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The Role of miR-132 in Pathogenesis and Therapeutic Targeting of Cardiovascular Disease

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Abstract **Review Article**

Cardiovascular disease (CVD) is a serious principal cause of death globally thrusting a huge economic load. There is no diagnostic and therapeutic strategy for the prevention of CVD. MiRNAs have been reported to play a significant role in cardiovascular pathologies. MicroRNA-132 (miR-132) is involved in cardiac apoptosis, impaired calcium handling, cardiac hypertrophy, pathological cardiac remodelling, oxidative stress, and angiogenesis. These cardiac pathophysiological effects are caused by miR-132-mediated downregulation of SIRT1, FoxO3, SERCA2A, and PTEN target gene expression. CDR-132L and other antimiR-132 long non-coding RNAs significantly inhibited miR-132 expression in pathophysiological cardiac remodelling and also cardiac apoptosis. These miR-132 targeting approaches can have great therapeutic potential. Present review intended to highlight the therapeutic and biomarker potential of miR-132 in the diagnosis and treatment of CVD various types. The potential clinical benefits of miR-132 inhibition through CDR-132L and other antimiR-132 long non-coding antisense oligonucleotides strategies have also been highlighted.

Keywords: Cardiovascular disease (CVD), MicroRNA-132 (miR-132), Biomarker, Therapeutic target, Cardiac remodelling, Long non-coding RNAs (lncRNAs).

INTRODUCTION

According to the stats cardiovascular disease (CVD) is a top-tier cause of death on global scale [1] will reach 23.6 million deaths annually by 2030.[2] The most common manifestations of cardiovascular diseases are peripheral artery disease (PAD), and coronary artery of myocardial infarction (and MI).[3] Undeterred by the advancements in the field of medicine and technology the risk of mortality and readmission due to heart failure (HF) prevailed up and around to 15% high within a year striking a massive economic freight. [4·5·6]

The high incidence rate and impairment in outcomes indicate that there is an urgent need of developing diagnostic and therapeutic options for the prevention of CVD.

MicroRNAs are small non-coding RNAs (ncRNAs) of about 18-25 nucleotides long which stall gene expression by binding to 3' untranslated regions of target messenger RNA provoking their target messenger RNA binding with ribosomes and inhibit their translation.[7·8·9] For the first time, microRNAs (miRNAs) were discovered in 1990.[10] So far more than 2300 human miRNA have been discovered censoriously involved in cellular differentiation, apoptotic, physiological, and pathophysiological processes via regulation of human 60% genes at post-transcriptional planate.[11·12·13] miRNA involvement in CVD has been documented for the previous 15 years. [14] In cardiovascular disease biology, microRNAs regulate processes intricate in the development and prolongation of the heart and its functions. Boarding affirmations advocated that miRNAs up or down

modulations lead to heart failure (HF).[15] Many miRNAs can be readily detected by the PCR technique.[16·17] Unregulated miRNAs have been associated with numerous cardiovascular pathologies.[18·19·20] MiRNA's role in CVD provides a new perspective on disease mechanisms and has revealed biomarker and therapeutic potential.[21] Amid them, miR-132 is deftly reported to be involved in hypertrophic, apoptotic, angiogenic, and fibrotic processes responsible for the pathological development of cardiac vascular diseases. This rationale indicates that miR-132 may be a possible potential biomarker and therapeutic target for cardiovascular diseases prevention and treatment.

MiR-132 a highly conserved microRNA present on chromosome 17 is clustered randomly in a tandem array sharing a common seed origin with miR-212.[22·23] The generation of miR-132 is regulated at the transcriptional level and during post-transcriptional events.[13·24] MiR-132 transcription is positively regulated by the cAMP response element-binding protein (CREB) [25] and is negatively regulated by repressor element 1 silencing transcription factor (REST). Besides of these miR-132 regulation occurs by extracellular signal-regulated kinase (ERK1/2) via downstream CREB phosphorylation and mitogen and stress-activated kinase (MSK).[26·27]

This review was carried out in accordance with the guidelines of systematic preferred reporting items for systematic and meta-analysis (PRISMA) holding in favoured reporting items.[28] A systematic documented literature search on the therapeutic and diagnostic significance potential of miR-132 in the cardiovascular disease was carried out following PRISMA (Fig. 1). Available research articles correlated to the subject were acknowledged by using the following search keywords; "role of miR-132 in the cardiovascular disease", "miR-132 therapeutic and diagnostic potential in cardiovascular disease", "miR-132 and CVD", "regulation of miR-132 in various cardiovascular diseases, etc. Overall x articles were found from PubMed central, Google Scholar and Embase. After the removal of duplicates total left articles were x. A total of x titles/abstracts were excluded because of no focus on the area of the study. The remaining x articles were reviewed for eligibility, from which only x research articles were established for eligibility. The left of the articles was repudiated due to irrelevant information, duplication, or language issues. A total of x exclusive, significant, and full-text research articles were selected for the data extraction.

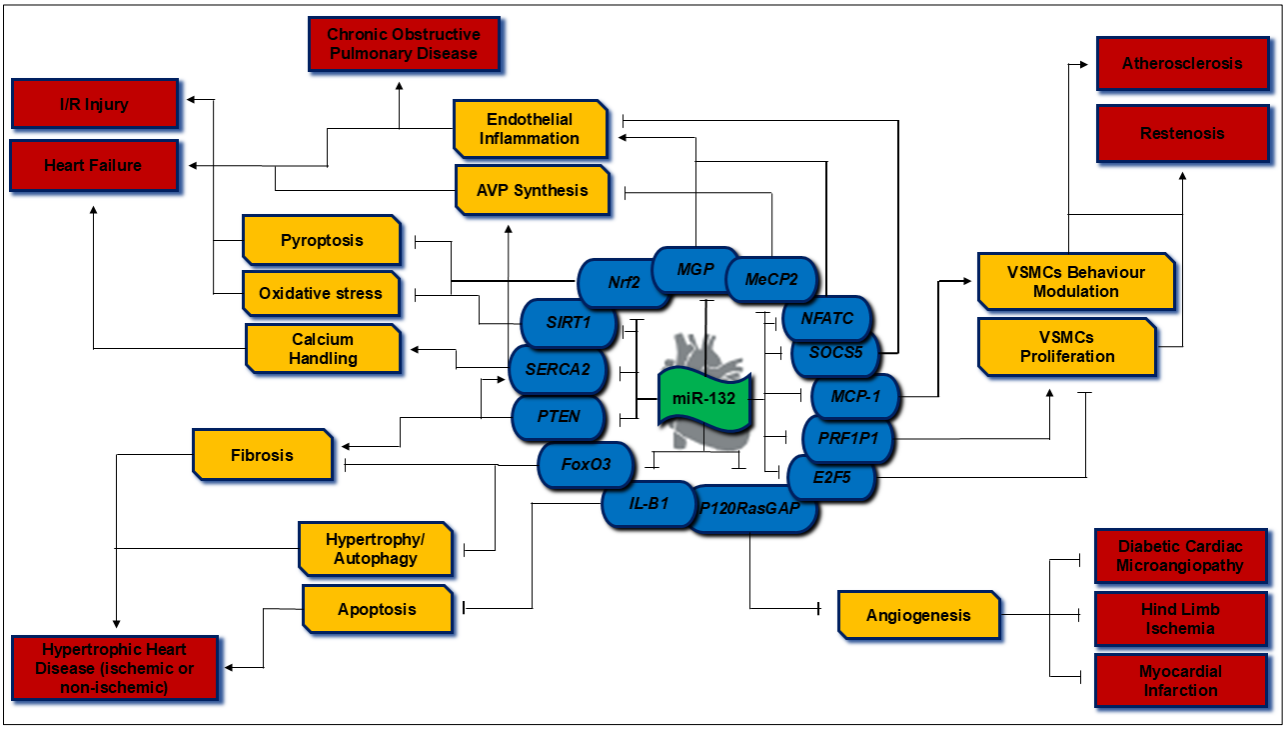

Fig.1: Relation of miR132 with different types of CVD's

Role of miR-132 in different types of cardiovascular diseases

Cardiovascular disease is a major death cause globally.[29] Previously it is reported that 17 million death resulted from cardiovascular disease.[30] Peripheral artery disease (PAH), atherosclerosis (AS), coronary artery disease (CAD), and ischemic cardiac stroke are the most common manifestations of CVD.(5) MiRNAs have a major crucial role in cardiac pathological processes including acute myocardial infarction (AMI), other CVD types such as AS, HF, cardiac hypertrophy and arrhythmias.[31·21] MiRNAs

have a significant role in regulating cardiovascular function and also have a major role in all aspects of cardiovascular biology.[32] We have emphasized the miR-132 because it is a highly characterized inducible gene.[33] miR-212/132 family which is reported to be a highly conserved family of miRNAs when upregulated backs the cardiac hypertension, vascular remodeling, and hypertension.[34]

