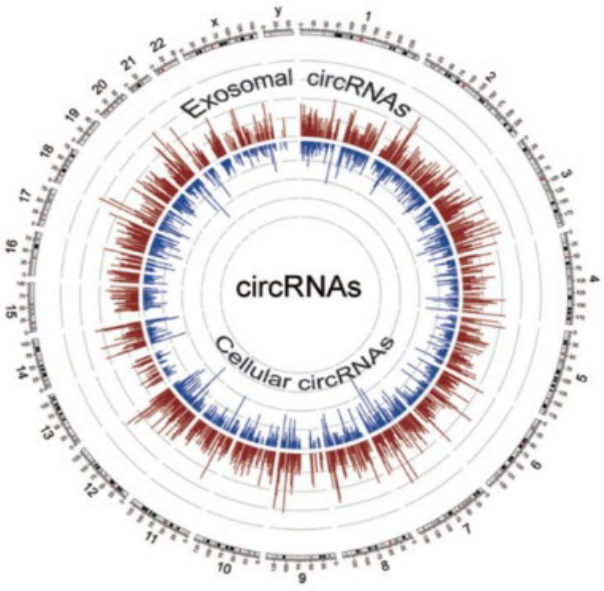

FIGURE 2

Schematic diagram of the structure of circRNA.

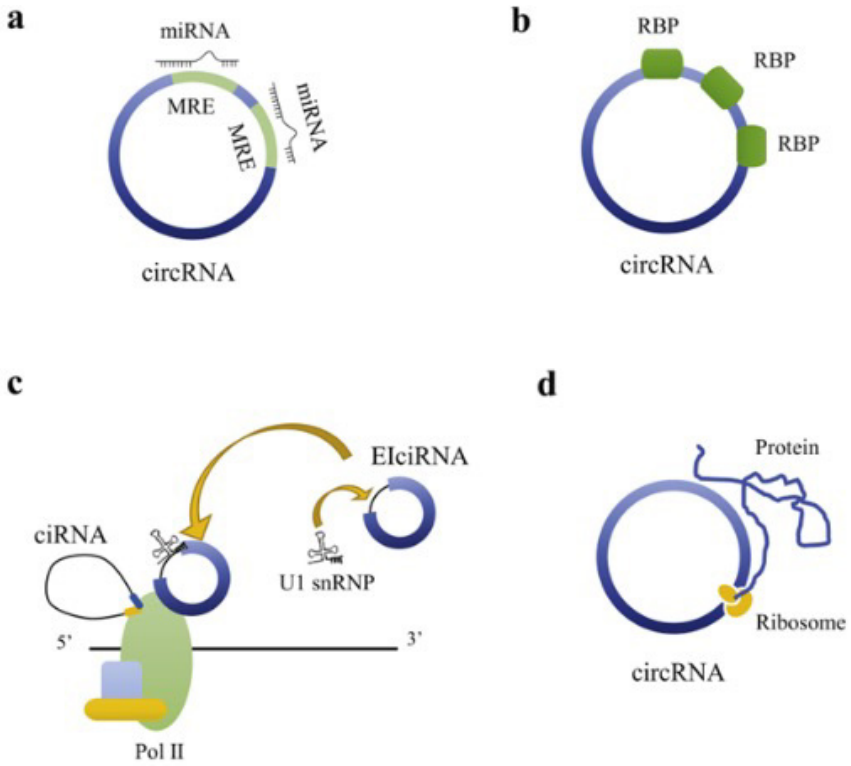

FIGURE 3

Regulatory mechanisms of circRNAs.

a. miRNA sponge. b. Regulation of protein binding. c. Regulates gene transcription. d. Encodes a function.

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This review paper provides a comprehensive overview of the current research status pertaining to lncRNA and circRNA in the context of cardiovascular diseases. It highlights the significant roles played by lncRNAs and circRNAs in the diagnosis, treatment, and drug development of cardiovascular diseases, and discusses their potential as promising tools for developing novel therapeutic strategies in clinical settings.

Research status of lncRNAs and circRNAs in CVD

Hypertension

Hypertension is a chronic condition characterized by elevated systemic arterial blood pressure, leading to functional or structural damage in organs such as the heart, brain, and kidneys[39, 40]. It is considered a major risk factor for cardiovascular diseases, including heart disease, stroke, and kidney disease[41, 42]. Recent studies have highlighted the regulatory role of lncRNA in the pathogenesis of hypertension, particularly in processes such as myocardial cell growth and differentiation, cell apoptosis and autophagy, and extracellular matrix synthesis and degradation. These processes are closely associated with the development and progression of hypertension [22, 43]. For instance, increased expression of MALAT1 has been observed in hypertension rat models and is linked to vascular smooth muscle cell proliferation and vascular remodeling[44, 45]. Conversely, H19 has been found to be downregulated in rat models, exerting a protective effect by modulating the p53 signaling pathway, suppressing cell proliferation, and attenuating vascular remodeling[37]. GAS5 has been identified as a key regulator of hypertension, modulating endothelial and vascular smooth muscle cell function through the β-catenin signaling pathway[46, 47]. Furthermore, studies conducted on the Chinese Han population have demonstrated a significant correlation between the expression level of CDKN2B-AS1 and the prevalence of hypertension[48], and single nucleotide polymorphisms in CDKN2B-AS1 have been associated with susceptibility to hypertension[49]. These findings highlight the involvement of lncRNAs in the pathogenesis of hypertension and offer potential targets for therapeutic interventions in the management of this condition.

The expression levels of circRNA have been found to be closely associated with the clinical manifestations and prognosis of hypertension[50]. Several studies have demonstrated the potential of circRNAs as biomarkers for hypertension[51, 52]. For instance, upregulated circ_0000284 has been identified as an independent risk factor for hypertension and has shown high diagnostic accuracy in clinical models[53]. Bioinformatics analysis has revealed that hsa_circ_0037897 may also serve as a risk factor for essential hypertension[54]. Additionally, five circRNAs, namely hsa_circ_0105130, hsa_circ_0109569, hsa_circ_0072659, hsa_circ_0079586, and hsa_circ_0064684, have been identified as being associated with essential hypertension[55]. Other circRNAs such as hsa_circ_0126991, hsa_circ_0014243, and hsa_circ_0037909 have also been recognized as potential biomarkers for essential hypertension[51, 56, 57]. Mechanistically, circRNAs can impact cardiovascular function by regulating the expression of transcription factors, microRNAs, and proteins, thereby influencing the development and progression of hypertension[58, 59]. For example, downregulated circ_0037078 has been found to promote the growth and angiogenesis of trophoblast cells through the miR-576-5p/IL1RAP axis, offering new insights into the understanding of pre-eclampsia, a common hypertensive disorder induced by pregnancy[60]. These findings highlight the significance of circRNAs in the pathophysiology of hypertension and suggest their potential utility as diagnostic biomarkers and therapeutic targets for this condition.

Coronary artery disease (CAD)

CAD is a complex cardiovascular disease characterized by the narrowing or blockage of coronary arteries. Its etiology involves various factors[61, 62]. LINC00657 has been identified as closely associated with the development of CAD. Overexpression of LINC00657 has been found to promote CAD progression, while downregulation of its expression reduces ischemia/reperfusion injury in the heart[22, 63]. ANRIL is involved in CAD progression through multiple

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mechanisms, including gene expression regulation, interference with the cell cycle, and apoptosis regulation. Guo F et al. have demonstrated the diagnostic potential of ANRIL in CAD when used in conjunction with miR-181b and the NF-κB signaling pathway[64]. The lncRNA H19, a commonly studied lncRNA, also plays a significant role in CAD[65]. Overexpressed H19 can promote apoptosis and myocardial fibrosis, thus accelerating the progression of coronary heart disease[66]. MIAT, another well-studied lncRNA, affects the growth, differentiation, and apoptosis of cardiomyocytes, influencing CAD progression through pathways involving inflammatory response and oxidative stress. MIAT can serve as a predictive marker for CAD[67]. HOTAIR, as described in the literature by Kim IJ et al., acts as an antagonist of cardiovascular disease by targeting miR-1 and miR-125 to inhibit apoptosis and regulate downstream genes, thereby preventing acute myocardial ischemia[68]. Additionally, other lncRNAs such as TONSL-AS1, which is downregulated in CAD, are associated with poor patient prognosis[69]. The low expression of CASC11, another lncRNA, is also linked to higher mortality in CAD patients[70, 71]. These findings underscore the significant roles of various lncRNAs in the pathogenesis of CAD and highlight their potential as diagnostic markers and therapeutic targets.

