



Advances in miR-132-Based Biomarker and Therapeutic Potential in the Cardiovascular System

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Atherosclerotic cardiovascular disease and subsequent heart failure threaten global health and impose a huge economic burden on society. MicroRNA-132 (miR-132), a regulatory RNA ubiquitously expressed in the cardiovascular system, is up- or down-regulated in the plasma under various cardiac conditions and may serve as a potential diagnostic or prognostic biomarker. More importantly, miR-132 in the myocardium has been demonstrated to be a master regulator in many pathological processes of ischemic or nonischemic heart failure in the past decade, such as myocardial hypertrophy, fibrosis, apoptosis, angiogenesis, calcium handling, neuroendocrine activation, and oxidative stress, through downregulating target mRNA expression. Preclinical and clinical phase 1b studies have suggested antisense oligonucleotide targeting miR-132 may be a potential therapeutic approach for ischemic or nonischemic heart failure in the future. This review aims to summarize recent advances in the physiological and pathological functions of miR-132 and its possible diagnostic and therapeutic potential in cardiovascular disease.

Keywords: miR-132, Biomarker (BM), therapeutic potential, CDR132L, heart failure

INTRODUCTION

With the aging of the population and improved survival of atherosclerotic cardiovascular disease (CVD), the prevalence of heart failure (HF) is increasing worldwide, imposing a huge economic burden on society (Cook et al., 2014; Virani et al., 2020). Despite current advances in drug and device treatment for chronic HF, especially for HF with reduced ejection fraction, the risk of death or readmission for HF within 1 year remains as high as 15% (Crespo-Leiro et al., 2016). Therefore, it is of great clinical relevance to find novel diagnostic and prognostic biomarkers for early diagnosis and risk stratification and new therapeutic drugs for improving the long-term prognosis of HF.

MicroRNAs (miRNAs), first discovered in the 1990s (Lee et al., 1993), are small non-coding RNAs of 18–25 nucleotides that post-transcriptionally regulate gene expression through binding to the 3' untranslated region (UTR) of their target messenger RNAs (mRNAs), resulting in mRNA degradation and/or translational repression (He and Hannon, 2004; van Rooij, 2011; Bernardo et al., 2012). To date, about 2,300 miRNAs have been identified in the human genome, which are critically involved in biological development, cell differentiation, apoptosis, and many other physiological and pathological processes by regulating up to 60% of human genes at the post-transcriptional level (Ambros, 2004; Latronico and Condorelli, 2009; Krol et al., 2010). Mounting evidence has suggested that many specific miRNAs are up- or down-regulated in the failing human heart (Thum et al., 2007). Among them, miR-132 is well documented to be abnormally expressed

under various cardiac stresses and play a pivotal role in regulating the pathological process of hypertrophy, fibrosis, apoptosis, and angiogenesis, which are implicated in the development and progression of ischemic heart failure, thus conferring miR-132 a potential diagnostic biomarker and therapeutic target for ischemic cardiovascular disease.

In the present review, we will discuss the available evidence for the use of miR-132 as diagnostic and prognostic biomarkers for cardiovascular diseases. Next, we will discuss the possible effects and mechanisms of action of aberrant miR-132 expression in the cardiovascular system (e.g., cardiomyocytes, cardiac fibroblasts, endothelial, and vascular smooth muscle cells). Finally, we will summarize the current knowledge and future challenges about antisense oligonucleotide inhibitors of miR-132 as promising therapeutic drugs for heart failure.

MIR-132 BIOGENESIS AND REGULATION

MiR-132 arises from the highly conserved miR-132/212 gene cluster arrayed in tandem on chromosome 17 in humans, with both miRNAs having identical seed regions and possibly sharing some common mRNA targets (Tognini and Pizzorusso, 2012; Wanet et al., 2012). Mature miR-132 mostly follows the canonical pathway of miRNA biogenesis. In brief, miR-132 genes are transcribed by RNA polymerase II from intergenic, intronic, or polycistronic loci to pri-miRNAs and processed in the nucleus by the Drosha-DGCR8 complex to pre-miRNAs of approximately 70 nucleotides. Mirtrons provide an alternative source to form pre-miRNA hairpins. Pre-miRNAs are then exported to the cytoplasm and cleaved by the Dicer-TRBP complex to imperfect miRNA: miRNA^{*} duplexes of 22 nucleotides. One strand of the duplex, the mature miRNA, is loaded into the miRNA-induced silencing complex to exert post-transcriptional negative regulation of target mRNA, while the complementary strand is degraded (Krol et al., 2010; van Rooij and Kauppinen, 2014). The biogenesis of miR-132 is regulated at multiple levels including transcription, Drosha or Dicer processing, RNA editing, argonaute modification and RNA decay (Krol et al., 2010; Ha and Kim, 2014). It has been demonstrated that the transcription of miR-132/212 itself is positively and negatively controlled by cAMP-response element binding (CREB) protein and repressor element 1 silencing transcription factor, respectively (Vo et al., 2005; Conaco et al., 2006; Wanet et al., 2012). Judit Remenyi, et al. further disclosed that the transcription of the miR-132/212 miRNA cluster is also strongly regulated by extracellular-signal-regulated kinase 1/2 (ERK1/2) signaling, in part through the downstream mitogen and stress-activated kinase and the phosphorylation of CREB (Remenyi et al., 2010).

MIR-132-BASED BIOMARKER POTENTIAL IN CARDIOVASCULAR DISEASE

The serum levels of miRNAs are highly stable, reproducible, and resistant to harsh conditions such as boiling, low/high pH,

extended storage, and freeze-thaw cycles for association with microparticles, RNA-binding protein, or high-density lipoproteins, (Chen et al., 2008; Cortez et al., 2011; Creemers et al., 2012). Besides, the medicines commonly used in the cardiovascular system, including heparin, angiotensin-converting enzyme inhibitors, beta-blockers, nitrates, statins, aspirin, clopidogrel, and n-3 polyunsaturated fatty acids, have been proven not to affect plasma levels of miR-132 (Masson et al., 2018; Li et al., 2019). The above characteristics of miRNAs or miR-132 make serum miR-132 a potential biomarker for disease diagnosis and risk assessment (Table 1).