Atherosclerosis (AS)

In atherosclerosis development cardiac endothelial dysfunctioning plays a crucial role.[35] MiR-132 causes inflammation in the cardiac endothelial by SIRT1 regulation modulation.[36] Previously it has been shown that vascular smooth muscle cells (VSMCs) make vascular walls and VSMCs' abnormal behaviour causes atherosclerosis. [37] It is also documented that miR-132 in VSMCs is significantly expressed in the in-vivo and modulates their behaviour during various stress conditions.[38] Numerous studies reported that miR-132 promotes the VSMCs phenotypic switching in case of atherosclerosis. It is seen that phenotype switching helps in the plaque formation in case of AS.[39] A study conducted by Jin *et al.,* in which they analysed Ang-II mediated regulatory microRNA profile in VSMCs. It is observed that Ang-II caused upregulation in the level of miR-132 in VSMCs which resulted in an increased level of monocyte chemotaxis protein-1 (MCP-1) through phosphate and tensin homolog (PTEN).[40] MiR-132 overexpression leads to VSMCs differentiation induced by cilostazol through PTEN expression inhibition showing miR-132 overexpression (fig. 1) adverse consequences which occured on differentiation of VSMCs.[41] Inhibition of VSMCs phenotypic switching can protect from advanced stages of AS disease. When miR132-3p is expressed along with the other three microRNAs (miR150-5p, miR141-5p, and miR138-5) are majorly invoked in phenotypic switching from synthetic to contractile. Hsa-miR132-3p with accession number MIMAT0000426 showed the phenotypic switch score of 1.56 and the con/syn average ratio obtained was 0.53.[42] Angiogenesis is the process which causes formation of new blood vescles from already existing blood vescles ones. Angiogenesis is involved in ischemic-related cardiovascular disease pathologies. MiR-132 higher expression as a proangiogenic microRNA is observed in the endothelial cells and atherosclerotic lesions in the mice model.[43] Phenotypic switching of VSMCs promotes plaque formation which is a prerequisite for AS development [39]. Combined marking diagnostic potential of miR-132, miR-133, miR-1, and miR-122 cognate with clinical atherosclerosis in patients (n = 182) with metabolic syndrome than any other single miRNA.[44] Loss of a functional gene called von Hippel Lindau [45] and hypoxia induction [46] caused increased levels of miR-132 by targeting RASA1 and Spred 1 leading to Ras MAPK pathway activation acting as an angiogenic switch.[47,23] In ischemic hearts, disease exosomes mediated delivery of miR-132 causes therapeutic angiogenesis.[48,49] Increased expression of miR-132 induced by isoproterenol is related to CREB phosphorylation by activation of mitogen-activated protein kinase pathway (MAPK/ERK).[50,51] On the other hand shreds of evidence showed that miR-132 has no major effect on cardiac capillary densities and on angiogenesis.[34,52] Even induction of antimiR-132 leads toward improved capillary density in the pressure overload-induced ischemic cardiomyopathy in the porcine animal model.[53]

Heart Failure (HF)

Heart failure (HF) is an intricate set of clinical disorders, which engenders faulty cardiac structure or dysfunction resulting in either ventricular filling or compromised ejection function.[54] Multiple heart diseases with clinical manifestations of fluid retention, dyspnoea, and fatigue. end up with HF. Owing to high indisposition and deaths from HF deaths no predominantly idyllic treatment plan.[55] Sarcoplasmic endoplasmic reticulum calcium ATPase 2 (SERCA-2) plays an important in cardiac muscle contraction and relaxation and impairment in the SERCA-2 expression can lead to cardiac impairment.[56] MiR-132/212 is found to be a regulator of SERCA-2 expression.[57] Previously it is documented that miR-132 down regulates SERCA2 activity by directly inhibiting the PTEN which is a direct target of miR212/132 and loss of function in cardiac cells leads to havoc decrease in cardiac contraction.[58,59] MiR-132/212 KO mice showed increased cardiac muscles contractility and defaulted expression of miR-132/212 along with SERCA-2 in the patients with end-stage HF leads to dilated, ischemic and hypertrophic cardiomyopathies.[60] Plenty of evidence suggested that miRNAs are involved in heart failure.[15] APCs transplantation anti-fibrotic and pro-angiogenic actions are mediated by miR-132 in-vitro in hypoxia and a murine model of MI.[61] For the first time when antimiR-132 has injected into an animal model, the level of FOXO3 regenerated alongside cardiac dilation, reduced cardiac mass, and left ventricular hypertrophy were reported.[62] Apoptosis resulting from cardiac stress, such as the case in case myocardial infarction, subsidizes an irreparable cardiomyocyte loss following adverse cardiac remodelling. It is well established that miR-132/212 frolics an anti-apoptotic role by triggering the phosphatidylinositol-3 kinase/protein B signalling pathway in cardiomyocytes.[52] Nrf2 a leucine zipper protein is called nuclear factor erthroyd2 related factor 2 which is responsible for the cellular resistance against oxidants showed increased expression during antimiR-132 treatment in the porcine model of pressure overloaded induced HF. Nrf2 prevents maladaptive cardiac refashioning and HF also conserves cardiac fibroblast and cardiomyocytes function.[63,64] Irrespective of this study Masson *et al.,* documented inverse results. They analysed the circulating level of miR-132 level in 953 symptomatic and chronic patients with HF and documented higher circulating levels of

miR-132. MiR-132 plasma level was independently associated with increased HF severity and envisaged lesser rates of fatal and non-fatal HF events. Following considerable risk factors (clinical, demographic, and echocardiographic) adjustments and standard N-terminal pro-B type natriuretic peptide (NT proBNP) concentration, miR-132 showed the coalition with HF hospitalization (confidence interval = 0.66 to 0.95, HR = 0.79, 95% and p = 0.01). NT proBNP and B-natriuretic peptide (BNP) both are considered the standard test for a confirmed diagnosis of HF.[65] In addition, miR-132 enhanced risk determination far from conventional risk elements for heart failure (HF) alongside the continual reclassifying index of 0.205 with a p-value of 0.001.[66·67] MiR-132 overexpression causes HF hospitalization and CVD deaths. MiR-132 inhibition results in improved cardiac remodelling in patients with non-ischemic heart failure (IHF). miR-132 inhibition by antimir-132 resulted in improved cardiac improved cardiac (systolic and diastolic) function in the animal models bylling.[68]

Cardiac fibrosis (CF)

Evidence revealed that angiotensin II regulates the expression of miR-132/212 in hypertensive humans and rats. the angiotensin II receptor (AT1R) signalling plays an intrinsic role in the regulation of miR-132 and miR-212 through activation of the heterotrimeric G protein known as Gαq dependent signalling pathway in HEK293N cells.[69] promoting myocardial fibrosis.[70] Indeed in bypass-operated patients, AT1R blocker treatment caused the downregulation of miR132 and also miR-212 in human arteries.[71] Previously it is proved that the miR-132/212 family regulates autophagy of cardiomyocytes and HF by regulating transcription of FoxO3 which is a pro autophagic and anti-hypertrophic transcription factor (TF) present in cardiomyocytes.[72·73·74] MiR-132 has a Profibrotic nature which was confirmed by Schimmel *et al.,* who confirmed that miR-132 enhances the proliferation and migration of the cardiac fibroblasts which it might be possible due to repression of autophagy by FoxO3 targeting.[75] Opposite to these findings, some studies have reported downregulation of miR-132 in HF mice and also Angiotensin II treated cardiac fibrosis. MiR-132 upregulation promotes inhibitory effects on cardiac fibrosis in rats with MI-induced HF. The same inhibitory effect was reported in the canine model with atrial fibrillation and also observed in the rats with dilated cardiomyopathy induced by doxorubicin.[76·77·70] Animal studies have shown that Ang-II converting enzyme blocker Ramipril a drug used for the acute kidney injury disease treatment also show cardio protective roles like fibrosis, apoptosis and cardiac hypertrophy by partial attenuation of miR-132 expression.[78] Profibrotic factor called TGF-β1 has a potent role in the fibrosis promotion and plays multiple roles in fibrosis remodelling via smad dependent pathways in various number of diseases.[79·80] During HF or myocardial ischemia, TGF-β1 signaling can induce fibrosis of cardiac fibroblasts and promote the synthesis of collagen and fibronectin, finally promoting myocardial fibrosis.[81]