Several studies have highlighted the important role of circRNAs in CAD. For instance, circRNA_010567 has been implicated in regulating the development and progression of CAD through the miR-141-3p/FOXP1 signaling pathway[72]. CircRNA_000203 expression levels not only impact the development and severity of CAD but also influence its progression by modulating gene expression, cell cycle, and apoptosis[73]. Overexpression of circRNA_000284 exacerbates myocardial ischemia/reperfusion injury, whereas its downregulation reduces such injury[74]. Hsa_circ_0124644 has been validated as a diagnostic marker for coronary heart disease, and its diagnostic efficacy increases when combined with hsa_circ_0098964[75]. Through cellular experiments, Zhou H et al. demonstrated that BTBD7_hsa_circ_0000563 may participate in CAD regulation, making it a potential novel diagnostic target for CAD[76]. Additionally, a review by Zhang S et al. summarized the regulatory roles of various circRNAs in CAD, including circSATB2, circRuSc2, circNFIB, circTtc3, circNCX1, and circFndc3b, as depicted in Figure 4[77]. These findings provide insights into the involvement of circRNAs in CAD pathogenesis and underscore their potential as diagnostic markers and therapeutic targets.

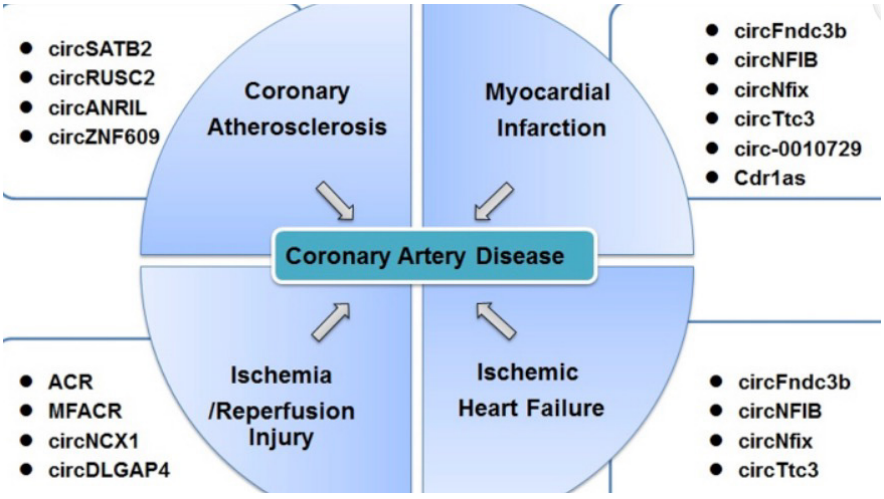

FIGURE 4
Some circRNAs associated with the pathogenesis of CAD.

Atrial fibrillation (AF)

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia characterized by rapid and irregular contractions of the atria

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[78, 79]. LncRNAs have been shown to influence the onset and progression of AF by regulating various cellular processes, including the cell cycle, apoptosis, ion channels, and other pathways[80]. For instance, the lncRNA LICPAR has been identified as a promoter of AF development through its regulation of the TGF-β/Smad signaling pathway[81]. Additionally, increased expression of MALAT1 has been observed in AF patients and is implicated in the development of AF by modulating apoptosis and cardiomyocyte superoxide dismutase expression, among other mechanisms[82]. Another lncRNA, ANRIL, which is associated with cardiovascular disease, exhibits upregulated expression in AF patients and can influence the onset and progression of AF by affecting the expression of ion channels, among other pathways[83, 84]. Conversely, FENDRR expression levels are significantly down-regulated in AF patients, and its overexpression has been found to substantially inhibit AF development[85]. In a study by Xie L et al., AF-related lncRNAs were analyzed using bioinformatics techniques, revealing a negative association between LINC00844 and resting dendritic cells, the ability of certain lncRNAs to suppress CD8+ T cells to enhance drug resistance, and the impact of differentially expressed lncRNAs on AF through immune and inflammatory signaling pathways [86]. Moreover, Dai H et al. demonstrated that the lncRNA NEAT1 negatively regulates the expression of miR-320-NPAS2 in cardiac fibroblasts, which not only exerts a significant influence on atrial fibrosis but also represents a potential target for the treatment of AF[87].

Recent studies have highlighted the significant role of circular RNAs (circRNAs) in the development and progression of AF [88]. For instance, Ruan ZB et al. conducted an analysis revealing that the hsa-miR-328 co-expression network is associated with the pathophysiology and pathogenesis of AF [89]. Notably, circCAMTA1 has been shown to influence AF progression by modulating the miR-214-3p/TGFBR1 signaling pathway and other pathways[90]. Similarly, circRNA_0004104 has been identified to target pathways such as the MAPK/TGF β signaling pathway, shedding light on the regulatory mechanisms underlying AF[91]. Zhang PP et al., through genome-wide profiling, discovered that hsa_circ_0000075 and hsa_circ_0082096 target the TGFβ signaling pathway implicated in AF pathogenesis[92]. Another recent study reported significant upregulation of hsa_circRNA025016 expression in the plasma of AF patients, indicating its potential as a biomarker for predicting new-onset AF after non-extracorporeal coronary artery bypass grafting[93]. In a study focused on nonvalvular persistent atrial fibrillation (NPAF), Zhang Y et al. identified ceRNA networks associated with circRNAs in NPAF patients using bioinformatics analysis, including hsa_circRNA002085 and hsa_circRNA001321, which may represent novel targets for clinical AF research[94]. Additionally, has_circ_0006314 and hsa_circ_0055387 have demonstrated potential predictive value for postoperative AF [95].

Heart Failure (HF)

HF is a cardiac condition characterized by insufficient blood delivery to various organs, leading to organ damage[96]. It commonly arises from underlying conditions such as coronary heart disease, high blood pressure, cardiomyopathy, and heart valve disease[97, 98]. HF often presents with symptoms like fatigue, dyspnea, chest tightness, palpitations, insomnia, and coughing, and in severe cases, it can result in sudden death [99]. Clinical treatments for HF typically involve medication (diuretics, ACE inhibitors, ARBs, beta-blockers, etc.) and surgery[100]. Despite advancements in modern medicine, many patients still face challenges in receiving effective treatment for HF[101]. Consequently, researchers are actively exploring novel therapeutic tools and targets, including lncRNAs. LncRNAs play crucial regulatory roles in the development and progression of HF, including the regulation of biological processes such as cardiomyocyte proliferation, apoptosis, and autophagy[102, 103]. For instance, the expression level of the well-known lncRNA H19 has been found to strongly correlate with HF severity[104, 105]. Additionally, upregulation of lncRNA MALAT1 expression has been observed after myocardial infarction, and it has been shown to regulate cardiomyocyte proliferation and apoptosis [106, 107]. LncRNA NEAT1 has also been implicated in HF, as its upregulation can induce cardiomyocyte apoptosis and myocardial fibrosis[108]. Liu N et al. identified lncHrt, a cardiomyocyte-enriched lncRNA that influences metabolism and the pathophysiological mechanisms associated with HF [109]. Furthermore, a research team from Japan discovered a novel lncRNA called Caren, which not only protects against HF by inactivating the DNA damage response and activating mitochondrial biosynthesis but also regulates gene translation and maintains cardiomyocyte homeostasis[110]. Gu Q et al. demonstrated that the lncRNA SOX2-OT affects ischemic HF by inhibiting miR-455-3p, which, in turn, mitigates the process

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by targeting TRAF6. These findings suggest that the SOX2-OT/miR-455-3p/TRAF6 axis could serve as a potential therapeutic target for ischemic HF[111].

The study of circRNAs in HF has gained considerable attention. One notable circRNA, circHIPK3, exhibits significantly high expression levels in the myocardial tissue of HF patients and positively correlates with the severity of cardiac HF[112, 113]. Furthermore, the expression level of circRNA cZNF292 has been associated with HF development [114]. Upregulated circRNA cZNF292 has been implicated in regulating HF through processes such as apoptosis and the inflammatory response in cardiac myocytes[115]. Additionally, research has highlighted the critical role of circRNA-microRNA-protein networks in HF, with circRNAs acting as "sponges" for miRNAs, thereby modulating miRNA expression levels and subsequently altering the expression and function of miRNA downstream targets[116]. For instance, circHipk3 stimulates cardiomyocyte proliferation by enhancing the acetylation of N1ICD, thereby increasing its stability and inhibiting degradation[117]. Moreover, circHipk3 functions as a sponge for miR-133a, leading to increased expression of connective tissue growth factor and activation of endothelial cells, suggesting its potential as a novel therapeutic target for preventing post-myocardial infarction HF[118]. The circRNA HRCR protects the heart from pathological hypertrophy and cardiac HF by targeting miR-223[119, 120]. Furthermore, hsa circ0062960 has been associated with HF, exhibiting a significant correlation with a key HF biomarker, serum brain natriuretic peptide[121].