Diagnostic Biomarker Potential

Recently, specific expression patterns of serum miR-132 have been documented associated with various cardiovascular diseases. Li, et al. evaluated the dynamic changes in plasma levels of miRNAs and cardiac troponin I (cTnI) of 35 acute myocardial infarction (AMI) patients and 55 matched controls, and found that the circulating level of miR-132-5p was maintained at a low level during the early phase of AMI and negatively correlated with cTnI. Receiver operating characteristic analysis suggested that miR-132-5p may serve as a novel promising diagnostic biomarker for the early diagnosis of AMI (Li et al., 2019). Unlike the diagnosis of AMI distinctly relying on cTnI measurement, early diagnosis of unstable angina pectoris (UAP) remains a major clinical challenge for no available biomarkers providing clinically useful information. Zeller et al. identified eight significantly lower miRNAs, including miR-132, in UAP patients ($n = 10$) than in non-coronary chest pain patients ($n = 10$) and healthy controls ($n = 10$), which facilitate the early diagnosis of UAP. A panel of three miRNAs (miR-132, -150, and -186) showed the highest discriminatory power, with an area under the receiver-operating characteristic curve (AUC) of 0.91 (95% confidence interval: 0.84–0.98), compared with high-sensitivity assayed troponin I (hsTnI) and a model including hsTnI, B-type natriuretic peptide, C-reactive protein, and cystatin C (4-marker combination) (AUC of 0.57 and 0.63, respectively) (Zeller et al., 2014). Liu et al. found that the plasma levels of miR-132 in HF patients with left ventricular ejection fraction less than 45% ($n = 65$) were downregulated compared with healthy controls ($n = 62$) (Liu et al., 2018a). Besides, studies also showed aberrant circulating miR-132 levels in patients without overt cardiovascular disease. Rawal, et al. demonstrated that the miR-132 levels in the plasma and myocardium of diabetes patients without any known history of cardiovascular disease were downregulated compared to healthy subjects, and associated with decreased capillaries and arterioles and increased endothelial cell apoptosis, which is a hallmark of microangiopathy. Thus, monitoring the circulating levels of miR-132 could potentially identify those individuals with preclinical diabetic cardiac microangiopathy (Rawal et al., 2017). More recently, Šatrauskienė et al. identified a cluster of four miRNAs including miR-132, miR-1, miR-122, and miR-133 related to subclinical atherosclerosis in patients with metabolic syndrome ($n = 182$), suggesting a more substantial diagnostic or prognostic value of combined miRNAs than any single miRNA (Šatrauskienė et al., 2021). The above-mentioned studies

TABLE 1 | Circulating miR-132 as potential diagnostic and prognostic biomarkers in cardiovascular disease.

Disease	Study design	Source	Change in expression vs. controls	Clinical application	References
AMI	35 AMI vs. 55 healthy controls	Plasma	↓	Diagnosis	Li et al. (2019)
UAP	10 UAP vs. 10 non-coronary chest pain vs. 10 healthy controls	Serum	↓	Diagnosis	Zeller et al. (2014)
HF	65 HF with LVEF ≤ 45% vs. 62 healthy controls	Plasma	↓	NA	Liu et al. (2018a)
DM	Patients with different duration of DM (1–5, 6–10, 11–15, and >15 years, <i>n</i> = 17, 18, 16, and 17, respectively) vs. age- matched non-DM	Plasma	↓	Identify diabetic cardiac microangiopathy	Rawal et al. (2017)
CAD	1,112 CAD including 430 ACS and 682 SAP, 4 years follow-up	Serum	NA	Higher miR-132 levels predict CV death in ACS patients	Karakas et al. (2017)
CHF	953 symptomatic CHF from GISSI-HF trial, 46.2 months follow-up	Plasma	NA	Higher miR-132 levels were associated with severe HF symptom, but predicted lower risk of HF readmission	Panico and Condorelli (2018)

AMI, acute myocardial infarction; UAP, unstable angina pectoris; HF, heart failure; NA, not applicable; DM, diabetes mellitus; CVD, cardiovascular disease; CAD, coronary artery disease; ACS, acute coronary syndrome; SAP, stable angina pectoris; CV, cardiovascular; CHF, chronic heart failure.

suggest that a reduction in plasma miR-132 levels, either singly used or combined with other miRNAs, may have an additive diagnostic value for patients with diabetic cardiac microangiopathy, unstable angina, myocardial infarction, and heart failure. However, the sample size of these studies was mostly small, and their conclusions still need to be further validated by larger clinical studies in the future.

Prognostic Biomarker Potential

Cardiovascular death risk stratification for patients with coronary artery disease is helpful to guide intensified secondary preventive therapies. Karakas et al. first assessed the association of circulating miRNAs levels with secondary adverse cardiovascular events in a cohort of 1,112 patients with documented coronary artery disease, including 430 patients with acute coronary syndrome and 682 patients with stable angina pectoris. During a median follow-up of 4.0 years, Cox regression analyses adjusted for age and gender indicated that miR-132 precisely predicted cardiovascular death (HR 2.85 per 1 SD increase, $p = 0.022$) in patients with acute coronary syndrome. The C-statistics showed excellent values for prediction of cardiovascular death (AUC for miR-132: 0.737) (Karakas et al., 2017). Instead, another study by Masson et al. drew the opposite results. The authors retrospectively analyzed the circulating levels of miR-132 in 953 patients with chronic, symptomatic heart failure from the GISSI-Heart Failure trial and showed that higher plasma levels of miR-132 were independently associated with increased HF severity (NYHA class and ischaemic etiology), but consistently predicted lower rates of fatal (all-cause or cardiovascular death) or non-fatal events (hospitalization for cardiovascular or HF reasons). After extensive adjustment for demographic, clinical, and echocardiographic risk factors and baseline N-terminal brain natriuretic peptide precursor (NT-proBNP) concentrations, miR-132 remained associated only with HF hospitalizations (HR 0.79, 95% confidence interval 0.66–0.95, $p = 0.01$). Of note, The association was observed in patients with HF of ischaemic etiology but not in those with HF of

non-ischaemic etiology (P for heterogeneity 0.08). Besides, miR-132 improved risk prediction beyond traditional risk factors for HF hospitalization with the continuous net reclassification index of 0.205 ($p = 0.001$) (Masson et al., 2018; Panico and Condorelli, 2018). Taken together, these results suggest that the translation of circulating miR-132 into clinical prognostic biomarkers may be hampered by lack of consistency or restricted to certain subgroups of patients, such as acute coronary syndrome and ischemic heart failure.