Myocardial Infarction (MI)

It is also reported that miR-132 is downregulated in the cardiac cells of MI-infected rats. Increased regulation of miR-132 leads to inhibition of apoptosis of cardiomyocytes and pathological cardiac remodelling. These beneficial effects are achieved supposed to be achieved by miR-132 mediated repression of interleukin-1β.[82] MiR-132 overexpression inhibits H2O2 mediated oxidative stress in the H9C2 cell lines resulting in improved apoptosis and cell feasibility under in-vitro environment I/R induced AMI in-vivo.[64·83] Cardiac fibroblasts are considered as the most numerous cardiac cells accounting for nearly 70% of the entire number of cardiac cells.[84·85] APCs transplantation anti-fibrotic and pro-angiogenic actions are mediated by miR-132 in-vitro in hypoxia and a murine model of MI.[61] Li *et al.,* estimated the lower expression of miR-132 which was inversely related to the cTnI in 35 patients compared with 55 parallel control in the early phase of AMI and the receiver operating curve (ROC) intimated that miR-132 can be a likely biomarker for AMI untimely phase detection.[86] Chen *et al.,* conducted a study in which they had shown a decreased level of miR-132 within a week of post-MI. In miR-132 KO mice the infarct size was greater than the wild-type mice and worse cardiac function was observed at 14 and 28 days. But when a 16 mg/kg dose of miR-132 mimic was injected then the infarct size was reduced and cardiac function also improved on day 28 following MI remodelling.[87] Conversely, it is also documented that miR-132 overexpression firstly increases at 12 h of post-MI and then starts to decrease at 24 h, but increases inconsequentially again within 1 month of post-MI. Though miR-132 loss improved cardiac contractility in MI mice, it also reduced cardiomyocytes angiogenesis and also their survival, eventually not improving general cardiac performance and fibrosis remodelling in 4 weeks of post-MI mice as compared with wild-type one.[88] Long non coding RNA muscle blind like splicing regulator 1 antisense RNA 1 (LncRNA MBNLA–AS1) negative regulates miR-132 and SOX4 which is a SRY-related high mortality group box 4 is a straight target of miR-132-3p and is regulated by LncRNA MBNLA–AS1 via mirR-132-3p. enhanced expression of SOX4 plartilay reduces the apoptotic effect of LncRNA MBNLA–AS1 in myocardial cells and LncRNA MBNLA–AS1 in case of acute myocardial infarction (AMI).[89]

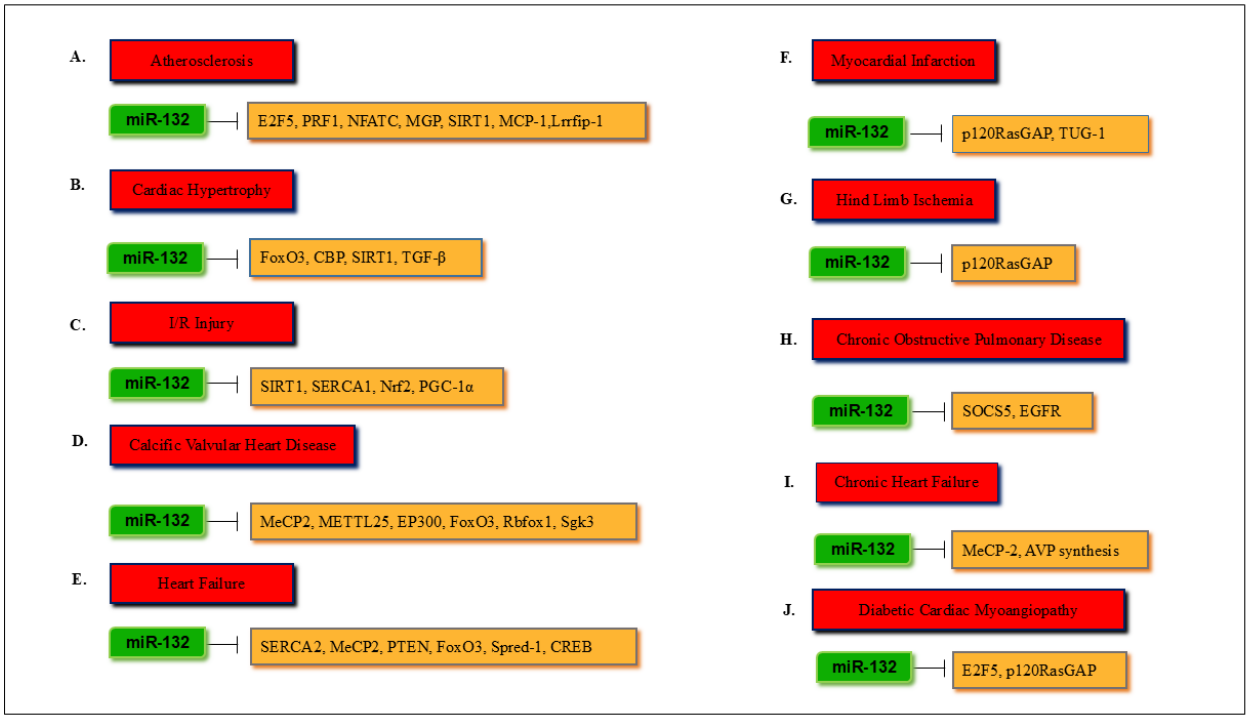

Fig.2: Inhibitory Role of mir-132 in regulation of different Genes in CVD Types

Myocardial Ischemic Reperfusion Injury I/R

MiR-132 inhibition by targeting silent information regulator type 1 gene (SIRT1) leads to activation of peroxisome proliferator-activated receptor-gamma 1 alpha coactivator (PGC1α) signalling resulting in oxidative stress inhibition and impression of interleukin-1 caspase-1, nucleotide oligomerization domain-like receptors, pyrin domain containing 3 (NLR3P) and mitigating myocardial ischemic reperfusion injury (I/R).[90] MiR-132 overexpression inhibits H2O2 mediated oxidative stress in the H9C2 cell lines resulting in improved apoptosis and cell feasibility under in-vitro environment I/R induced AMI in-vivo.[64·8] Intracellular delivery of miR-132 after ischemic injury improves endothelial graft survival and also blood perfusion.[91]

Acute Coronary Syndrome (ACS)

In acute coronary syndrome (ACS) two entities: unstable angina pectoris (UAP) and acute myocardial infarction are present. Karakas *et al.,* initially evaluated circulating miR-132 extent and cardiovascular events in 1112 patients having CAD. Out of 1112 patients, there are stable angina pectoris (SAP) patients 682, and 430 the acute coronary syndrome. After 4 years of median follow-up, Cox regression evaluation twiddle for gender and age showed that miR-132 has accurately forecasted cardiovascular death ($p = 0.022$, HR = 2.85 per 1 SD increase). C-statistics manifested sublime values of cardiovascular mortality (AUC = 0.737 for miR-132).[92] Zeller *et al.,* documented a lower expression level of miR-132 in UAP patients (n = 10).[93]

Diabetic Cardiac Myoangiopathy (DM)

Rawal *et al.,* demonstrated that miR-132 impairment alongside miR-126 is an initial change in the diabetic heart molecular signalling causing proangiogenic and antiangiogenic genes dysregulation. These gene modification results in the development of diabetic microangiopathy.[94] MiR-132 low and transcription factor 5 (E2F5) high expression levels are reported in the VSMCs obtained from diabetic rats or treated with high glucose. In this case upregulation of miR-132 results in the E2F5 down-regulation which proved to be beneficial in the proliferation and migration inhibition of high glucose VSMCs or diabetic rats.[95]

Role of miR-132 in other types of CVD

Pulmonary arterial hypertension (PAH)

Pulmonary arterial hypertension (PAH) is a progressive disease caused by aberrant remodelling of smooth muscle cells (PASMCs) of small pulmonary arteries.[41] MiR-132 inhibits the PASMCs proliferation by directly targeting phosphatase and tensin homolog (PTEN) which is to be disclosed in the development of PAH. So, miR-132 by regulating PASMCs via targeting PTEN can be used as a therapeutic target for PAH treatment.[96]

Calcific valvular heart disease or (CVHD)

Calcific valvular heart disease or CVHD which is considered as third most cardiovascular pathology after hypertension and CAD can be treated with adventitial pericytes (APCs) which have shown great therapeutic potential in models of MI and ischemic limb injury.[97·98·99·100]

Ischemic Heart Disease (IHD)

Ma *et al.,* documented that miR-132 delivery via exosomes in the mesenchymal stem cells derived exosomes (MSCDs) enhances the process of angiogenesis in peri-infarcted zone and improves heart function.[101]

Towards clinical applications of miR-132 in CVD

MiRNAs at the serum levels are very stable towards harsh conditions such as high temperature, boiling, changes in pH, freezing-thawing effect, proteins that bind RNA, high-density lipoproteins, and extended cold storage.[102,103 ,104] Irrespective of studies that had demonstrated that miR-132 can be used as a biomarker for the detection of CVD, a lot of factors have to be addressed such as the effect of drugs, food, age, and gender whether such factors affect miR-132 or not before clinical applications. MiR-132 showed differential expression patterns in different CVD types so the threshold biomarker potential has to be determined.