Atherosclerosis (AS)

AS is a chronic and progressive disease influenced by various factors, including disorders in lipid metabolism, inflammatory responses, apoptosis, and proliferation[122]. These biological processes are regulated by multiple signaling pathways and molecular mechanisms, includi ng the involvement of non-coding RNAs (ncRNAs). Recent studies have highlighted the significant regulatory roles of ncRNAs, such as lncRNAs and circRNAs, in the development and progression of atherosclerosis[123, 124]. These ncRNAs can impact AS progression by regulating various biological processes, including cell proliferation, apoptosis, inflammatory response, and extracellular matrix synthesis and degradation[125, 126]. Elevated expression of lncRNA H19 in AS has been shown to promote its development and progression by inhibiting vascular endothelial cell apoptosis and promoting smooth muscle cell proliferation and extracellular matrix synthesis[127]. Silencing the expression of lncRNA AK136714 has proven effective in reducing endothelial cell injury and inhibiting AS [128]. Upregulation of MALAT1 contributes to inflammatory responses and extracellular matrix degradation, thereby promoting AS development[37]. Conversely, downregulation of MALAT1 reduces the inflammatory response and extracellular matrix degradation, thus inhibiting AS progression [129]. Furthermore, ANRIL expression positively correlates with the extent of AS, and this lncRNA can regulate AS by modulating vascular endothelial cell proliferation, apoptosis, inflammatory response, and oxidative stress[130-132]. In animal experiments, Li P et al. demonstrated that knockdown of the lncRNA HIF1A-AS2 or ATF2 reduced inflammation in AS mice[133]. Additionally, lncRNA NORAD has been found to significantly inhibit endothelial cell senescence, endothelial cell apoptosis, and AS through the NF-κB and p53-p21 signaling pathways and IL-8[134].

In the regulatory mechanisms of atherosclerosis (AS), several circRNAs have been implicated. Pu Z et al. reported the involvement of circACTA2, circ-SATB2, and circCCDC66 in regulating vascular smooth muscle cell (VSMC) growth through miRNA sponging, thereby affecting AS formation [135]. Moreover, circRNAs have been shown to influence the onset and development of AS by regulating processes such as apoptosis, inflammatory response, and oxidative stress[136]. These findings provide new insights into the role of circRNAs in AS and offer potential avenues for AS treatment. For instance, Holdt LM et al. demonstrated that circANRIL induced nucleolar stress and p53 activation, leading to apoptosis induction and proliferation inhibition, which are crucial cellular functions in AS[137]. Zhang X et al. reported that circRSF1 regulated ox-LDL-induced vascular endothelial cell proliferation, apoptosis, and inflammation through the miR-135b-5p/HDAC1 axis, suggesting its potential in AS diagnosis and treatment[138]. Additionally, Du N et al. found that circRNA_102541 was highly expressed in AS samples and its knockdown significantly hindered cell proliferation. They also discovered that circRNA_102541 targeted the miR-296-5p/PLK1 axis, thereby participating in HUVEC cell apoptosis[139]. These findings contribute to our understanding of AS pathogenesis and provide insights into the potential therapeutic targets involving circRNAs.

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Stroke

Stroke refers to a condition in which blood vessels in the brain become blocked or ruptured, leading to insufficient or interrupted blood supply to the brain. This results in necrosis and softening of brain tissue, leading to neurological dysfunction[140]. Ischemic stroke and hemorrhagic stroke are the two common types of strokes[141]. Xiang Y et al. identified the overexpression of lncRNA MEG3 in ischemic stroke samples through RNA sequencing technology. They found that its downstream target, miR-424-5p, was underexpressed. Mouse experiments demonstrated that MEG3 accelerated the progression of ischemic stroke by inhibiting the target miR-424-5p in the affected cells[142]. In recent studies, MALAT1 expression was significantly upregulated in endothelial cells under conditions of oxygen-glucose deficiency (OGD) and in middle cerebral artery occlusion (MCAO) mouse models of stroke[143]. In clinical samples, MALAT1 expression levels were significantly increased in stroke patients and positively correlated with the severity of the stroke[144]. Subsequent experimental findings indicated that MALAT1 promoted neuronal apoptosis and inflammatory response after stroke, thereby exacerbating brain injury[145]. Conversely, H19 expression levels were found to be significantly decreased in post-stroke rat models[146]. Overexpression of H19 significantly reduced brain damage and promoted neuronal survival and recovery following stroke[147, 148]. On the other hand, NEAT1 expression levels were found to be upregulated in mouse models of stroke, and NEAT1 was found to promote inflammatory response and neuronal apoptosis after stroke, thus aggravating brain injury[149, 150]. Additionally, Bao MH et al. reviewed the aforementioned lncRNAs (MEG3, H19, and MALAT1) and discovered their potential involvement in neurogenesis, angiogenesis, and inflammation through gene regulation mechanisms such as DNA transcription, RNA folding, and methylation[151]. These findings contribute to a better understanding of the function and mechanisms of lncRNAs in ischemic stroke.

In recent years, more and more studies have shown that circRNA plays an important role in neuroinflammatory response and brain injury after stroke by regulating extracellular RNA [152]. For example, one study discovered elevated levels of circTLK1 in acute ischemic stroke and demonstrated that its knockout resulted in the amelioration of neuronal damage and improvement in neurological function[153]. Chen W et al. found that the circUCK2/miR-125b-5p/GDF11 axis attenuated apoptosis in cerebral ischemia-reperfusion injury using cellular experiments and animal models, suggesting its significance as a signaling pathway in ischemic stroke[154]. Yang L et al. observed in animal experiments that circSCMH1 enhanced the recovery mechanism in stroke models[155]. Han B et al. identified the upregulation of circHECTD1 in a mouse stroke model through microarray analysis. They found that circHECTD1 acted as an endogenous sponge for miR142, inhibiting miR142 activity and suppressing astrocyte activation through autophagy[156, 157]. Other literature suggests the effectiveness of circRNA 0025984 in reducing ischemic stroke damage and its protective effect on astrocytes through the miR-143-3p/TET1/ORP150 pathway[158]. Ma Z et al. identified four circRNAs (hsa-circ-0000607, hsa-circ-0051778, hsa-circ-0007850, and hsa-circ-0049637) associated with the immune mechanism of acute ischemic stroke, showing a significant positive correlation with neutrophils. These findings may offer new insights for stroke treatment[159]. These circRNAs are significantly positively correlated with neutrophils, which may provide new ideas for the treatment of stroke.

Aneurysm

Aneurysm is a condition characterized by the localized dilation of arterial walls, commonly found in cerebral arteries, aorta, renal arteries, and abdominal arteries[160]. The development of aneurysms can be influenced by factors such as arteriosclerosis, hypertension, and genetic predisposition[161, 162]. Emerging evidence suggests that lncRNAs play a significant role in the occurrence and progression of aneurysms. For instance, targeting the lncRNA HOTAIR has been shown to inhibit the proliferation and invasion of aneurysm cells while promoting their apoptosis[163]. Man H et al. demonstrated that lncRNA GASL1 was downregulated in patients with intracranial aneurysms

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and that its overexpression promotes the proliferation of human VSMCs and inhibits TGF-β1 expression, thereby affecting the formation of intracranial aneurysms[164]. Another important lncRNA involved in aneurysms is MALAT1, which participates in the occurrence and development of aneurysms by regulating pathways such as apoptosis and vascular remodeling[165, 166]. Additionally, studies have suggested a potential association between lncRNAs NEAT1, TUG1, and aneurysm occurrence and development[167, 168]. These findings highlight the importance of lncRNAs in understanding the underlying mechanisms of aneurysm pathology.

Studies have shown that VSMC is one of the key factors triggering intracranial aneurysms[169, 170]. Recent studies have shed light on the role of circRNAs in regulating VSMC function and their potential implications for anti-cranial aneurysm therapies. Ding X et al. identified circRNA DOCK1 as a key regulator of VSMCs, and through the regulation of the miR-409-3p/MCL1 axis, it may offer a new avenue for circRNA-based therapies targeting intracranial aneurysms [171]. Another circRNA, circ_0020397, was found to be downregulated in intracranial aneurysms. This circRNA can modulate GREM1 expression in VSMCs via miR-502-5p, thereby influencing the pathogenesis of intracranial aneurysms[172]. Additionally, Teng L et al. demonstrated that hsa_circ_0021001, which is downregulated in the peripheral blood of patients with intracranial aneurysms, correlates with aneurysm rupture and Hunt and Hess levels. It shows promise as a potential biomarker for clinical diagnosis[173]. Zhang Z et al. explored two signaling pathways associated with intracranial aneurysms, namely circRNA_0079586/miR-183-5p/MPO and circRNA_RanGAP1/miR-877-3p/MPO[174]. These findings, derived from cell and animal models, highlight the potential of circRNAs in aneurysm research, although further clinical studies are needed to val

Cardiomyopathy

Cardiomyopathies encompass various types such as hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy[175, 176]. The exact etiology of these conditions is not fully understood, but it is known that they can be influenced by factors including genetics, metabolic abnormalities, cardiac stress, infections, and toxins[177, 178]. Several lncRNAs have been implicated in the development and progression of different cardiomyopathies. For example, lncRNA MIAT is found to be highly expressed in hypertrophic cardiomyopathy and can modulate the proliferation and apoptosis of cardiomyocytes by regulating the expression of miR-24, thereby contributing to disease development [179]. In dilated cardiomyopathy, the expression of lncRNA H19 is significantly upregulated, and its dysregulation can impact cardiomyocyte apoptosis and hypertrophy, potentially promoting the progression of the disease[180]. LncRNA CHRF has been identified as playing a crucial role in myocardial cell proliferation, heart development, and the pathological state of the myocardium. Its dysregulation is closely associated with the occurrence and progression of cardiomyopathy[181]. Another lncRNA, Bvht, is closely linked to cardiac morphology and development. It is involved in biological processes such as cardiomyocyte proliferation, differentiation, and myocardial pathology[182, 183]. Furthermore, lncRNA MIAT has been found to be highly expressed in pathological conditions like myocardial hypertrophy and fibrosis. Its dysregulation may contribute to the development and progression of cardiomyopathy by influencing signaling pathways related to apoptosis and mitochondrial function[184, 185].