PHYSIOLOGICAL AND PATHOLOGICAL ROLES OF MIR-132 IN CARDIOVASCULAR DISEASE

Through reviewing the existing literature, we've come to the conclusion that miR-132 may play a crucial role in regulating pathophysiological processes of cardiovascular disease, including myocardial hypertrophy, autophagy, fibrosis, apoptosis, angiogenesis, calcium handling, neuroendocrine activation, oxidative stress, and endothelial and vascular smooth muscle cell biology (Table 2).

Pro-Hypertrophic and Anti-Autophagic Properties

Pathological cardiac hypertrophy is a hallmark characteristic of heart failure of different etiology. Ucar et al. first reported that both miR-132 and miR-212 were upregulated in cardiomyocytes upon different hypertrophic stimuli both *in vitro* and *in vivo*, such as angiotensin II (AngII), insulin-like growth factor-1, phenylephrine/isoprenaline, and fetal calf serum, and were independently sufficient to induce hypertrophy. Cardiomyocyte-specific overexpression of miR-132/212 leads to pathological cardiac hypertrophy, heart failure, and death in mice. Conversely, miR-132/212-deficient mice or pharmacological inhibition by antagomiR against miR-132/212

TABLE 2 | MiR-132 targets and functions in pathophysiologic process of cardiovascular disease.

Functions	Injury model or mode of action	Upregulation/ downregulation	Target molecule	Target pathway	References
Pro-hypertrophy and anti-autophagy	<i>In vivo</i> AngII, PE/ISO, and TCA	Upregulation	FoxO3	Calcineurin/NAFT↑	Ucar et al. (2012) Eskildsen et al. (2013)
Profibrosis	<i>In vitro</i> AngII	Upregulation	MMP-9, FoxO3	NA	Jiang et al. (2013) Schimmel et al. (2021)
Antifibrosis	<i>In vivo</i> MI, <i>in vitro</i> AngII <i>In vivo</i> DCM	Upregulation Downregulation	PTEN PTEN	PI3K/Akt↓ PI3K/Akt↑	Wang et al. (2020) Zhang et al. (2019)
Antiapoptosis	<i>In vitro</i> miR-212/132-Transgenic H9c2	Upregulation	FoxO3	PI3K/Akt↑	Ucar et al. (2012)
Proangiogenesis	<i>In vivo</i> MI	Downregulation	NA	Interleukin-1β↑	Zhao et al. (2020)
	<i>In vivo</i> MI and hind-limb ischaemia	Upregulation	p120RasGAP, Spred1	Ras-MAPK↑	Lei et al. (2015) Katare et al. (2011)
Impaired calcium handling	End-stage heart failure patients of different etiologies <i>In vivo</i> I/R injury	Upregulation	SERCA2	NA	Lei et al. (2021)
Interaction with AVP synthesis	Intravenous antagomir-132	Downregulation	NCX1 MeCP2	NA AVP synthesis↓	Hong et al. (2015) Bijkerk et al. (2018)
Redox regulation	<i>In vivo</i> and <i>in vitro</i> I/R injury	Upregulation	SIRT1	PGC-1α/NRF2↓	Zhou et al. (2020)
Induction of a Pro-inflammatory Phenotype in EC	<i>In vitro</i> TNF-α-treated EC	Upregulation	SIRT1	SREBP-1c Metabolic Pathway↓	Zhang et al. (2014)
	<i>In vitro</i> ox-LDL-treated EC	Upregulation	MGP	JNK↑ NF-κB↑	Fu et al. (2018)
Modulation of VSMC behavior	<i>In vivo</i> catheter injury	Upregulation	Lrrfip1	Erk1/2 phosphorylation↑	Choe et al. (2013)
	<i>In vivo</i> and <i>in vitro</i> DM	Upregulation	E2F5	NA	Xu et al. (2019)
	<i>In vivo</i> and <i>in vitro</i> AngII	Upregulation	PTEN	MCP-1↑	Jin et al. (2012)

AngII, angiotensin; PE/ISO, phenylephrine/isoprenaline; TAC, transaortic constriction; FoxO3, forkhead box protein O3; NAFT, nuclear factor of activated T-cells; MMP-9, matrix metalloproteinase-9; PTEN, phosphatase and tensin homolog; PI3K, phosphatidylinositol3-kinase; Akt, protein kinase B; DCM, dilated cardiomyopathy; TG, transgenic; IL-1β, interleukin-1β; p120RasGAP, p120 Ras GTPase-activating protein; Spred1, Sprouty-related Ena/VASP homology-1 domain-containing protein1; MAPK, mitogen-activated protein kinase; SERCA2, sarcoplasmic reticulum Ca(2+)-ATPase; I/R, ischemia/reperfusion; NCX1, Na(+)-Ca(2+) exchanger 1; MeCP2, methyl-CpG-binding protein 2; PGC-1α, proliferator-activated receptor-gamma coactivator-1α; NRF2, nuclear factor erythroid 2-related factor 2; EC, endothelial; TNF-α, tumor necrosis factor-α; SIRT1, silent information regulator 1; SREBP-1c, sterol regulatory element binding protein-1c; ox-LDL, oxidized low-density lipoprotein; MGP, matrix Gla protein; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor Kappa B; VSMC, Vascular smooth muscle cell; LRRFIP1, leucine-rich repeat (in Flightless 1) interacting protein-1; Erk1/2, extracellular-signal-regulated kinase 1/2; DM, diabetes mellitus; E2F5, E2F transcription factor 5; MCP-1, monocyte chemoattractant protein-1.