Potential Clinical Benefits of miR-132 Expression Inhibition in CVD

Various studies have documented that overexpression of miR-132 is involved in various physiological and pathophysiological of CVD. MiR-132 overexpression causes HF hospitalization and CVD deaths. MiR-132 inhibition results in improved cardiac remodelling in patients with non-ischemic heart failure (IHF). miR-132 inhibition by antimir-132 resulted in improved cardiac (systolic and dismproved cardiac (systolic and diastolic) function in the animal models by miRNA sponge aiming tmiR-132/212 has effectively reduced cardiac hypertrophy induced by pressure overload in-vivo and showed better in-vitro effectiveness than present gold average antagomiRs in obstructing miRNA function.[105] No longstanding useful effect of miR-132 on cardiac function has been documented after permanent coronary ligation in the mice model (Lei *et al.,*, 2020). For the first time when antimiR-132 has injected into an animal model, the level of FOXO3 regenerated alongside cardiac dilation, reduced cardiac mass, and left ventricular hypertrophy were reported.[62] In a study, when CHF pigs were administered with intravenous CDR132L to 1 month after MI for 3 to 5 months and measured the effectiveness, the study established that CDR132L injection achieved considerably reverse cardiac remodelling, as demonstrated by abridged left ventricular end-systolic volume also left atrial volume on MRI scan and reduced myocardial interstitial fibrosis and cardiomyocyte mass.[68] antagomiR-132 treatment of pressure overload-induced cardiomyopathy porcine model showed improved capillary density.[53]

Despite the fact that miR-132 targeting by anitmiR-132 in large animals improved cardiac remodelling and also improved cardiac function [68], miR-132 KO has also shown no long-term beneficial cardiac function.[88] miRNA sponge especially targeting the miR-132 has shown more effective to attenuate pressure overload-induced cardiac hypertrophy (CH) than the traditional gold standard animiR-132 inhibition technique.[105] So the optimal strategy for miR-132 inhibition remained unclarified.

Therapeutic potential of CDR132L mediated miR-132 blocking in CVD

antimiR-132 has the significant potential for inhibiting the effect of miR-132.[62,53] Furthermore, the inclusion of long noncoding RNA increases the thermodynamic stability of the duplex creation with existing target mRNA. The protective and other pharmacodynamics parameters of the CDR132L were assessed in a randomized phase 1b placebo-controlled study (NCT04045405). CDR132L is an earlier miR-132 inhibitor antisense microRNA.[106]

Hinkel *et al.,* settled a conventional unusual preclinical porcine animal model having non-ischemic pressure overload hypertrophy by inserting an endovascular reduction stent in the descendant thoracic aorta and evaluated the effectiveness of antimiR-132 intracoronary administration at the stent embedding time and later weeks. They found that antimiR-132 mediated decreased cross-sectional area of cardiomyocyte, hindered fibrosis, recovered capillary density, and left ventricular ejection fraction (LVEF). The value of antimiR-132wascontrol was 48.9 ± 1.0% vs 36.1 ± 1.7% respectively at the 8 weeks' time pass.[53,107] Hinkel *et al.,* results showed that CDR132L has significantly treated cardiac hypertrophic disease which is resulted by non-ischemic etiologies like systematic hypertension or aortic stenosis [108]. For inhibiting miR-132 CDR132L synthetic long noncoding RNAs (LNR) is the first antisense oligonucleotide inhibitor which is also optimized (antimiR-132).[109,62] In cardiac vascular diseases, a higher expression of miR-132 is involved in pathological cardiac remodelling. In a study post-MI, HF pig animal models undertook 90 mi left anterior descending artery occlusion trailed by reperfusion (I/R) the pigs one-month post-MI were put under treatment. For the assessment of efficacy biomarkers, hemodynamic and magnetic resonance imaging tests were performed. Animals were injected with CDR132L through intravenous injection on the monthly basis for 3 to 5 months. A substantial EF improvement was observed in the treated animal groups. MRI results showed that the EF value up surged to 7.96% and 7.14% after 3 and 5 months of treatment respectively. Moreover, CDR132L likewise improved diastolic function as demonstrated by reduced edge-diastolic pressure-volume relation and the minimum rate of variation of left ventricular (LV) pressure demonstrated through hemodynamic assay and decreased level of plasma in NT-proBNP.[68]

Täubel *et al.,* conducted a first human Phase 1b randomized, double-blind, placebo-controlled therapeutic trials to assess pharmacokinetic

characteristics, and effectiveness of CDR132L in chronic ischemic heart failure (CHF) patients by targeting miR-132. A total of 28 patients had left ventricular ejection fraction (LVEF) of 30% to 50% and NT-proBNP more than 125 ng/L. Age of 30 to 80 years old tangled in this study and indiscriminately assigned at 5:2 to the CDR132L group (cases total cases, in each cohort with 5 patients getting 0.32, 1, 3, and 10 mg/kg body weight of CDR132L, correspondingly) and placebo group (8 cases with 0.9% saline). Following 6 weeks screening duration, subjects were given two dosages of CDR132L or placebo via intravenous injection on 1 and 28 days correspondingly, and the trial was completed on the 112th day. In this study, CDR132L was inoffensive and tolerated well. CDR132L clinical treatment stemmed in a constant and strident decrease in plasma miR-132 magnitude in a dosage-dependent fashion. For the patients with ischemic chronic heart failure getting CDR132L standard clinical treatment, CDR132L can additionally decrease the median level of NT-proBNP up to 20% and tapered the QRS wave compared to placebo, and increases inessential cardiac fibrosis biomarkers additionally.[106]

It will be precocious to conclude whether this method of miRNA targeting will be beneficial in humans or not. The safety and efficacy of CDR132L according to the above-reported studies dispense a great incitement for more research in HF patients.[110]

Potential Clinical Benefits of miR-132 Overexpression in CVD

Present documented literature suggested that overexpression of miR-132 is involved in various cardiac pathologies and this is a reason that most therapies based on miR-132 inhibition and very less studies documented the miR-132 overexpression benefits in cardiac events. Apoptosis resulting from cardiac stress, such as the case in case myocardial infarction, subsidizes an irreparable cardiomyocyte loss following adverse cardiac remodelling. It is well established that miR-132/212 frolics an anti-apoptotic role by triggering the phosphatidylinositol-3 kinase/protein B signalling pathway in cardiomyocytes.[52] In-vitro overexpression of miR-132 in cardiomyocytes causes increased resistance against hypoxia, cell (H9c2) death due to glucose deprivation, and hydrogen peroxide (H2O2).[64·77·88] It is also reported that miR-132 is downregulated in the cardiac cells of MI-infected rats. Upregulation of miR-132 leads to inhibition of apoptosis of cardiomyocytes and pathological cardiac remodelling. These beneficial effects are achieved supposed to be achieved by miR-132 mediated repression of interleukin-1β.[82] The harmful effects of drugs on the cardiomyocytes can be diminished by overexpression of miR-132. In a study cardiomyocyte toxicity induced due to doxorubicin had been reversed by miR-132 overexpression. A mouse model was made doxorubicin mediated cardiomyocytes toxic and miR122/132 enhanced expression had been achieved by adenovirus (AVV). Resultantly there was an improved mass and wall thickness of LV, improved EF, and reduced apoptosis induced by doxorubicin.[111] Chen *et al.,* conducted a study in which they had shown a decreased level of miR-132 within a week of post-MI. In miR-132 KO mice the infarct size was greater than the wild-type mice and worse cardiac function was observed at 14 and 28 days. But when a 16 mg/kg dose of miR-132 mimic was injected then the infarct size was reduced and cardiac function also improved on day 28 following MI remodelling.[87] MiR-132 was essentially expressed by adventitial pericytes (APCs) and overexpressed resulting in enhanced phosphate stimulation, causing APCs' confrontation to calcification by reducing the expression of many target genes related to osteogenic differentiation. Swine cardiac valve treatment with APCs-derived acclimatized medium provides them with resistance against enhanced phosphate-induced osteogenesis. This effect is refuted with the use of a miR-132-silenced APCs medium.[112]