CircRNAs have emerged as important regulators of heart development and have been implicated in the pathological processes of cardiovascular diseases[186]. In the context of hypertrophic cardiomyopathy, a study by Guo Q et al. identified a circRNA-associated ceRNA network, revealing that circRNAs such as hsa_circ_0043762, hsa_circ_0036248, and hsa_circ_0071269 may serve as risk factors in the development of hypertrophic cardiomyopathy[187]. Another investigation demonstrated that circRNA_000203 in cardiomyocytes can modulate cardiomyocyte hypertrophy by regulating the NF-kB signaling pathway[188]. Additionally, several other circRNAs have been implicated in cardiomyopathy. For instance, circRNA_010567 has been associated with cardiomyocyte apoptosis and the pathological state of the myocardium, and it represents a potential diagnostic and therapeutic target for

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cardiomyopathy[118, 189]. CircRNA_100290, CircRNA_101237, and others are generally highly expressed in pathological myocardial states and may be involved in the occurrence and progression of cardiomyopathy, impacting processes such as cardiomyocyte apoptosis, myocardial fibrosis, and cardiomyocyte proliferation[190, 191].

Pericarditis

Pericarditis, characterized by inflammation of the pericardium, can manifest with symptoms such as chest pain, shortness of breath, fatigue, and fever[192]. In severe cases, pericarditis can lead to complications such as heart failure and arrhythmias [193, 194]. Viral or bacterial infections, drug allergies, and autoimmune diseases are among the common causes of pericarditis[195]. In terms of lncRNAs, a study identified that lncRNA TUG1 can attenuate hypertrophy of the hypertrophic myocardium by targeting the mir-34a/dkk1/wnt-β-catenin signaling pathway[196]. These findings suggest that lncRNAs may contribute to the pathogenesis and progression of pericarditis by regulating relevant signaling pathways. Additionally, lncRNA MALAT1 has been found to be upregulated in pericarditis, and its upregulation is closely associated with increased inflammatory response and pericardial fibrosis[197]. Although there is limited research on circRNAs in pericarditis, studies have shown that circRNAs play important regulatory roles in biological processes such as inflammatory response, apoptosis, autophagy, and oxidative stress[198, 199]. Since these biological processes are also implicated in the occurrence and development of pericarditis, future research could explore the regulatory roles of circRNAs in the pathophysiological processes associated with pericarditis. Such investigations may provide new insights and strategies for the diagnosis and treatment of pericarditis.

Outlook and Conclusion

NcRNAs, specifically lncRNAs and circRNAs, have emerged as valuable tools in CVD research. The dysregulation of lncRNAs and circRNAs has been associated with the initiation and progression of CVD, sparking interest in understanding their regulatory mechanisms within the cardiovascular system. Recent investigations have highlighted the involvement of lncRNAs and circRNAs in various biological processes critical to cardiovascular function, including cardiomyocyte proliferation, apoptosis, and autophagy, as well as the regulation of vascular endothelial cell function and VSMC proliferation and migration. Consequently, these ncRNAs present promising targets for the diagnosis and treatment of CVD. Although the precise roles of lncRNAs and circRNAs in cardiovascular pathogenesis remain incompletely elucidated, they offer novel research avenues for unraveling the intricacies of CVD development and progression. Further investigations are warranted to comprehensively explore their potential applications in the diagnosis and treatment of CVD.

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Conflict of interest statement

All authors declare that there are no conflicts of interest.

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Availability of data and materials

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Author Contribution

(1) Conception and design of the study, or acquisition of data, or analysis and interpretation of data: Jun Jiang.

(2) Drafting the article or revising it critically for important intellectual content: Jun Jiang and Xiaofeng Hu.

(3) Final approval of the version to be submitted: Jun Jiang and Xiaofeng Hu.

References

1. Li, J., et al., Atherosclerosis Vascular Endothelial Secretion Dysfunction and Smooth Muscle Cell Proliferation. Journal of Healthcare Engineering, 2022. 2022.

2. Cao, Z.-Q., X. Yu, and P. Leng, Research progress on the role of gal-3 in cardio/cerebrovascular diseases. Biomedicine & Pharmacotherapy, 2021. 133: p. 111066.

3. Liang, J., et al., Discussion on Treatment of Atherosclerosis From Liver Theory. Journal of Liaoning University of Traditional Chinese Medicine, 2018.

4. Li, M. and J. Zhang, Circulating MicroRNAs: potential and emerging biomarkers for diagnosis of cardiovascular and cerebrovascular diseases. BioMed Research International, 2015. 2015.

5. Barnes, R.P., J.C.A. Lacson, and H. Bahrami, HIV infection and risk of cardiovascular diseases beyond coronary artery disease. Current atherosclerosis reports, 2017. 19: p. 1-9.

6. Asri, A.K., et al., Global greenness in relation to reducing the burden of cardiovascular diseases: ischemic heart disease and stroke. Environmental Research Letters, 2020. 15(12): p. 124003.

7. Piché, M.-E., A. Tchernof, and J.-P. Després, Obesity phenotypes, diabetes, and cardiovascular diseases. Circulation research, 2020. 126(11): p. 1477-1500.

8. Riegel, B., et al., Self-care for the prevention and management of cardiovascular disease and stroke: A scientific statement for healthcare professionals from the American Heart Association. Journal of the American Heart Association, 2017. 6(9): p. e006997.

9. Eddy, S.R., Non–coding RNA genes and the modern RNA world. Nature Reviews Genetics, 2001. 2(12): p. 919-929.

10. Taft, R.J., et al., Non-coding RNAs: regulators of disease. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland, 2010. 220(2): p. 126-139.

11. Li, C., et al., Roles and mechanisms of exosomal non-coding RNAs in human health and diseases. Signal transduction and targeted therapy, 2021. 6(1): p. 383.

12. Liu, S. and W. Chong, Roles of LncRNAs in regulating mitochondrial dysfunction in septic cardiomyopathy. Frontiers in Immunology, 2021. 12: p. 802085.

13. Wang, J., et al., The role of lncRNAs in osteogenic differentiation of bone marrow mesenchymal stem cells. Current stem cell research & therapy, 2020. 15(3): p. 243-249.

14. Ballantyne, M.D., R.A. McDonald, and A.H. Baker, lncRNA/MicroRNA interactions in the vasculature. Clinical Pharmacology & Therapeutics, 2016. 99(5): p. 494-501.

15. Tang, X.J., W. Wang, and S.S. Hann, Interactions among lncRNAs, miRNAs and mRNA in colorectal cancer. Biochimie, 2019. 163: p. 58-72.

16. Villegas, V.E. and P.G. Zaphiropoulos, Neighboring gene regulation by antisense long non-coding RNAs. International journal of molecular sciences, 2015. 16(2): p. 3251-3266.

17. Chang, Z., et al., Epigenetic mechanisms of drug resistance in fungi. Fungal Genetics and Biology, 2019. 132: p. 103253.

18. Statello, L., et al., Gene regulation by long non-coding RNAs and its biological functions. Nature reviews Molecular cell biology, 2021. 22(2): p. 96-118.

19. Xu, J.-z., J.-l. Zhang, and W.-g. Zhang, Antisense RNA: the new favorite in genetic research. Journal of Zhejiang University-SCIENCE B, 2018. 19(10): p. 739-749.

20. Carlevaro-Fita, J., et al., Cytoplasmic long noncoding RNAs are frequently bound to and degraded at ribosomes in human cells. Rna, 2016. 22(6): p. 867-882.

21. Archer, K., et al., Long non-coding RNAs as master regulators in cardiovascular diseases. International journal of molecular sciences, 2015. 16(10): p. 23651-23667.

22. Lorenzen, J.M. and T. Thum, Long noncoding RNAs in kidney and cardiovascular diseases. Nature Reviews Nephrology, 2016. 12(6): p. 360-373.