rescued pressure overload-induced hypertrophy and prevented heart failure (Ucar et al., 2012). Mechanistically, it was proved that the miR-132/212 family regulates both cardiac hypertrophy and cardiomyocyte autophagy by translationally repressing forkhead box protein O3(FoxO3), a powerful anti-hypertrophic and pro-autophagic transcription factor in cardiomyocytes (Ni et al., 2006; Sengupta et al., 2009; Ronnebaum and Patterson, 2010), leading to hyperactivation of pro-hypertrophic calcineurin/nuclear factor of activated T-cells signaling and impaired autophagic response upon starvation. In line with these findings, Eskildsen et al. demonstrated that the expression of miR-132 was significantly increased in the heart, aortic wall, and kidney, as well as in the plasma of rats with hypertension and cardiac hypertrophy induced by 10 days of AngII infusion (Eskildsen et al., 2013). Narasimhan et al. further revealed that the increased cardiomyocyte expression of miR-132 induced by isoproterenol was related to increased phosphorylation of CREB through activation of the mitogen-activated protein kinase (MAPK)/ERK pathway (Narasimhan et al., 2018).

Profibrotic Potential

Cardiac fibrosis, characterized by the deposition of excessive extracellular matrix mainly derived from fibroblasts, leads to stiffness of the heart and compromised heart contractility. It is well documented that miR-132/212 functions as master signaling switches to fine-tune the AngII actions in cardiac fibroblasts (CFs). With the global array analysis of AngII-induced miRNA expression, Jeppesen et al. identified five miRNAs, including the miR-132/212 family in primary cultures of CFs that were upregulated by AngII through activation of Gαq/ERK1/2-dependent signaling (Jeppesen et al., 2011). Eskildsen et al. further undertook a detailed analysis of miR-132/212 molecular targets to unravel the role of miR-132 and miR-212 in AngII signaling networks in CFs and found that miR-132/212 overexpression increased fibroblast cell size and affected several hundred genes expression, including a wide panel of receptors, signaling molecules and transcription factors (Eskildsen et al., 2015). Jiang et al. revealed that the levels of miR-132 in CFs were upregulated by AngII and identified matrix metalloproteinase-9 as the target of miR-132 (Jiang et al., 2013). Recently, Schimmel

et al. have further confirmed the profibrotic nature of miR-132 through enhancing proliferation and migration activity of primary human cardiac fibroblasts, which was possibly attributed to autophagy repression through targeting FoxO3 (Schimmel et al., 2021). However, there also exist some other studies indicating an opposite view that miR-132 levels are down-regulated in the heart of heart failure rats and Ang-II treated CFs and upregulation of miR-132 exerts inhibitory effects on cardiac fibrosis in MI-induced heart failure rats, doxorubicin-induced dilated cardiomyopathy rat, and canine model of atrial fibrillation (Qiao et al., 2017; Zhang et al., 2019; Wang et al., 2020).

Prosurvival Action on Cardiomyocytes

Apoptosis in response to cardiac stress, such as myocardial infarction, contributes to an irreversible loss of cardiomyocytes and subsequent adverse remodeling. It is well demonstrated that miR-132/212 plays an anti-apoptotic role by activating the phosphatidylinositol-3 kinase/protein kinase B pathway in cardiomyocytes (Ucar et al., 2012). Overexpression of miR-132 in cardiomyocytes *in vitro* contributes to enhanced resistance to hypoxia, hydrogen peroxide, and hypoxia and glucose deprivation-induced cell death (Liu et al., 2018a; Lei et al., 2020a; Zhang et al., 2020). Besides, *in vivo* studies have shown that miR-132 was downregulated in cardiomyocytes from MI rats compared to sham-operated rats, and overexpression of miR-132 mitigated cardiomyocyte apoptosis and myocardial remodeling, and this effect may be achieved in part through inhibition of interleukin-1 β (Zhao et al., 2020). Chen et al. also showed that miR-132 gradually decreased within 7 days post-MI, and the infarct size in miR-132 knockout (KO) mice was larger than that in wild-type mice at postoperative day 14 and day 28, and the cardiac function was worse. MiR-132 mimics at a dose of 16 mg/kg improved cardiac function and reduced infarct size in mice 28 days after MI modeling (Chen et al., 2019). However, Lei et al. reported that the expression of miR-132 initially increased at 12 h post-MI, then decreased at 24 h, but increased nonsignificantly again in later phases within 1 month post-MI. Although miR-132 loss enhanced cardiac contractile function in mice with MI, it also attenuated cardiomyocytes survival and angiogenesis, ultimately not improving overall cardiac performance or fibrosis remodeling 4 weeks post-MI compared with wild-type mice (Lei et al., 2020a).

Angiogenesis Regulation

Angiogenesis is essential for maintaining oxygen and nutrients supplies to the myocardial tissue, and angiogenesis impairment is involved in the pathogenesis of ischemic heart disease. Accumulating evidence suggests that miRNAs play key roles in regulating vascular endothelium response to angiogenic stimuli, serving as a promising therapeutic approach for ischemic heart diseases involving insufficient vasculature (Fish and Srivastava, 2009). MiR-132 is a proangiogenic miRNA that is highly expressed in endothelial cells and in atherosclerotic lesions in ApoE^{-/-} mice (Xiong et al., 2015). Upon angiogenic stimulation, such as hypoxia (Burek et al., 2019) or loss of functional von Hippel-Lindau gene (Lei et al., 2020b), the miR-132 levels are increased and function as an angiogenic

switch by targeting p120 Ras GTPase-activating protein (p120RasGAP, also named RASA1) and Spred1 in the endothelium and thereby leading to Ras-MAPK pathway activation and induction of neovascularization (Anand et al., 2010; Lei et al., 2015). A time-course study in type 2 diabetic mouse model revealed that the down-regulation of miR-132 preceded the development of microangiopathy in the diabetic heart, and therapeutic normalization of miR-132 in *ex vivo* diabetic aortic rings and *in vitro* high glucose-treated human umbilical vein endothelial cells restored their angiogenic potential (Rawal et al., 2017). Moreover, it was documented that miR-132/212 KO mice showing impaired arteriogenic responses after ischemia in the hind limbs compared with wild-type mice (Lei et al., 2015), while intracellular delivery of miR-132 via biodegradable nanoparticles improved endothelial graft survival and blood perfusion after ischemic injury (Gomes et al., 2013).