Conversely, it is also documented that miR-132 overexpression firstly increases at 12 h of post-MI and then starts to decrease at 24 h, but increases inconsequentially again within 1 month of post-MI. Though miR-132 loss improved cardiac contractility in MI mice, it also reduced cardiomyocyte's angiogenesis and also their survival, eventually not improving general cardiac performance and fibrosis remodelling in 4 weeks of post-MI mice as compared with wild-type one.[88]

Limitations of miR-132 delivery or inhibition and future perspectives

Multiple animals and human studies showed that miR-132 inhibition can reduce HF hospitalizations and deaths due to CVD. But it is still not clear whether inhibition of miR-132 in ischemic and non-ischemic HF can improve cardiac remodelling and it has to be addressed in future studies. Although administration of antimiR-132 can prevent short-term systolic and diastolic cardiac function the fact is that knocking down of miR-132 has no long-term beneficial effects in MI after the coronary artery ligation in mice models.[88] miR-132 is widely expressed and has different effects on different cell types and different organs.[113] For suppression of miR-132 expression in cardiac hypertrophy causes a delay in wound healing and neurodegenerative diseases.[114·47] Thus, further studies are required for the assessment of the safe effects of antimiR-132 target-specific administration. Although various approaches such as adeno-associated virus, liposomes, and miR-132 sponges are used for the effective delivery of miR-132 [9·39] but still none of these approaches is considered a standard approach for miR-132 delivery. In the future, more research on optimal therapeutic strategies and safe drug delivery is required to be documented before implementation into clinical practices to prevent heart failure.

CONCLUSION

The above-presented studies documented that miR-132 expression plays a significant role in cardiac pathologies. The deregulation of miR-132 drives toward cardiac pathology. miR-132 has great biomarker and therapeutic promises in myocardial infarction (MI), atherosclerosis (AS), unstable angina pectoris (UAP), infarcted heart (IH), ischemic injury (I/R), and heart failure (HF). In cardiac stress and various pathological conditions, the miR-132 level gets increased and targets SIRT 1, PTEN, FoxO3, and SERCA2A are downregulated as mentioned in table 1. CDR-132L along with other antimiR-132 has significant down regulatory effects on miR-132 leading to improved cardiac function by reducing cardiac mass. But the reported studies contain a small sample size and most studies have been conducted on animal models. Besides these various studies have used cell lines in their studies. So, the therapeutic and diagnostic potential of miR-132 in various CVD types remained yet unclear.

REFERENCES

1. WHO. Cardiovascular diseases. Bull Pan Am Health Organ [Internet]. 1984 [cited 2022 Jun 4];18(3):302–5. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, *et al.,* Heart Disease and Stroke Statistics—2021 Update. Circulation [Internet]. 2021 Feb 23 [cited 2022 Jun 9];E254–743. Available from: https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000950
3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, *et al.,* Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation [Internet]. 2015 Jan 27 [cited 2022 Jun 5];131(4):e29–39. Available from: https://pubmed.ncbi.nlm.nih.gov/25520374/
4. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol [Internet]. 2014 Feb 15 [cited 2022 May 28];171(3):368–76. Available from: https://pubmed.ncbi.nlm.nih.gov/24398230/
5. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, *et al.,* Heart disease and stroke statistics—2020 update: A report from the American Heart Association. Circulation. Lippincott Williams and Wilkins; 2020. p. E139–596.
6. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, *et al.,* European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail [Internet]. 2016 Jun 1 [cited 2022 May 28];18(6):613–25. Available from: https://pubmed.ncbi.nlm.nih.gov/27324686/
7. He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet [Internet]. 2004 Jul [cited 2022 May 28];5(7):522–31. Available from: https://pubmed.ncbi.nlm.nih.gov/15211354/
8. Van Rooij E. The art of microRNA research. Circ Res [Internet]. 2011 Jan 21 [cited 2022 May 28];108(2):219–34. Available from: https://pubmed.ncbi.nlm.nih.gov/21252150/
9. Bernardo BC, Charchar FJ, Lin RCY, McMullen JR. A MicroRNA Guide for Clinicians and Basic Scientists: Background and Experimental Techniques [Internet]. Vol. 21, Heart Lung and Circulation. Elsevier; 2012 [cited 2022 May 29]. p. 131–42. Available from: http://www.heartlungcirc.org/article/S1443950611012625/fulltext
10. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell [Internet]. 1993 Dec 3 [cited 2022 May 28];75(5):843–54. Available from: https://pubmed.ncbi.nlm.nih.gov/8252621/
11. Ambros V. The functions of animal microRNAs. Nat 2004 4317006 [Internet]. 2004 Sep 15 [cited 2022 May 29];431(7006):350–5. Available from: https://www.nature.com/articles/nature02871
12. Latronico MVG, Condorelli G. MicroRNAs and cardiac pathology. Nat Rev Cardiol [Internet]. 2009 [cited 2022 May 29];6(6):418–29. Available from: https://pubmed.ncbi.nlm.nih.gov/19434076/
13. Krol J, Loedige I, Filipowicz W. The widespread regulation of microRNA biogenesis, function and decay [Internet]. Vol. 11, Nature Reviews Genetics. Nature Publishing Group; 2010 [cited 2022 May 29]. p. 597–610. Available from: https://www.nature.com/articles/nrg2843
14. Condorelli G, Latronico MVG, Cavarretta E. microRNAs in Cardiovascular Diseases: Current Knowledge and the Road Ahead. J Am Coll Cardiol. 2014 Jun 3;63(21):2177–87.
15. Thum T, Galuppo P, Wolf C, Fiedler J, Kneitz S, Van Laake LW, *et al.,* MicroRNAs in the human heart: a clue to fetal gene reprogramming in heart failure. Circulation [Internet]. 2007 [cited 2022 May 29];116(3):258–67. Available from: https://pubmed.ncbi.nlm.nih.gov/17606841/
16. Siemelink MA, Zeller T. Biomarkers of coronary artery disease: the promise of the transcriptome. Curr Cardiol Rep [Internet]. 2014 Aug 1 [cited 2022 Jun 4];16(8). Available from: https://pubmed.ncbi.nlm.nih.gov/24950674/
17. Etheridge A, Lee I, Hood L, Galas D, Wang K. Extracellular microRNA: a new source of biomarkers. Mutat Res [Internet]. 2011 Dec 1 [cited 2022 Jun 4];717(1–2):85–90. Available from: https://pubmed.ncbi.nlm.nih.gov/21402084/
18. Navickas R, Gal D, Laucevičius A, Taparauskaite A, Zdanyte M, Holvoet P. Identifying circulating microRNAs as biomarkers of cardiovascular