23. Hou, K., et al., Prediction and identification of sulfur-responding circular RNA in Chlamydomonas reinhardtii. Shenzhen Daxue Xuebao (ligong Ban), 2020. 37(3): p. 221-223.

24. Qin, M., G. Wei, and X. Sun, Circ-UBR5: an exonic circular RNA and novel small nuclear RNA involved in RNA splicing. Biochemical and biophysical research communications, 2018. 503(2): p. 1027-1034.

25. Verduci, L., et al., CircRNAs: role in human diseases and potential use as biomarkers. Cell death & disease, 2021. 12(5): p. 468.

26. Guil, S. and M. Esteller, RNA–RNA interactions in gene regulation: the coding and noncoding players. Trends in biochemical sciences, 2015. 40(5): p. 248-256.

DOI 10.58832/ctr.2023.7.6.1

27. Liu, G., et al., E2F3 promotes liver cancer progression under the regulation of circ-PRKAR1B. Molecular Therapy-Nucleic Acids, 2021. 26: p. 104-113.

28. Shen, B. and K. Sun, Exosomal circular RNAs: A new frontier in the metastasis of digestive system tumors. Oncology Letters, 2021. 22(6): p. 1-13.

29. Mahmoudi, E., et al., Depolarization-associated CircRNA regulate neural gene expression and in some cases may function as templates for translation. Cells, 2019. 9(1): p. 25.

30. Su, Q. and X. Lv, Revealing new landscape of cardiovascular disease through circular RNA-miRNA-mRNA axis. Genomics, 2020. 112(2): p. 1680-1685.

31. Tang, Y., et al., Circular RNA in cardiovascular disease: Expression, mechanisms and clinical prospects. Journal of cellular and molecular medicine, 2021. 25(4): p. 1817-1824.

32. Gong, X., et al., Circular RNA circEsyt2 regulates vascular smooth muscle cell remodeling via splicing regulation. The Journal of Clinical Investigation, 2021. 131(24).

33. Wan, H., et al., CircRNAs in diabetic cardiomyopathy. Clinica Chimica Acta, 2021. 517: p. 127-132.

34. Zhang, W., et al., Non-coding RNA involvement in the pathogenesis of diabetic cardiomyopathy. Journal of Cellular and Molecular Medicine, 2019. 23(9): p. 5859-5867.

35. Yu, H., et al., Circ_0003423 Alleviates ox-LDL-Induced Human Brain Microvascular Endothelial Cell Injury via the miR-589-5p/TET2 Network. Neurochemical Research, 2021: p. 1-12.

36. Xie, Q., et al., What is the impact of human umbilical cord mesenchymal stem cell transplantation on clinical treatment? Stem cell research & therapy, 2020. 11: p. 1-13.

37. Tang, N., et al., Noncoding RNA s as therapeutic targets in atherosclerosis with diabetes mellitus. Cardiovascular therapeutics, 2018. 36(4): p. e12436.

38. Wu, M., M. Xun, and Y. Chen, Circular RNAs: regulators of vascular smooth muscle cells in cardiovascular diseases. Journal of Molecular Medicine, 2022. 100(4): p. 519-535.

39. Maiuolo, J., et al., The contribution of gut microbiota and endothelial dysfunction in the development of arterial hypertension in animal models and in humans. International Journal of Molecular Sciences, 2022. 23(7): p. 3698.

40. Vaughan, C.J. and N. Delanty, Hypertensive emergencies. The Lancet, 2000. 356(9227): p. 411-417.

41. Lackland, D.T. and M.A. Weber, Global burden of cardiovascular disease and stroke: hypertension at the core. Canadian Journal of Cardiology, 2015. 31(5): p. 569-571.

42. Aburto, N.J., et al., Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. Bmj, 2013. 346.

43. Gomes, C.P., et al., The function and therapeutic potential of long non-coding RNAs in cardiovascular development and disease. Molecular Therapy-Nucleic Acids, 2017. 8: p. 494-507.

44. Han, Y., et al., Role of long non-coding RNAs in pulmonary arterial hypertension. Cells, 2021. 10(8): p. 1892.

45. Lei, S., et al., LncRNA-SMILR modulates RhoA/ROCK signaling by targeting miR-141 to regulate vascular remodeling in pulmonary arterial hypertension. American Journal of Physiology-Heart and Circulatory Physiology, 2020. 319(2): p. H377-H391.

46. Wang, Y.-N.-Z., et al., Long noncoding RNA-GAS5: a novel regulator of hypertension-induced vascular remodeling. Hypertension, 2016. 68(3): p. 736-748.

47. Esawy, M.M., et al., LncRNA-GAS5 and β-Catenin as Independent Predictors of Asymptomatic Organ Damage in Nondiabetic Hypertensive Patients. ACS Omega, 2023.

48. Huang, K., et al., Effects of CDKN2B-AS1 polymorphisms on the susceptibility to coronary heart disease. Molecular genetics & genomic medicine, 2019. 7(11): p. e955.

49. Bayoglu, B., et al., Polymorphisms in the long non-coding RNA CDKN2B-AS1 may contribute to higher systolic blood pressure levels in hypertensive patients. Clinical biochemistry, 2016. 49(10-11): p. 821-827.

50. Xu, S.-L., et al., Circular RNAs Regulate Vascular Remodelling in Pulmonary Hypertension. Disease Markers, 2022. 2022.

51. Zaiou, M., Circular RNAs in hypertension: challenges and clinical promise. Hypertension Research, 2019. 42(11): p. 1653-1663.

52. Ali, M.K., et al., The role of circular RNAs in pulmonary hypertension. European Respiratory Journal, 2022. 60(6).

53. Chen, M., et al., Circ_0000284: A risk factor and potential biomarker for prehypertension and hypertension. Hypertension Research, 2022: p. 1-10.

54. Tao, Z., et al., Hsa_circ_0037897 may be a risk factor for essential hypertension via hsa-miR-145-5p. Clinical and Experimental Hypertension, 2021. 43(3): p. 281-286.

55. Zhang, Z., et al., Circulating circular RNAs as biomarkers for the diagnosis of essential hypertension with carotid plaque. Clinical and Experimental Hypertension, 2022. 44(7): p. 601-609.

56. Prestes, P.R., et al., A guide to the short, long and circular RNAs in hypertension and cardiovascular disease. International Journal of Molecular Sciences, 2020. 21(10): p. 3666.

57. Liu, L., et al., Microarray profiling of circular RNA identifies hsa_circ_0126991 as a potential risk factor for essential hypertension. Cytogenetic and Genome Research, 2019. 157(4): p. 203-212.

58. Lin, F., et al., Advances in research on the circRNA-miRNA-mRNA network in coronary heart disease treated with traditional Chinese medicine. Evidence-Based Complementary and Alternative Medicine, 2020. 2020: p. 1-10.

59. Wang, Q., et al., Circular RNAs in pulmonary hypertension: Emerging biological concepts and potential mechanism. Animal Models and Experimental Medicine, 2022. 5(1): p. 38-47.

60.Zou, H. and Q. Mao, Circ_0037078 promotes trophoblast cell proliferation, migration, invasion and angiogenesis by miR-576-5p/IL1RAP axis. American Journal of Reproductive Immunology, 2022. 87(1): p. e13507.

61. Ambrose, J.A. and M. Singh, Pathophysiology of coronary artery disease leading to acute coronary syndromes. F1000prime reports, 2015. 7.

62. Newburger, J.W., et al., Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation, 2004. 110(17): p. 2747-2771.

63. Peng, J., Y. Zhan, and Y. Zong, METTL3-mediated LINC00657 promotes osteogenic differentiation of mesenchymal stem cells via miR-144-3p/BMPR1B axis. Cell and Tissue Research, 2022. 388(2): p. 301-312.

64. Guo, F., et al., The interplay of Lnc RNA ANRIL and miR-181b on the inflammation-relevant coronary artery disease through mediating NF-κ B signalling pathway. Journal of cellular and molecular medicine, 2018. 22(10): p. 5062-5075.

65. Huang, J., et al., LncRNA H19 rs4929984 variant is associated with coronary artery disease susceptibility in han chinese female population.

DOI 10.58832/ctr.2023.7.6.1

Biochemical Genetics, 2021: p. 1-22.

66. Li, X., et al., lncRNA H19 alleviated myocardial I/RI via suppressing miR-877-3p/Bcl-2-mediated mitochondrial apoptosis. Molecular Therapy-Nucleic Acids, 2019. 17: p. 297-309.

67. Tan, J.-K., et al., LncRNA MIAT knockdown alleviates oxygen-glucose deprivation-induced cardiomyocyte injury by regulating JAK2/STAT3 pathway via miR-181a-5p. Journal of Cardiology, 2021. 78(6): p. 586-597.

68. Kim, I.-J., et al., Association between HOTAIR lncRNA polymorphisms and coronary artery disease susceptibility. Journal of personalized medicine, 2021. 11(5): p. 375.