MiR-132 not only regulates the target gene *in situ* but also acts as a paracrine mediator in affecting angiogenesis at distant sites. Katare et al. reported that transplantation of human pericyte progenitor cells exerted proangiogenic and antifibrotic effects in the infarcted heart through secretion of miR-132 and targeted inhibition of p120RasGAP and methyl-CpG-binding protein 2 (MeCP2), respectively, whereas miR-132 KO in pericytes abrogated these beneficial effects (Katare et al., 2011). Exosomes are effective vectors delivering miR-132 efficiently to the tissue of interest to induce therapeutic angiogenesis for ischemic heart disease (Kir et al., 2018; Moghiman et al., 2021). Barile et al. showed that infarcted hearts injected with miR-132 and miR-210-enriched exosomes from human cardiac progenitor cells exhibited less cardiomyocyte apoptosis, enhanced angiogenesis, and improved ejection fraction compared with those injected with control medium (Barile et al., 2014). Ma et al. also confirmed that delivery of miR-132 via mesenchymal stem cell-derived exosomes in the ischemic hearts of mice markedly enhanced the neovascularization in the peri-infarct zone and preserved heart functions (Ma et al., 2018).

In contrast to the above evidence suggesting that miR-132 has a proangiogenic effect, some studies have concluded otherwise that miR-132 has no major effects on angiogenesis or cardiac capillary densities *in vivo* (Ucar et al., 2012; Kumaraswamy et al., 2014), and even in a pressure overload-induced porcine cardiomyopathy model, antagomiR targeting miR-132 improves capillary density (Hinkel et al., 2021). Therefore, there is still no consistent conclusion on the effect of miR-132 on angiogenesis, which needs to be further clarified in future studies.

Impaired Calcium Handling

Cyclic changes of intracellular calcium concentration are involved in regulating the excitation-contraction coupling of cardiomyocytes (Bers, 2002). It is well known that cardiac sarcoplasmic reticulum Ca(2+)-ATPase (SERCA2) plays a crucial role in modulating cardiac contraction and relaxation by regulating intracellular calcium processing, and attenuated SERCA2 expression or activity leads to impaired calcium handling associated with contractile dysfunction and heart

failure progression (Frank et al., 2003). Wahlquist et al. first documented that miR-132/212 can suppress green fluorescent protein expression in the SERCA2 3'-UTR reporter, indicating miR-132/212 may be a regulator of SERCA2 (Wahlquist et al., 2014). Later, Foinquinos et al. demonstrated that overexpression of miR-132 in cardiomyocytes compromised contractile kinetics, which could be normalized by anti-miR-132 treatment by, at least in part, restoring SERCA2 expression (Foinquinos et al., 2020). Lei et al. showed that miR-132/212 overexpression prolongs calcium decay in isolated neonatal rat cardiomyocytes, whereas cardiomyocytes isolated from miR-132/212 KO mice display enhanced contractility in comparison to wild type controls. The authors also found upregulation of miR-132/212 and reduced SERCA2 protein expression in end-stage heart failure patients of different etiologies, including dilated cardiomyopathy, hypertrophic cardiomyopathy, and ischemic cardiomyopathy (Lei et al., 2021). Besides, it was also suggested that elevated miR-132/212 can lower SERCA2 activity indirectly via inhibition of PTEN, which is a direct target of miR-132/212 and loss of function in cardiomyocytes leading to a dramatic decrease in contractility (Crackower et al., 2002; Ruan et al., 2009). Another study by Hong et al. showed that delivery of miR-132 blunted intracellular Ca(2+) overload through targeting the Na(+)-Ca(2+) exchanger 1, protecting cardiomyocytes against hypoxia-induced apoptosis (Hong et al., 2015).

Interaction With Neuroendocrine Activation

AngII controls blood pressure and adverse ventricular remodeling in the pathological process of heart failure through activation of angiotensin II type 1 receptor (AT1R). It has been reported that AngII upregulates the expression of miR-132 by activating the Gαq/ERK1/2 pathway while AT1R blockers reduce plasma levels of miR-132 in human patients (Eskildsen et al., 2013). On the other hand, miR-132 fine-tunes AngII responsiveness by translationally repressing AT1R expression by directly binding to sequence recognition sites in the coding region of human AT1R mRNA (Elton et al., 2008). In addition, animal studies have shown that angiotensin-converting enzyme inhibitor ramipril for the treatment of acute kidney injury can simultaneously inhibit cardiac hypertrophy, fibrosis, and apoptosis, and these cardioprotective effects are partially related to the attenuated miR-132 expression (Rana et al., 2015). Arginine vasopressin (AVP) has been recognized as an important contributor to heart failure development through water retention, hyponatremia, and arterial vasoconstriction (Iovino et al., 2018). Bijkerk et al. identified miR-132 as the first miRNA maintaining the water and osmotic balance in the body by regulating the hypothalamic AVP gene mRNA expression. Specifically, miR-132 can promote AVP synthesis and release into blood by targeting MeCP2 expression, which acts on renal aquaporin-2 and promotes water reabsorption. MiR-132 silencing by anti-miR in mice causes severe weight loss due to acute diuresis and increased plasma osmolality, along with reduced AVP production and apical aquaporin-2 expression (Bijkerk et al., 2018). Thus, miR-132 anti-miR may be of therapeutic value in acquired hypervolemic/hyponatremic conditions, such as congestive heart failure.