disease: a systematic review. Cardiovasc Res [Internet]. 2016 Sep 1 [cited 2022 Jun 4];111(4):322–37. Available from: https://pubmed.ncbi.nlm.nih.gov/27357636/
19. Ahlin F, Arfvidsson J, Vargas KG, Stojkovic S, Huber K, Wojta J. MicroRNAs as circulating biomarkers in acute coronary syndromes: A review. Vascul Pharmacol. 2016 Jun 1;81:15–21.
20. Schulte C, Karakas M, Zeller T. microRNAs in cardiovascular disease - clinical application. Clin Chem Lab Med [Internet]. 2017 May 1 [cited 2022 Jun 4];55(5):687–704. Available from: https://pubmed.ncbi.nlm.nih.gov/27914211/
21. Small EM, Olson EN. Pervasive roles of microRNAs in cardiovascular biology. Nature [Internet]. 2011 Jan 1 [cited 2022 Jun 4];469(7330):336. Available from: /pmc/articles/PMC3073349/
22. Tognini P, Pizzorusso T. MicroRNA212/132 family: Molecular transducer of neuronal function and plasticity [Internet]. Vol. 44, International Journal of Biochemistry and Cell Biology. Int J Biochem Cell Biol; 2012 [cited 2022 Jun 1]. p. 6–10. Available from: https://pubmed.ncbi.nlm.nih.gov/22062950/
23. Anand S, Majeti BK, Acevedo LM, Murphy EA, Mukthavaram R, Scheppke L, *et al.,* MicroRNA-132-mediated loss of p120RasGAP activates the endothelium to facilitate pathological angiogenesis. Nat Med [Internet]. 2010 Aug 1 [cited 2022 Jun 17];16(8):909–14. Available from: https://www.nature.com/articles/nm.2186
24. Rooij E, Kauppinen S. Development of microRNA therapeutics is coming of age. EMBO Mol Med [Internet]. 2014 Jul [cited 2022 Jun 1];6(7):851–64. Available from: https://pubmed.ncbi.nlm.nih.gov/24935956/
25. Cheng HYM, Papp JW, Varlamova O, Dziema H, Russell B, Curfman JP, *et al.,* microRNA Modulation of Circadian-Clock Period and Entrainment. Neuron. 2007 Jun 7;54(5):813–29.
26. Wanet A, Tacheny A, Arnould T, Renard P. MiR-212/132 expression and functions: Within and beyond the neuronal compartment. Nucleic Acids Res [Internet]. 2012 Jun 1 [cited 2022 Jun 1];40(11):4742–53. Available from: https://academic.oup.com/nar/article/40/11/4742/2409307
27. Conaco C, Otto S, Han JJ, Mandel G. Reciprocal actions of REST and a microRNA promote neuronal identity. Proc Natl Acad Sci U S A [Internet]. 2006 Feb 14 [cited 2022 Jun 1];103(7):2422–7. Available from: https://pubmed.ncbi.nlm.nih.gov/16461918/
28. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, *et al.,* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ [Internet]. 2009 Jul 21 [cited 2022 Jun 4];339. Available from: https://www.bmj.com/content/339/bmj.b2700
29. Brown IAM, Diederich L, Good ME, DeLalio LJ, Murphy SA, Cortese-Krott MM, *et al.,* Vascular Smooth Muscle Remodeling in Conductive and Resistance Arteries in Hypertension: VSMC in hypertension. Arterioscler Thromb Vasc Biol [Internet]. 2018 [cited 2022 Jul 26];38(9):1969. Available from: /pmc/articles/PMC6205219/
30. Shafei AES, Ali MA, Ghanem HG, Shehata AI, Abdelgawad AA, Handal HR, *et al.,* Mesenchymal stem cell therapy: A promising cell-based therapy for treatment of myocardial infarction. J Gene Med [Internet]. 2017 Dec 1 [cited 2022 Jul 30];19(12):e2995. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jgm.2995
31. Small EM, Frost RJA, Olson EN. MicroRNAs Add a New Dimension to Cardiovascular Disease. Circulation [Internet]. 2010 Mar 2 [cited 2022 Jul 30];121(8):1022–32. Available from: https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.109.889048
32. Barwari T, Joshi A, Mayr M. MicroRNAs in Cardiovascular Disease. J Am Coll Cardiol [Internet]. 2016 Dec 13 [cited 2022 Jul 26];68(23):2577–84. Available from: https://pubmed.ncbi.nlm.nih.gov/27931616/
33. Vo N, Klein ME, Varlamova O, Keller DM, Yamamoto T, Goodman RH, *et al.,* A cAMP-response element binding protein-induced microRNA regulates neuronal morphogenesis. Proc Natl Acad Sci U S A [Internet]. 2005 Nov 8 [cited 2022 Jun 1];102(45):16426–31. Available from: https://pubmed.ncbi.nlm.nih.gov/16260724/
34. Kumarswamy R, Volkmann I, Beermann J, Napp LC, Jabs O, Bhayadia R, *et al.,* Vascular importance of the miR-212/132 cluster. Eur Heart J [Internet]. 2014 Dec 1 [cited 2022 Jul 26];35(45):3224–31. Available from: https://academic.oup.com/eurheartj/article/35/45/3224/2481440
35. Gimbrone MA, García-Cardeña G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. Circ Res [Internet]. 2016 Feb 19 [cited 2022 Jul 26];118(4):620–36. Available from: https://pubmed.ncbi.nlm.nih.gov/26892962/
36. Zhang L, Huang D, Wang Q, Shen D, Wang Y, Chen B, *et al.,* MiR-132 inhibits expression of SIRT1 and induces pro-inflammatory processes of vascular endothelial inflammation through blockade of the SREBP-1c metabolic pathway. Cardiovasc drugs Ther [Internet]. 2014 Aug 1 [cited 2022 Jul 26];28(4):303–11. Available from: https://pubmed.ncbi.nlm.nih.gov/24924687/
37. Bochaton-Piallat ML, Gabbiani G. Modulation of smooth muscle cell proliferation and migration: Role of smooth muscle cell heterogeneity. Handb Exp Pharmacol [Internet]. 2005 [cited 2022 Jul 26];170:645–63. Available from: https://link.springer.com/chapter/10.1007/3-540-

27661-0_24
38. Farina FM, Hall IF, Serio S, Zani S, Climent M, Salvarani N, *et al.,* miR-128-3p Is a Novel Regulator of Vascular Smooth Muscle Cell Phenotypic Switch and Vascular Diseases. Circ Res [Internet]. 2020 Jun 5 [cited 2022 Aug 7];126(12):e120–35. Available from: https://pubmed.ncbi.nlm.nih.gov/32216529/
39. Chistiakov DA, Orekhov AN, Bobryshev Y V. Vascular smooth muscle cell in atherosclerosis. Acta Physiol [Internet]. 2015 May 1 [cited 2022 Jun 14];214(1):33–50. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/apha.12466
40. Jin W, Reddy MA, Chen Z, Putta S, Lanting L, Kato M, *et al.,* Small RNA sequencing reveals MicroRNAs that modulate angiotensin II effects in vascular smooth muscle cells. J Biol Chem [Internet]. 2012 May 4 [cited 2022 Jul 26];287(19):15672–83. Available from: http://www.jbc.org/article/S0021925820462131/fulltext
41. Chen WJ, Chen YH, Hsu YJ, Lin KH, Yeh YH. MicroRNA-132 targeting PTEN contributes to cilostazol-promoted vascular smooth muscle cell differentiation. Atherosclerosis [Internet]. 2018 Jul 1 [cited 2022 Jul 26];274:1–7. Available from: http://www.atherosclerosis-journal.com/article/S0021915018302156/fulltext
42. Zhang J, Starkuviene V, Erfle H, Wang Z, Gunkel M, Zeng Z, *et al.,* High-content analysis of microRNAs involved in the phenotype regulation of vascular smooth muscle cells. Sci Reports 2022 121 [Internet]. 2022 Mar 3 [cited 2022 Jun 14];12(1):1–13. Available from: https://www.nature.com/articles/s41598-022-07280-7
43. Xiong M, Jia C, Cui J, Wang P, Du X, Yang Q, *et al.,* Shexiang Tongxin dropping pill attenuates atherosclerotic lesions in ApoE deficient mouse model. J Ethnopharmacol [Internet]. 2015 Jan 15 [cited 2022 Jun 2];159:84–92. Available from: https://pubmed.ncbi.nlm.nih.gov/25449459/
44. Šatrauskienė A, Navickas R, Laucevičius A, Krilavičius T, Užupytė R, Zdanytė M, *et al.,* MiR-1, miR-122, miR-132, and miR-133 are related to subclinical aortic atherosclerosis associated with metabolic syndrome. Int J Environ Res Public Health [Internet]. 2021 Feb 2 [cited 2022 Jun 1];18(4):1–14. Available from: https://pubmed.ncbi.nlm.nih.gov/33557426/
45. Lei Z, Klasson TD, Brandt MM, van de Hoek G, Logister I, Cheng C, *et al.,* Control of Angiogenesis via a VHL/miR-212/132 Axis. Cells. 2020 Apr 19;9(4).
46. Burek M, König A, Lang M, Fiedler J, Oerter S, Roewer N, *et al.,* Hypoxia-Induced MicroRNA-212/132 Alter Blood-Brain Barrier Integrity Through Inhibition of Tight Junction-Associated Proteins in Human and Mouse Brain Microvascular Endothelial Cells. Transl Stroke Res [Internet]. 2019 Dec 1 [cited 2022 Jul 26];10(6):672–83. Available from: https://link.springer.com/article/10.1007/s12975-018-0683-2
47. Lei Z, van Mil A, Brandt MM, Grundmann S, Hoefer I, Smits M, *et al.,* MicroRNA-132/212 family enhances arteriogenesis after hindlimb ischaemia through modulation of the Ras-MAPK pathway. J Cell Mol Med [Internet]. 2015 Aug 1 [cited 2022 Jul 26];19(8):1994–2005. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/jcmm.12586
48. Heo JS, Kim S. Human adipose mesenchymal stem cells modulate inflammation and angiogenesis through exosomes. Sci Rep [Internet]. 2022 Dec 1 [cited 2022 Aug 8];12(1). Available from: https://pubmed.ncbi.nlm.nih.gov/35177768/
49. Moghiman T, Barghchi B, Esmaeili SA, Shabestari MM, Tabaee SS, Momtazi-Borojeni AA. Therapeutic angiogenesis with exosomal microRNAs: an effectual approach for the treatment of myocardial ischemia. Heart Fail Rev [Internet]. 2021 Jan 1 [cited 2022 Jul 19];26(1):205–13. Available from: https://link.springer.com/article/10.1007/s10741-020-10001-9
50. Narasimhan G, Carrillo ED, Hernández A, García MC, Sánchez JA. Protective Action of Diazoxide on Isoproterenol-Induced Hypertrophy Is Mediated by Reduction in MicroRNA-132 Expression. J Cardiovasc Pharmacol [Internet]. 2018 Nov 1 [cited 2022 Jul 26];72(5):222–30. Available from: https://journals.lww.com/cardiovascularpharm/Fulltext/2018/11000/Protective_Action_of_Diazoxide_on.3.aspx
51. Remenyi J, Hunter CJ, Cole C, Ando H, Impey S, Monk CE, *et al.,* Regulation of the miR-212/132 locus by MSK1 and CREB in response to neurotrophins. Biochem J. 2010 Jun 1;428(2):281–91.
52. Ucar A, Gupta SK, Fiedler J, Erikci E, Kardasinski M, Batkai S, *et al.,* The miRNA-212/132 family regulates both cardiac hypertrophy and cardiomyocyte autophagy. Nat Commun [Internet]. 2012 [cited 2022 Jun 25];3:1078. Available from: /pmc/articles/PMC3657998/
53. Hinkel R, Batkai S, Bähr A, Bozoglu T, Straub S, Borchert T, *et al.,* AntimiR-132 Attenuates Myocardial Hypertrophy in an Animal Model of Percutaneous Aortic Constriction. J Am Coll Cardiol [Internet]. 2021 Jun 15 [cited 2022 Jun 2];77(23):2923–35. Available from: https://pubmed.ncbi.nlm.nih.gov/34112319/
54. Metra M, Teerlink JR. Heart failure. Lancet (London, England) [Internet]. 2017 Oct 28 [cited 2022 Jul 24];390(10106):1981–95. Available from: https://pubmed.ncbi.nlm.nih.gov/28460827/
55. Yu L, Tu Y, Jia X, Fang K, Liu L, Wan L, *et al.,* Resveratrol Protects Against Pulmonary Arterial