69. Wu, L., et al., LncRNA TONSL-AS1 participates in coronary artery disease by interacting with miR-197. Microvascular Research, 2021. 136: p. 104152.

70. Chen, J. and J. Dang, LncRNA CASC11 was downregulated in coronary artery disease and inhibits transforming growth factor-β 1. Journal of International Medical Research, 2020. 48(3): p. 0300060519889187.

71. Lu, Y., et al., Contribution of lncRNA CASC8, CASC11, and PVT1 genetic variants to the susceptibility of coronary heart disease. Journal of Cardiovascular Pharmacology, 2021. 77(6): p. 756-766.

72. Zhou, B. and J.W. Yu, A novel identified circular RNA, circRNA_010567, promotes myocardial fibrosis via suppressing miR-141 by targeting TGF-β1. Biochemical & Biophysical Research Communications, 2017: p. 769-775.

73. Tang, C.M., et al., CircRNA_000203 enhances the expression of fibrosis-associated genes by derepressing targets of miR-26b-5p, Col1a2 and CTGF, in cardiac fibroblasts. Scientific Reports, 2017. 7: p. 40342.

74. Zhengbiao, Z., et al., Circular RNA_HIPK3-Targeting miR-93-5p Regulates KLF9 Expression Level to Control Acute Kidney Injury. Computational and Mathematical Methods in Medicine, 2023. 2023.

75. Zhao, Z., et al., Peripheral blood circular RNA hsa_circ_0124644 can be used as a diagnostic biomarker of coronary artery disease. Scientific reports, 2017. 7(1): p. 39918.

76. Zhou, H., et al., Identification of circular RNA BTBD7_hsa_circ_0000563 as a novel biomarker for coronary artery disease and the functional discovery of BTBD7_hsa_circ_0000563 based on peripheral blood mononuclear cells: a case control study. Clinical Proteomics, 2022. 19(1): p. 37.

77. Zhang, S., et al., Regulatory roles of circular RNAs in coronary artery disease. Molecular Therapy-Nucleic Acids, 2020. 21: p. 172-179.

78. Van Wagoner, D.R. and J.M. Nerbonne, Molecular basis of electrical remodeling in atrial fibrillation. Journal of molecular and cellular cardiology, 2000. 32(6): p. 1101-1117.

79. Lourenço, A., et al. Left atrial ejection fraction estimation using SEGANet for fully automated segmentation of CINE MRI. in Statistical Atlases and Computational Models of the Heart. M&Ms and EMIDEC Challenges: 11th International Workshop, STACOM 2020, Held in Conjunction with MICCAI 2020, Lima, Peru, October 4, 2020, Revised Selected Papers 11. 2021. Springer.

80. Babapoor-Farrokhran, S., D. Gill, and R.T. Rasekhi, The role of long noncoding RNAs in atrial fibrillation. Heart Rhythm, 2020. 17(6): p. 1043-1049.

81. Wang, H., et al., Long non-coding RNA LICPAR regulates atrial fibrosis via TGF-β/Smad pathway in atrial fibrillation. Tissue and Cell, 2020. 67: p. 101440.

82. Wu, C., et al., Noncoding RNAs and Cardiac Fibrosis. Reviews in Cardiovascular Medicine, 2023. 24(2): p. 63.

83. Yang, P., et al., Long non-coding RNA ANRIL interacts with microRNA-34a and microRNA-125a, and they all correlate with disease risk and severity of Parkinson's disease. Journal of Clinical Laboratory Analysis, 2022. 36(1): p. e24037.

84. Wang, W., et al., Research progress of LncRNAs in atrial fibrillation. Molecular Biotechnology, 2022. 64(7): p. 758-772.

85. Bektik, E., D.B. Cowan, and D.-Z. Wang, Long non-coding RNAs in atrial fibrillation: pluripotent stem cell-derived cardiomyocytes as a model system. International Journal of Molecular Sciences, 2020. 21(15): p. 5424.

86. Xie, L., et al., Identification of atrial fibrillation-related lncRNA based on bioinformatic analysis. Disease Markers, 2022. 2022.

87. Dai, H., et al., LncRNA nuclear-enriched abundant transcript 1 regulates atrial fibrosis via the miR-320/NPAS2 axis in atrial fibrillation. Frontiers in Pharmacology, 2021. 12: p. 647124.

88. Jiang, S., et al., The integrative regulatory network of circRNA, microRNA, and mRNA in atrial fibrillation. Frontiers in genetics, 2019. 10: p. 526.

89. Ruan, Z.-B., et al., Genome-wide analysis of circular RNA expression profiles in patients with atrial fibrillation. International journal of clinical and experimental pathology, 2020. 13(8): p. 1933.

90. Zhang, L., et al., CircCAMTA1 facilitates atrial fibrosis by regulating the miR-214-3p/TGFBR1 axis in atrial fibrillation. Journal of Molecular Histology, 2022: p. 1-11.

91. Gao, Y., et al., The potential regulatory role of hsa_circ_0004104 in the persistency of atrial fibrillation by promoting cardiac fibrosis via TGF-β pathway. BMC cardiovascular disorders, 2021. 21: p. 1-11.

92. Zhang, P.-P., J. Sun, and W. Li, Genome-wide profiling reveals atrial fibrillation-related circular RNAs in atrial appendages. Gene, 2020. 728: p. 144286.

93. Khan, M.S., et al., RNAs and gene expression predicting postoperative atrial fibrillation in cardiac surgery patients undergoing coronary artery bypass grafting. Journal of Clinical Medicine, 2020. 9(4): p. 1139.

94. Zhang, Y., et al., Characterization of circRNA-associated ceRNA networks in patients with nonvalvular persistent atrial fibrillation. Molecular Medicine Reports, 2019. 19(1): p. 638-650.

95. Chen, Y., et al., Analysis of infiltrated immune cells in left atriums from patients with atrial fibrillation and identification of circRNA biomarkers for postoperative atrial fibrillation. Frontiers in Genetics, 2022. 13.

96. Kemp, C.D. and J.V. Conte, The pathophysiology of heart failure. Cardiovascular Pathology, 2012. 21(5): p. 365-371.

97. Tresch, D.D., Clinical manifestations, diagnostic assessment, and etiology of heart failure in elderly patients. Clinics in geriatric medicine, 2000. 16(3): p. 445-456.

98. Ruys, T.P., et al., Heart failure in pregnant women with cardiac disease: data from the ROPAC. Heart, 2014. 100(3): p. 231-238.

99. Mann, D.L. and M. Chakinala, Heart failure: pathophysiology and diagnosis. Harrison, s. Principles of Internal Medicine, 2015. 20: p. 4383-402.

100. Edelmann, F., et al., Chronic heart failure. Deutsches Ärzteblatt International, 2018. 115(8): p. 124.

101. Ponikowski, P., et al., Heart failure: preventing disease and death worldwide. ESC heart failure, 2014. 1(1): p. 4-25.

102. Fang, Y., et al., Recent advances on the roles of LncRNAs in cardiovascular disease. Journal of Cellular and Molecular Medicine, 2020. 24(21): p. 12246-12257.

103. Han, D., Q. Gao, and F. Cao, Long noncoding RNAs (LncRNAs)—the dawning of a new treatment for cardiac hypertrophy and heart failure.

DOI 10.58832/ctr.2023.7.6.1

Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 2017. 1863(8): p. 2078-2084.

104. Greco, S., et al., Long noncoding RNA dysregulation in ischemic heart failure. Journal of translational medicine, 2016. 14: p. 1-14.

105. El Azzouzi, H., P.A. Doevendans, and J.P.G. Sluijter, Long non-coding RNAs in heart failure: an obvious lnc. Annals of Translational Medicine, 2016. 4(9).

106. Hu, H., et al., Knockdown of lncRNA MALAT1 attenuates acute myocardial infarction through miR-320-Pten axis. Biomedicine & Pharmacotherapy, 2018. 106: p. 738-746.

107. Gong, X., et al., Long noncoding RNA MALAT1 promotes cardiomyocyte apoptosis after myocardial infarction via targeting miR-144-3p. bioscience reports, 2019. 39(8).

108. Ge, Z., et al., Long noncoding RNA NEAT1 promotes cardiac fibrosis in heart failure through increased recruitment of EZH2 to the Smad7 promoter region. Journal of Translational Medicine, 2022. 20: p. 1-16.

109. Liu, N., et al., LncRNA LncHrt preserves cardiac metabolic homeostasis and heart function by modulating the LKB1-AMPK signaling pathway. Basic Research in Cardiology, 2021. 116(1): p. 48.

110. Sato, M., et al., The lncRNA Caren antagonizes heart failure by inactivating DNA damage response and activating mitochondrial biogenesis. Nature communications, 2021. 12(1): p. 2529.