Redox Regulation

Nuclear factor erythroid 2-related factor 2 (NRF2), is a basic leucine zipper protein that promotes an array of antioxidant genes and phase II detoxifying enzymes expression by binding to antioxidant response elements, playing an important role in maintaining the normal function of cardiomyocytes and cardiac fibroblasts and preventing maladaptive cardiac remodeling and heart failure (Li et al., 2009; Chen and Maltagliati, 2018). Zhou et al. showed that inhibition of miR-132 activated peroxisome proliferator-activated receptor-γ coactivator-1α/NRF2 signaling by targeting silent information regulator 1 (SIRT1), leading to inhibition of oxidative stress and the expression of pyrotic related proteins nucleotide-bound oligomeric domain-like receptor proteins 3, caspase-1, and interleukin-1, ultimately ameliorating myocardial ischemia-reperfusion injury (Zhou et al., 2020). Consistently, Hinkel et al. found that anti-miR-132 treatment increased myocardial NRF2 expression compared to untreated control in a porcine model of pressure-overload-induced heart failure (Hinkel et al., 2021). However, some studies have suggested the opposite results that overexpression of miRNA-132 inhibited oxidative stress induced by H₂O₂ in H9C2 cells (Liu et al., 2018b), improving cell viability and apoptosis *in vitro* and alleviating ischemia/reperfusion-induced AMI *in vivo* (Su et al., 2020).

Endothelium and Vascular Smooth Muscle Cells Behavior Modulation

Endothelial dysfunction is supposed to be the initial step toward atherosclerosis development (Gimbrone and García-Cardena, 2016). Recent studies have shown that miR-132 may be involved in the process of atherosclerosis and ischemic heart disease by adversely affecting the biological behavior of vascular endothelium. Zhang et al. showed that miR-132 induces pro-inflammatory processes of vascular endothelial inflammation through negatively regulating the expression of SIRT1. Besides, miR-132 promoted apoptosis of HUVECs induced by tumor necrosis factor-α and inhibited its proliferation, viability, and migration (Zhang et al., 2014). Similarly, Fu et al. documented that miR-132 was upregulated in HUVECs under oxidized low-density lipoprotein treatment, which could further decrease the expression of matrix Gla protein (MGP), resulting in increased migration and adhesion-related molecule release through activation of the c-Jun N-terminal kinase and nuclear factor Kappa B pathways (Fu et al., 2018).

Vascular smooth muscle cells (VSMCs) are essential components of the vascular wall, and their abnormal behaviors contribute to various vascular diseases such as atherosclerosis, restenosis, and hypertension (Bochaton-Piallat and Gabbiani, 2005). MiR-132 is abundantly expressed in VSMCs *in vivo* and regulates the biological behavior of VSMCs in response to various types of stress (Elton et al., 2008). Choe et al. demonstrated that miR-132 was upregulated in the rat carotid artery after catheter injury, facilitating to prevent neointimal hyperplasia by regulating VSMCs proliferation, differentiation, and migration. Transfection of a miR-132 mimic significantly inhibited the proliferation and migration of VSMCs and induced

VSMCs differentiation and apoptosis through downregulation of the expression of target LRRFIP1 and phosphorylation of ERK1/2 (Choe et al., 2013). Consistently, Xu et al. reported that the expression of miR-132 was significantly decreased and E2F transcription factor 5 (E2F5) upregulated in high glucose-treated VSMCs or those obtained from diabetic rats. Upregulation of miR-132 significantly inhibited the proliferation and migration of diabetic rat or high-glucose-treated VSMCs by targeting E2F5 (Xu et al., 2019). Other studies have suggested that miR-132 may promote a phenotypic switch of VSMCs that is conducive to atherosclerosis. Wen Jin, et al. analyzed the miRNAs profiles regulated by Ang II in VSMCs by using a small RNA sequencing method and documented that the miR-132/212 cluster is upregulated by Ang II in a time- and dose-dependent manner, resulting in increased monocyte chemotaxis protein-1 (MCP-1) expression at least in part through suppression of phosphatase and tensin homolog (PTEN) in rat VSMCs. Notably, the aorta of Ang II-infused mice showed similar upregulation of miR-132 and MCP-1, supporting an *in vivo* relevance (Jin et al., 2012). Chen et al. reported that over-expression of miR-132 in VSMCs led to an attenuation of cilostazol-induced VSMCs differentiation via inhibiting PTEN expression, indicating the adverse effects of miR-132 on VSMCs differentiation (Chen et al., 2018).

MIR-132-BASED THERAPEUTIC POTENTIAL IN CARDIOVASCULAR DISEASE

There are two main types of miR-132-based therapeutics, one is to suppress abnormally upregulated miR-132 through miR-132 inhibition, and the other is to restore attenuated miR-132 through miR-132 supplement. For this purpose, many strategies have been developed to manipulate miR-132 activity *in vivo*, including antisense oligonucleotides (ASOs) with different chemical modifications for miR-132 inhibition and double-stranded miR-132 mimics for miR-132 restoration. Besides, numerous miR-132 delivery tools have also been developed and include the use of a cholesterol moiety, miRNA sponges, liposomes, adeno-associated viruses, exosomes, and nanoparticles (Chistiakov et al., 2012; Bernardo et al., 2015).

Therapeutic Potential of miR-132 Inhibition in Cardiovascular Disease

CDR132L is a first-in-class, optimized, synthetic locked nucleic acid (LNA) antisense oligonucleotide inhibitor of miR-132 (antimiR-132) (Lu and Thum, 2019; Foinquinos et al., 2020). The inclusion of LNA nucleotides in the antisense oligonucleotide increases both stability and thermodynamic strength of duplex formation with complementary target mRNA (Elmén et al., 2008). Foinquinos et al. first tested the efficacy of antimiR-132 in miR-132/212 transgenic mice. The miR-132/212 transgenic mice showed severe left ventricular hypertrophy, decreased ejection fraction and cardiac dilatation. Pharmacologic inhibition of miR-