Hypertension in Rats via Activation of Silent Information Regulator 1. Cell Physiol Biochem [Internet]. 2017 Jun 1 [cited 2022 Jul 24];42(1):55–67. Available from: https://www.karger.com/Article/FullText/477115

56. Frank KF, Bölck B, Erdmann E, Schwinger RHG. Sarcoplasmic reticulum Ca2+-ATPase modulates cardiac contraction and relaxation. Cardiovasc Res [Internet]. 2003 Jan 1 [cited 2022 Jul 19];57(1):20–7. Available from: https://academic.oup.com/cardiovascres/article/57/1/20/374216
57. Wahlquist C, Jeong D, Rojas-Muñoz A, Kho C, Lee A, Mitsuyama S, *et al.,* Inhibition of miR-25 improves cardiac contractility in the failing heart. Nat 2014 5087497 [Internet]. 2014 Mar 12 [cited 2022 Jul 19];508(7497):531–5. Available from: https://www.nature.com/articles/nature13073
58. Ruan H, Li J, Ren S, Gao J, Li G, Kim R, *et al.,* Inducible and cardiac specific PTEN inactivation protects ischemia/reperfusion injury. J Mol Cell Cardiol. 2009 Feb 1;46(2):193–200.
59. Crackower MA, Oudit GY, Kozieradzki I, Sarao R, Sun H, Sasaki T, *et al.,* Regulation of Myocardial Contractility and Cell Size by Distinct PI3K-PTEN Signaling Pathways. Cell. 2002 Sep 20;110(6):737–49.
60. Lei Z, Wahlquist C, el Azzouzi H, Deddens JC, Kuster D, van Mil A, *et al.,* miR-132/212 Impairs Cardiomyocytes Contractility in the Failing Heart by Suppressing SERCA2a. Front Cardiovasc Med. 2021 Mar 19;8.
61. Katare R, Riu F, Mitchell K, Gubernator M, Campagnolo P, Cui Y, *et al.,* Transplantation of human pericyte progenitor cells improves the repair of infarcted heart through activation of an angiogenic program involving micro-RNA-132. Circ Res [Internet]. 2011 Sep 30 [cited 2022 Jun 17];109(8):894–906. Available from: http://circres.ahajournals.org
62. Foinquinos A, Batkai S, Genschel C, Viereck J, Rump S, Gyöngyösi M, *et al.,* Preclinical development of a miR-132 inhibitor for heart failure treatment. Nat Commun [Internet]. 2020 Dec 1 [cited 2022 Jun 17];11(1). Available from: /pmc/articles/PMC6994493/
63. Li J, Ichikawa T, Villacorta L, Janicki JS, Brower GL, Yamamoto M, *et al.,* Nrf2 protects against maladaptive cardiac responses to hemodynamic stress. Arterioscler Thromb Vasc Biol [Internet]. 2009 Nov [cited 2022 Jun 2];29(11):1843–50. Available from: https://pubmed.ncbi.nlm.nih.gov/19592468/
64. Liu X, Tong Z, Chen K, Hu X, Jin H, Hou M. The Role of miRNA-132 against Apoptosis and Oxidative Stress in Heart Failure. Biomed Res Int. 2018;2018.
65. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, *et al.,* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. Eur Heart J [Internet]. 2012 [cited 2022 Jun 2];33(14):1787–847. Available from: https://pubmed.ncbi.nlm.nih.gov/22611136/
66. Masson S, Batkai S, Beermann J, Bär C, Pfanne A, Thum S, *et al.,* Circulating microRNA-132 levels improve risk prediction for heart failure hospitalization in patients with chronic heart failure. Eur J Heart Fail [Internet]. 2018 Jan 1 [cited 2022 Jun 1];20(1):78–85. Available from: https://pubmed.ncbi.nlm.nih.gov/29027324/
67. Panico C, Condorelli G. microRNA-132: a new biomarker of heart failure at last? [Internet]. Vol. 20, European Journal of Heart Failure. Eur J Heart Fail; 2018 [cited 2022 Jun 1]. p. 86–8. Available from: https://pubmed.ncbi.nlm.nih.gov/29052296/
68. Batkai S, Genschel C, Viereck J, Rump S, Bär C, Borchert T, *et al.,* CDR132L improves systolic and diastolic function in a large animal model of chronic heart failure. Eur Heart J [Internet]. 2021 Jan 7 [cited 2022 Jun 17];42(2):192–201. Available from: https://academic.oup.com/eurheartj/article/42/2/192/5934677
69. Jeppesen PL, Christensen GL, Schneider M, Nossent AY, Jensen HB, Andersen DC, *et al.,* Angiotensin II type 1 receptor signalling regulates microRNA differentially in cardiac fibroblasts and myocytes. Br J Pharmacol [Internet]. 2011 Sep [cited 2022 Jun 12];164(2):394–404. Available from: https://pubmed.ncbi.nlm.nih.gov/21449976/
70. Wang G, Wang R, Ruan Z, Liu L, Li Y, Zhu L. MicroRNA-132 attenuated cardiac fibrosis in myocardial infarction-induced heart failure rats. Biosci Rep [Internet]. 2020 Sep 1 [cited 2022 Jul 27];40(9). Available from: /bioscirep/article/40/9/BSR20201696/226310/MicroRNA-132-attenuated-cardiac-fibrosis-in
71. Eskildsen T V., Jeppesen PL, Schneider M, Nossent AY, Sandberg MB, Hansen PBL, *et al.,* Angiotensin II Regulates microRNA-132/-212 in Hypertensive Rats and Humans. Int J Mol Sci 2013, Vol 14, Pages 11190-11207 [Internet]. 2013 May 27 [cited 2022 Jun 12];14(6):11190–207. Available from: https://www.mdpi.com/1422-0067/14/6/11190/htm
72. Ronnebaum SM, Patterson C. The FoxO family in cardiac function and dysfunction. Annu Rev Physiol [Internet]. 2010 Mar 17 [cited 2022 Jul 27];72:81–94. Available from: https://pubmed.ncbi.nlm.nih.gov/20148668/
73. Sengupta A, Molkentin JD, Yutzey KE. FoxO Transcription Factors Promote Autophagy in Cardiomyocytes *. J Biol Chem [Internet]. 2009 Oct 9 [cited 2022 Jul 23];284(41):28319–31. Available from: http://www.jbc.org/article/S0021925820383514/fulltext
74. Ni YG, Berenji K, Wang N, Oh M, Sachan N, Dey