111. Gu, Q., et al., LncRNA promoted inflammatory response in ischemic heart failure through regulation of miR-455-3p/TRAF6 axis. Inflammation Research, 2020. 69: p. 667-681.

112. Fu, Y. and H. Sun, Biogenesis, cellular effects, and biomarker value of circHIPK3. Cancer Cell International, 2021. 21(1): p. 256.

113. Wu, C., et al., The regulation mechanisms and clinical application of microRNAs in myocardial infarction: a review of the recent 5 years. Frontiers in Cardiovascular Medicine, 2022. 8: p. 2205.

114. Wang, L., et al., Circular RNAs in cardiovascular diseases. Circular RNAs: Biogenesis and Functions, 2018: p. 191-204.

115. Bär, C., S. Chatterjee, and T. Thum, Long noncoding RNAs in cardiovascular pathology, diagnosis, and therapy. Circulation, 2016. 134(19): p. 1484-1499.

116. Fan, X., et al., Circular RNAs in cardiovascular disease: an overview. BioMed research international, 2017. 2017.

117. Si, X., et al., circRNA Hipk3 induces cardiac regeneration after myocardial infarction in mice by binding to Notch1 and miR-133a. Molecular Therapy-Nucleic Acids, 2020. 21: p. 636-655.

118. Wen, Z.-J., et al., Emerging roles of circRNAs in the pathological process of myocardial infarction. Molecular Therapy-Nucleic Acids, 2021. 26: p. 828-848.

119. Wang, K., et al., A circular RNA protects the heart from pathological hypertrophy and heart failure by targeting miR-223. European heart journal, 2016. 37(33): p. 2602-2611.

120. Wang, P., et al., MiR-223 promotes cardiomyocyte apoptosis by inhibiting Foxo3a expression. Eur Rev Med Pharmacol Sci, 2018. 22(18): p. 6119-6126.

121. Yang, M., X. Wang, and T. Wang, Regulation of mitochondrial function by noncoding RNAs in heart failure and its application in diagnosis and treatment. Journal of Cardiovascular Pharmacology, 2021. 78(3): p. 377-387.

122. Xue, Q., et al., Functional roles and mechanisms of ginsenosides from Panax ginseng in atherosclerosis. Journal of ginseng research, 2021. 45(1): p. 22-31.

123. Wang, Y., et al., Long non-coding RNAs in coronary atherosclerosis. Life sciences, 2018. 211: p. 189-197.

124. Cheng, C., et al., CircRnas in atherosclerosis, with special emphasis on the spongy effect of circRnas on miRnas. Cell Cycle, 2022: p. 1-15.

125. Kang, L., et al., Identification of differently expressed mRNAs in atherosclerosis reveals CDK6 Is regulated by circHIPK3/miR-637 axis and promotes cell growth in human vascular smooth muscle cells. Frontiers in Genetics, 2021. 12: p. 596169.

126. Singh, D., V. Rai, and D.K. Agrawal, Non-Coding RNAs in Regulating Plaque Progression and Remodeling of Extracellular Matrix in Atherosclerosis. International Journal of Molecular Sciences, 2022. 23(22): p. 13731.

127. Fan, Z., S. Liu, and H. Zhou, LncRNA H19 regulates proliferation, apoptosis and ECM degradation of aortic smooth muscle cells via miR-1-3p/ADAM10 axis in thoracic aortic aneurysm. Biochemical Genetics, 2022. 60(2): p. 790-806.

128. Li, X., et al., Targeting non-coding RNAs in unstable atherosclerotic plaques: Mechanism, regulation, possibilities, and limitations. International Journal of Biological Sciences, 2021. 17(13): p. 3413.

129. Feng, F., et al., Role of Long Noncoding RNAs in the Regulation of Cellular Immune Response and Inflammatory Diseases. Cells, 2022. 11(22): p. 3642.

130. Holdt, L.M., et al., ANRIL expression is associated with atherosclerosis risk at chromosome 9p21. Arteriosclerosis, thrombosis, and vascular biology, 2010. 30(3): p. 620-627.

131. Song, C.-L., et al., Effect of circular ANRIL on the inflammatory response of vascular endothelial cells in a rat model of coronary atherosclerosis. Cellular Physiology and Biochemistry, 2017. 42(3): p. 1202-1212.

132. Chen, L., et al., ANRIL and atherosclerosis. Journal of Clinical Pharmacy and Therapeutics, 2020. 45(2): p. 240-248.

133. Li, P., et al., Inhibition of long noncoding RNA HIF1A-AS2 confers protection against atherosclerosis via ATF2 downregulation. Journal of advanced research, 2020. 26: p. 123-135.

134. Bian, W., et al., Downregulation of LncRNA NORAD promotes Ox-LDL-induced vascular endothelial cell injury and atherosclerosis. Aging (Albany NY), 2020. 12(7): p. 6385.

135. Pu, Z., J. Lu, and X. Yang, Emerging roles of circular RNAs in vascular smooth muscle cell dysfunction. Frontiers in Genetics, 2022. 12: p. 2639.

136. Cao, Q., et al., Circular RNAs in the pathogenesis of atherosclerosis. Life sciences, 2020. 255: p. 117837.

137. Holdt, L.M., et al., Circular non-coding RNA ANRIL modulates ribosomal RNA maturation and atherosclerosis in humans. Nature communications, 2016. 7(1): p. 12429.

138. Zhang, X., et al., CircRNA RSF1 regulated ox-LDL induced vascular endothelial cells proliferation, apoptosis and inflammation through modulating miR-135b-5p/HDAC1 axis in atherosclerosis. Biological Research, 2021. 54.

139. Du, N., M. Li, and D. Yang, Hsa_circRNA_102541 regulates the development of atherosclerosis by targeting miR-296-5p/PLK1 pathway. Irish Journal of Medical Science (1971-), 2021: p. 1-7.

140. Zhang, Y., Y. Cao, and C. Liu, Autophagy and ischemic stroke. Autophagy: Biology and Diseases: Clinical Science, 2020: p. 111-134.

141. Ojaghihaghighi, S., et al., Comparison of neurological clinical manifestation in patients with hemorrhagic and ischemic stroke. World journal of emergency medicine, 2017. 8(1): p. 34.

142. Xiang, Y., et al., LncRNA MEG3 targeting miR-424-5p via MAPK signaling pathway mediates neuronal apoptosis in ischemic stroke. Aging (Albany NY), 2020. 12(4): p. 3156.

143. Guo, D., et al., Down-regulation of Lncrna MALAT1 attenuates neuronal cell death through suppressing Beclin1-dependent autophagy

DOI 10.58832/ctr.2023.7.6.1

by regulating Mir-30a in cerebral ischemic stroke. Cellular Physiology and Biochemistry, 2017. 43(1): p. 182-194.

144. Chen, J., et al., Long non-coding RNA MALAT1 serves as an independent predictive biomarker for the diagnosis, severity and prognosis of patients with sepsis. Molecular Medicine Reports, 2020. 21(3): p. 1365-1373.

145. Cao, D.-w., et al., The lncRNA Malat1 functions as a ceRNA to contribute to berberine-mediated inhibition of HMGB1 by sponging miR-181c-5p in poststroke inflammation. Acta Pharmacologica Sinica, 2020. 41(1): p. 22-33.

146. Yang, J., et al., LncRNAs a new target for post-stroke recovery. Current Pharmaceutical Design, 2020. 26(26): p. 3115-3121.

147. Gan, L., et al., Long noncoding RNA H19 mediates neural stem/progenitor cells proliferation, differentiation and apoptosis through the p53 signaling pathway after ischemic stroke. Biochemical and Biophysical Research Communications, 2022. 597: p. 8-15.

148. Fan, J., et al., LncRNAs stand as potent biomarkers and therapeutic targets for stroke. Frontiers in aging neuroscience, 2020. 12: p. 594571.

149. Jin, F., et al., Transcriptome-wide analysis to identify the inflammatory role of lncRNA Neat1 in experimental ischemic stroke. Journal of inflammation research, 2021. 14: p. 2667.

150. Chen, M., et al., Long non-coding RNAs and circular RNAs: insights into microglia and astrocyte mediated neurological diseases. Frontiers in Molecular Neuroscience, 2021. 14: p. 745066.

151. Bao, M.-H., et al., Long non-coding RNAs in ischemic stroke. Cell death & disease, 2018. 9(3): p. 281.

152. Shen, L., et al., Non-coding RNA and neuroinflammation: implications for the therapy of stroke. Stroke and Vascular Neurology, 2019. 4(2).

153. Wu, F., et al., Circular RNA TLK1 aggravates neuronal injury and neurological deficits after ischemic stroke via miR-335-3p/TIPARP. Journal of Neuroscience, 2019. 39(37): p. 7369-7393.

154. Chen, W., et al., Overexpression of circRNA circUCK2 attenuates cell apoptosis in cerebral ischemia-reperfusion injury via miR-125b-5p/GDF11 signaling. Molecular Therapy-Nucleic Acids, 2020. 22: p. 673-683.