132 by intravenous injection of antimiR-132 reduced the expression level of miR-132 in the myocardium and restored the expression level of FoxO3, eventually reducing cardiac mass and ventricular dilatation while improving ejection fraction (Foinquinos et al., 2020). In a blind, randomized, placebo-controlled study, Batkai et al. administered monthly intravenous CDR132L to chronic heart failure pigs 1 month after myocardial infarction for 3 or 5 months and assessed the efficacy with magnetic resonance imaging (MRI), hemodynamic, and biomarker tests. The study found that CDR132L treatment achieved sufficient tissue exposure to significantly reverse cardiac remodeling, as evidenced by reduced left ventricular end-systolic volume and left atrial volume on MRI scan and attenuated myocardial interstitial fibrosis and cardiomyocyte size assessed by histology, resulting in improved LVEF by 7.96 and 7.14% as measured by MRI after 3 and 5 months of treatment, respectively, as compared with placebo. Besides, CDR132L also ameliorated diastolic function as evidenced by decreased end-diastolic pressure–volume relationship and minimum rate of change of left ventricular pressure determined by hemodynamic assay, and reduced the plasma level of NT-proBNP (Batkai et al., 2021). Recently, Hinkel et al. established a novel preclinical porcine model of nonischemic pressure-overload hypertrophy by placing a reduction stent in the descending thoracic aorta and assessed the efficacy of intracoronary administration of antimiR-132 at the time of stent implantation and 4 weeks later, finding that antimiR-132 reduces cardiomyocyte cross-sectional area, retards fibrosis, and improves capillary density and LV ejection fraction (antimiR-132 vs. untreated control, $48.9 \pm 1.0\%$ vs. $36.1 \pm 1.7\%$, respectively at the 8-week time point (Hinkel et al., 2021; Robson, 2021). The results of Hinkel et al. suggest that CDR132L has potential clinical application in hypertrophic heart disease caused by non-ischemic etiologies, such as aortic stenosis or systemic hypertension (Condorelli and Ferrante, 2021). A first-in-human Phase 1b randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate the safety, pharmacokinetic characteristics, and efficacy of CDR132L in patients with chronic ischemic heart failure receiving standard treatment. A total of 28 patients with LVEF of 30–50% or NT-proBNP ≥ 125 ng/L, age of 30–80 years old, and BMI of 18–28 kg/m² were included in this study and randomly assigned at 5:2 to CDR132L group (20 cases in total, five patients in each cohort receiving 0.32, 1, 3, and 10 mg/kg body weight of CDR132L, respectively) and placebo group (eight cases, 0.9% saline). After a 6-week screening period, subjects were given two doses of CDR132L or placebo by intravenous injection on day 1 and day 28, respectively, and the trial ended on day 112. In this study, CDR132L was safe and well-tolerated. CDR132L treatment resulted in a sustained and sharp decrease in plasma miR-132 levels in a dose-dependent manner. For patients with ischemic chronic heart failure receiving standard treatment, CDR132L can further reduce the median level of NT-proBNP and narrow the QRS wave relative to placebo, and improve nonsignificantly cardiac fibrosis biomarkers as well (Täubel et al., 2021). This is the first human study to target miR-132 and represents a milestone in the field of miRNA therapy for cardiovascular disease. While it is too early to determine whether this

strategy will be effective in humans, the study's evidence of the safety and efficacy of CDR132L provides great encouragement for further research in patients with heart failure (Baker and Giacca, 2021; Nicholls, 2021).

Therapeutic Potential of miR-132 Overexpression in Cardiovascular Disease

Given that the majority of current evidence suggests that miR-132 overexpression is involved in cardiac pathology, most of the miR-132-based therapies mainly focused on miR-132 inhibition, and only a few studies have explored the possible cardiac benefits of miR-132 upregulation. Gupta et al. showed that miR-132 overexpression can prevent cardiac toxicity caused by chemotherapeutic drugs. The authors established a mouse model of doxorubicin-induced cardiotoxicity and found that adeno-associated virus (AAV)9-mediated overexpression of miR-212/132 can counteract doxorubicin-induced cardiotoxicity, increase left ventricular mass and wall thickness, decrease doxorubicin-mediated apoptosis, and ultimately improve ejection fraction, which is partly related to the inhibition of target storage-inducing transmembrane protein 2 (Gupta et al., 2019). Jover et al. first reported that miR-132 was constitutively expressed by adventitial pericytes (APCs) and upregulated following high phosphate stimulation, playing a key role in the human APCs resistance to calcification through downregulating several target genes relevant to osteogenic differentiation. Treatment of swine cardiac valves with APCs-derived conditioned medium conferred them with resistance to high phosphate-induced osteogenesis, with this effect being negated when using the medium of miR-132-silenced APCs (Jover et al., 2021).

CLINICAL PERSPECTIVES AND FUTURE CHALLENGES

Challenges of Plasma miR-132 Level as a Biomarker

Despite a few small clinical studies have suggested that plasma levels of miR-132 are potential diagnostic or prognostic biomarkers for cardiovascular diseases, several issues need to be addressed before clinical application, such as whether miR-132 levels are affected by food and drugs, and whether they are affected by common comorbidities such as old age, atrial fibrillation, liver or renal insufficiency, and anemia. Does miR-132 provide additional value beyond current traditional risk factors? What is the optimal threshold for diagnosing or indicating a poor prognosis of cardiovascular disease?

Who Might Benefit From miR-132 Inhibition?

The current evidence supporting miR-132 inhibition as a potential therapeutic approach for heart failure is mainly derived from several animal models with experimental MI and a phase 1b clinical study demonstrating a further reduction in the

level of NTpro-BNP in patients with ischemic heart failure receiving standard treatment. Whether miR-132 inhibition can reduce heart failure hospitalization or cardiovascular death in patients with ischemic heart failure and improve cardiac remodeling in patients with non-ischemic heart failure remains to be addressed in future studies.

What is the Optimal Therapeutic Strategy for miR-132 Inhibition?

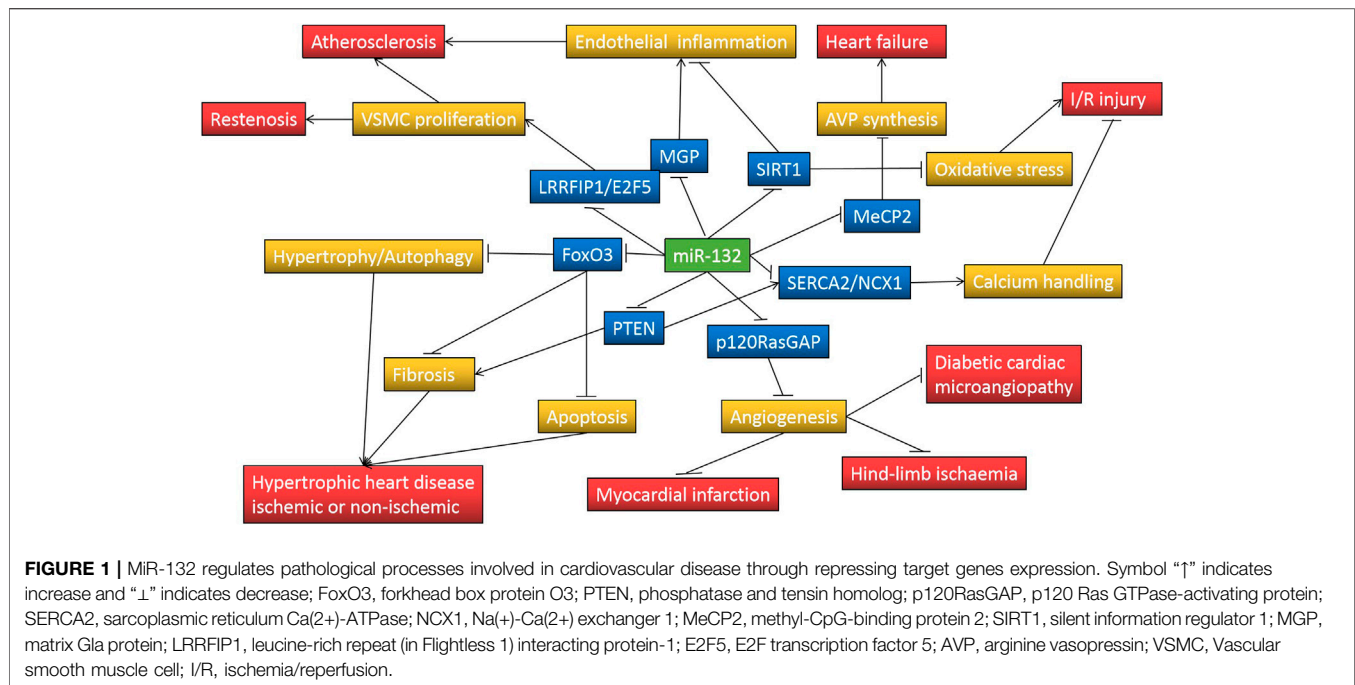
Although antimiR-132 targeting miR-132 administered to large animals post-MI has been proven effective in alleviating cardiac remodeling, improving cardiac systolic and diastolic functions, and reducing NT-proBNP (Batkai et al., 2021), knockdown of miR-132/212 has been documented to have no long-term beneficial effect on cardiac function after permanent coronary ligation in mice (Lei et al., 2020a). Besides, a circular miRNA sponge targeting the miR-132/212 family has been recently constructed to effectively attenuate pressure overload-induced cardiac hypertrophy *in vivo* and show greater *in vitro* efficacy than the current gold standard antagomiRs in inhibiting miRNA function (Lavenniah et al., 2020). Thus, the optimal therapeutic strategy for miR-132 silencing in the treatment of myocardial infarction remains unknown and needs to be further clarified.

Is Systemic Delivery of AntimiR-132 Safe?

Although the short-term safety of systemic administration of antimiR-132 has been preliminarily confirmed in large animal models and clinical phase 1b study (Foinquinos et al., 2020; Täubel et al., 2021), the concern of long-term off-target effects of systemic delivery still needs to be addressed with caution, given the fact that miR-132 is widely expressed and exhibits different functions in different organs or cell types. For example, while inhibiting cardiac hypertrophy, systemic delivery of antimiR-132 may simultaneously increase the risk of neurodegenerative diseases or delay wound healing (Li et al., 2015; El Fatimy et al., 2018). In addition, the high stability of antagomiRs and LNA can also be a double-edged sword, increasing their side effects in other organs (Kwekkeboom et al., 1979). Thus, further studies are required to comprehensively evaluate the long-term safety of systemic delivery of antimiR-132.

Cell-Specific Delivery of AntimiR-132 May Hold Promise

To circumvent issues of possible off-target effect, high costs, and low efficacy of systemic delivery, cell-specific targeted delivery has become a research hotspot in recent years (Kwekkeboom et al., 1979; Boon and Dimmeler, 2015). Several viral and non-viral vector-based delivery systems, including adenoviral, liposomal, polymer-based nanoparticles, and natural microvesicles/exosomes, have hence been developed to deliver miRNAs inhibitor or mimic specifically and efficiently to the tissue of interest (Kir et al., 2018). It is supposed that the cell-specific delivery of antimiR-132 may likely replace current systemic delivery in the future.



CONCLUSION

Several clinical studies have suggested that decreased plasma miR-132 levels have additional diagnostic value in acute myocardial infarction, unstable angina, heart failure, and even subclinical atherosclerosis, and may be associated with poor prognosis in patients with heart failure. However, most of these studies have small sample sizes or are retrospective, the reliability of their conclusions needs to be further confirmed by other large prospective studies. In addition, many preclinical studies have documented that the expression of miR-132 in the myocardium is up-regulated under various cardiac stresses and drives some basic pathological processes of heart failure, such as cardiac hypertrophy, fibrosis, and impaired calcium handling, through downregulation of FOXO3A, SERCA2a, PTEN, SIRT1 and other target gene expression, while targeted inhibition of miR-132 by anti-miR-132 attenuates cardiac hypertrophy and improves cardiac function (Figure 1). It is encouraging that anti-miR-132 has also been demonstrated for the first time in phase 1b clinical

trial to further reduce NT-proBNP in patients with ischemic heart failure receiving standard treatment and that the drug is safe and well-tolerated. In the future, more evidence needs to be accumulated on its indications, optimal therapeutic strategy and delivery tool, and long-term safety before translation into clinical practice as a novel anti-heart failure drug.

AUTHOR CONTRIBUTIONS

KX and CC wrote the manuscript. YW, MW, and LL examined the final draft.

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