155. Yang, L., et al., Extracellular vesicle–mediated delivery of circular RNA SCMH1 promotes functional recovery in rodent and nonhuman primate ischemic stroke models. Circulation, 2020. 142(6): p. 556-574.

156. Dai, Q., et al., Downregulation of circular RNA HECTD1 induces neuroprotection against ischemic stroke through the microRNA-133b/TRAF3 pathway. Life Sciences, 2021. 264: p. 118626.

157. Han, B., et al., Novel insight into circular RNA HECTD1 in astrocyte activation via autophagy by targeting MIR142-TIPARP: implications for cerebral ischemic stroke. Autophagy, 2018. 14(7): p. 1164-1184.

158. Zhou, D., et al., Circular RNA 0025984 ameliorates ischemic stroke injury and protects astrocytes through miR-143-3p/TET1/ORP150 pathway. Molecular Neurobiology, 2021. 58(11): p. 5937-5953.

159. Ma, Z., et al., The Construction and Analysis of Immune Infiltration and Competing Endogenous RNA Network in Acute Ischemic Stroke. Frontiers in Aging Neuroscience, 2022.

160. Humphrey, J. and C. Taylor, Intracranial and abdominal aortic aneurysms: similarities, differences, and need for a new class of computational models. Annu. Rev. Biomed. Eng., 2008. 10: p. 221-246.

161. Annambhotla, S., et al., Recent advances in molecular mechanisms of abdominal aortic aneurysm formation. World journal of surgery, 2008. 32: p. 976-986.

162. Peshkova, I.O., G. Schaefer, and E.K. Koltsova, Atherosclerosis and aortic aneurysm–is inflammation a common denominator? The FEBS journal, 2016. 283(9): p. 1636-1652.

163. Spin, J.M., et al., Non-coding RNAs in aneurysmal aortopathy. Vascular Pharmacology, 2019. 114: p. 110-121.

164. Man, H. and W. Bi, Expression of a novel long noncoding RNA (lncRNA), GASL1, is downregulated in patients with intracranial aneurysms and regulates the proliferation of vascular smooth muscle cells in vitro. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 2019. 25: p. 1133.

165. Wu, Z.-y., et al., Long noncoding RNAs in key cellular processes involved in aortic aneurysms. Atherosclerosis, 2020. 292: p. 112-118.

166. Rikhtegar, R., et al., Non-coding RNAs role in intracranial aneurysm: general principles with focus on inflammation. Life sciences, 2021. 278: p. 119617.

167. Cai, B., et al., STAT3-induced up-regulation of lncRNA NEAT1 as a ceRNA facilitates abdominal aortic aneurysm formation by elevating TULP3. Bioscience reports, 2020. 40(1).

168. Zhou, H., et al., Long noncoding RNAs in pathological cardiac remodeling: a review of the update literature. BioMed research international, 2019. 2019.

169. Penn, D.L., et al., The role of vascular remodeling and inflammation in the pathogenesis of intracranial aneurysms. Journal of clinical neuroscience, 2014. 21(1): p. 28-32.

170. Chalouhi, N., et al., Biology of intracranial aneurysms: role of inflammation. Journal of Cerebral Blood Flow & Metabolism, 2012. 32(9): p. 1659-1676.

171. Ding, X., et al., CircRNA DOCK1 Regulates miR-409-3p/MCL1 Axis to Modulate Proliferation and Apoptosis of Human Brain Vascular Smooth Muscle Cells. Frontiers in Cell and Developmental Biology, 2021. 9: p. 655628.

172. Yin, K. and X. Liu, Circ_0020397 regulates the viability of vascular smooth muscle cells by up-regulating GREM1 expression via miR-502-5p in intracranial aneurysm. Life Sciences, 2021. 265: p. 118800.

173. Teng, L., et al., Circular RNA hsa_circ_0021001 in peripheral blood: a potential novel biomarker in the screening of intracranial aneurysm. Oncotarget, 2017. 8(63): p. 107125.

174. Zhang, Z., et al., CircRNA_0079586 and circRNA_RanGAP1 are involved in the pathogenesis of intracranial aneurysms rupture by regulating the expression of MPO. Scientific Reports, 2021. 11(1): p. 19800.

175. Schaufelberger, M., Cardiomyopathy and pregnancy. Heart, 2019. 105(20): p. 1543-1551.

176. Hughes, S.E. and W.J. McKenna, New insights into the pathology of inherited cardiomyopathy. Heart, 2005. 91(2): p. 257-264.

177. Lee, T.M., et al., Pediatric cardiomyopathies. Circulation research, 2017. 121(7): p. 855-873.

178. Schultheiss, H.-P., et al., Dilated cardiomyopathy. Nature reviews Disease primers, 2019. 5(1): p. 32.

179. Yang, C., Y. Zhang, and B. Yang, MIAT, a potent CVD-promoting lncRNA. Cellular and Molecular Life Sciences, 2022. 79(1): p. 43.

180. Zhang, Y., et al., The long non-coding RNA H19 promotes cardiomyocyte apoptosis in dilated cardiomyopathy. Oncotarget, 2017. 8(17): p. 28588.

181. Gao, J., et al., The role and molecular mechanism of non-coding RNAs in pathological cardiac remodeling. International journal of molecular sciences, 2017. 18(3): p. 608.

182. Klattenhoff, C.A., et al., Braveheart, a long noncoding RNA required for cardiovascular lineage commitment. Cell, 2013. 152(3): p. 570-583.

183. Xie, L., et al., The roles of lncRNA in myocardial infarction: molecular mechanisms, diagnosis biomarkers, and therapeutic

DOI 10.58832/ctr.2023.7.6.1

perspectives. Frontiers in cell and developmental biology, 2021. 9: p. 680713.

184. Yang, L., et al., Ablation of lncRNA Miat attenuates pathological hypertrophy and heart failure. Theranostics, 2021. 11(16): p. 7995-8007.

185. Zhou, X., et al., lncRNA MIAT functions as a competing endogenous RNA to upregulate DAPK2 by sponging miR-22-3p in diabetic cardiomyopathy. Cell death & disease, 2017. 8(7): p. e2929-e2929.

186. Yu, Z., et al., CircRNAs open a new era in the study of cardiovascular disease. International Journal of Molecular Medicine, 2021. 47(1): p. 49-64.

187. Guo, Q., et al., Comprehensive construction of a circular RNA-associated competing endogenous RNA network identified novel circular RNAs in hypertrophic cardiomyopathy by integrated analysis. Frontiers in genetics, 2020. 11: p. 764.

188. Li, H., et al., Circular RNA circRNA_000203 aggravates cardiac hypertrophy via suppressing miR-26b-5p and miR-140-3p binding to Gata4. Cardiovascular research, 2020. 116(7): p. 1323-1334.

189. Zhao, Q., et al., CircRNA 010567 plays a significant role in myocardial infarction via the regulation of the miRNA-141/DAPK1 axis. Journal of Thoracic Disease, 2021. 13(4): p. 2447.

190. Jin, L., et al., Circular RNA Rbms1 inhibited the development of myocardial ischemia reperfusion injury by regulating miR-92a/BCL2L11 signaling pathway. Bioengineered, 2022. 13(2): p. 3082-3092.

191. Gan, J., et al., Circular RNA_101237 mediates anoxia/reoxygenation injury by targeting let-7a-5p/IGF2BP3 in cardiomyocytes. International Journal of Molecular Medicine, 2020. 45(2): p. 451-460.

192. Doctor, N.S., et al., Acute pericarditis. Progress in cardiovascular diseases, 2017. 59(4): p. 349-359.

193. Aghagoli, G., et al., Cardiac involvement in COVID-19 patients: Risk factors, predictors, and complications: A review. Journal of cardiac surgery, 2020. 35(6): p. 1302-1305.

194. Babapoor-Farrokhran, S., et al., Arrhythmia in COVID-19. SN Comprehensive Clinical Medicine, 2020. 2: p. 1430-1435.

195. Caforio, A.L., et al., Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. European heart journal, 2013. 34(33): p. 2636-2648.

196. Fang, Q., et al., LncRNA TUG1 alleviates cardiac hypertrophy by targeting miR-34a/DKK1/Wnt-β-catenin signalling. Journal of Cellular and Molecular Medicine, 2020. 24(6): p. 3678-3691.

197. Tikhomirov, R., et al., Exosomes: from potential culprits to new therapeutic promise in the setting of cardiac fibrosis. Cells, 2020. 9(3): p. 592.

198. Li, J., et al., Circular RNAs: Biogenesis, Biological Functions, and Roles in Myocardial Infarction. International Journal of Molecular Sciences, 2023. 24(4): p. 4233.

199. da Silva, A.M.G., et al., Long non-coding RNA and circular RNA: new perspectives for molecular pathophysiology of atrial fibrillation. Molecular Biology Reports, 2023: p. 1-11.