A, *et al.,* Foxo Transcription Factors Blunt Cardiac Hypertrophy by Inhibiting Calcineurin Signaling. Circulation [Internet]. 2006 Sep 12 [cited 2022 Jul 27];114(11):1159–68. Available from: https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.106.637124

75. Schimmel K, Stojanović SD, Huang CK, Jung M, Meyer MH, Xiao K, *et al.,* Combined high-throughput library screening and next generation RNA sequencing uncover microRNAs controlling human cardiac fibroblast biology. J Mol Cell Cardiol. 2021 Jan 1;150:91–100.
76. Qiao G, Xia D, Cheng Z, Zhang G. miR-132 in atrial fibrillation directly targets connective tissue growth factor. Mol Med Rep [Internet]. 2017 Oct 1 [cited 2022 Jul 27];16(4):4143–50. Available from: http://www.spandidos-publications.com/10.3892/mmr.2017.7045/abstract
77. Zhang J, Xu H, Gong L, Liu L. MicroRNA-132 protects H9c2 cells against oxygen and glucose deprivation-evoked injury by targeting FOXO3A. J Cell Physiol [Internet]. 2019 Jun 18 [cited 2022 Jun 25];235(1):176–84. Available from: https://europepmc.org/article/MED/31210352
78. Rana I, Velkoska E, Patel SK, Burrell LM, Charchar FJ. MicroRNAs mediate the cardioprotective effect of angiotensin-converting enzyme inhibition in acute kidney injury. Am J Physiol - Ren Physiol [Internet]. 2015 [cited 2022 Jul 27];309(11):F943–54. Available from: https://journals.physiology.org/doi/10.1152/ajprenal.00183.2015
79. Wang S, Meng X, Ng Y, Ma F, Zhou S, Oncotarget YZ, *et al.,* TGF-β/Smad3 signalling regulates the transition of bone marrow-derived macrophages into myofibroblasts during tissue fibrosis. ncbi.nlm.nih.gov [Internet]. [cited 2022 Aug 9]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4891006/
80. Yao Y, Hu C, Song Q, Li Y, Da X, Yu Y, *et al.,* ADAMTS16 activates latent TGF-β, accentuating fibrosis and dysfunction of the pressure-overloaded heart. Cardiovasc Res [Internet]. 2020 Apr 1 [cited 2022 Aug 9];116(5):956–69. Available from: https://academic.oup.com/cardiovascres/article/116/5/956/5531136
81. Li PF, He RH, Shi SB, Li R, Wang QT, Rao GT, *et al.,* Modulation of miR-10a-mediated TGF-β1/Smads signaling affects atrial fibrillation-induced cardiac fibrosis and cardiac fibroblast proliferation. Biosci Rep. 2019 Feb 8;39(2).
82. Zhao Z, Du S, Shen S, Wang L. microRNA-132 inhibits cardiomyocyte apoptosis and myocardial remodeling in myocardial infarction by targeting IL-1β. J Cell Physiol [Internet]. 2020 Mar 1 [cited 2022 Jun 25];235(3):2710–21. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jcp.29175
83. Su Q, Liu Y, Lv XW, Dai RX, Yang XH, Kong BH. LncRNA TUG1 mediates ischemic myocardial injury by targeting miR-132-3p/HDAC3 axis. Am J Physiol Heart Circ Physiol [Internet]. 2020 Feb 1 [cited 2022 Jun 2];318(2):H332–44. Available from: https://pubmed.ncbi.nlm.nih.gov/31858814/
84. Takeda N, Manabe I, Uchino Y, Eguchi K, Matsumoto S, Nishimura S, *et al.,* Cardiac fibroblasts are essential for the adaptive response of the murine heart to pressure overload. J Clin Invest [Internet]. 2010 Jan 1 [cited 2022 Jul 26];120(1):254. Available from: /pmc/articles/PMC2798693/
85. Porter KE, Turner NA. Cardiac fibroblasts: at the heart of myocardial remodeling. Pharmacol Ther [Internet]. 2009 Aug [cited 2022 Jul 26];123(2):255–78. Available from: https://pubmed.ncbi.nlm.nih.gov/19460403/
86. Li H, Zhang P, Li F, Yuan G, Wang X, Zhang A, *et al.,* Plasma miR-22-5p, miR-132-5p, and miR-150-3p Are Associated with Acute Myocardial Infarction. Biomed Res Int. 2019;2019.
87. Chen L, Wang GY, Dong JH, Cheng XJ. MicroRNA-132 improves myocardial remodeling after myocardial infarction. Eur Rev Med Pharmacol Sci [Internet]. 2019 [cited 2022 Jun 25];23(14):6299–306. Available from: https://pubmed.ncbi.nlm.nih.gov/31364135/
88. Lei Z, Fang J, Deddens JC, Metz CHG, van Eeuwijk ECM, el Azzouzi H, *et al.,* Loss of miR-132/212 Has No Long-Term Beneficial Effect on Cardiac Function After Permanent Coronary Occlusion in Mice. Front Physiol. 2020 Jun 16;11:590.
89. Liu W, Lin W, Yu L. Long non-coding RNA muscleblind like splicing regulator 1 antisense RNA 1 (LncRNA MBNL1-AS1) promotes the progression of acute myocardial infarction by regulating the microRNA-132-3p/SRY-related high-mobility-group box 4 (SOX4) axis. Bioengineered [Internet]. 2022 [cited 2022 Jul 30];13(1):1424–35. Available from: https://www.tandfonline.com/doi/abs/10.1080/21655979.2021.2018974
90. Zhou Y, Li KS, Liu L, Li SL. MicroRNA-132 promotes oxidative stress-induced pyroptosis by targeting sirtuin 1 in myocardial ischaemia-reperfusion injury. Int J Mol Med [Internet]. 2020 [cited 2022 Jun 2];45(6):1942–50. Available from: https://pubmed.ncbi.nlm.nih.gov/32236570/
91. Gomes RSM, Neves RP Das, Cochlin L, Lima A, Carvalho R, Korpisalo P, *et al.,* Efficient pro-survival/angiogenic miRNA delivery by an MRI-detectable nanomaterial. ACS Nano [Internet]. 2013 Apr 23 [cited 2022 Jul 19];7(4):3362–72. Available from: https://pubs.acs.org/doi/full/10.1021/nn400171w
92. Karakas M, Schulte C, Appelbaum S, Ojeda F, Lackner KJ, Münzel T, *et al.,* Circulating microRNAs strongly predict cardiovascular death in patients with coronary artery disease-results from

the large AtheroGene study. Eur Heart J [Internet]. 2017 Feb 1 [cited 2022 Jun 1];38(7):516–23. Available from: https://pubmed.ncbi.nlm.nih.gov/27357355/

93. Zeller T, Tanja T, Ojeda F, Reichlin T, Twerenbold R, Tzikas S, *et al.,* Assessment of microRNAs in patients with unstable angina pectoris. Eur Heart J [Internet]. 2014 Aug 14 [cited 2022 Jun 1];35(31):2106–14. Available from: https://pubmed.ncbi.nlm.nih.gov/24727883/
94. Rawal S, Munasinghe PE, Shindikar A, Paulin J, Cameron V, Manning P, *et al.,* Down-regulation of proangiogenic microRNA-126 andmicroRNA-132 are earlymodulators of diabetic cardiacmicroangiopathy. Cardiovasc Res [Internet]. 2017 Jan 1 [cited 2022 Jun 1];113(1):90–101. Available from: https://pubmed.ncbi.nlm.nih.gov/28065883/
95. Xu Q, Liang Y, Liu X, Zhang C, Liu X, Li H, *et al.,* MiR-132 inhibits high glucose-induced vascular smooth muscle cell proliferation and migration by targeting E2F5. Mol Med Rep [Internet]. 2019 Aug 1 [cited 2022 Jul 19];20(2):2012–20. Available from: http://www.spandidos-publications.com/10.3892/mmr.2019.10380/abstract
96. Zeng ZH, Wu WH, Peng Q, Sun YH, Liu JX. MicroRNA-132 mediates proliferation and migration of pulmonary smooth muscle cells via targeting PTEN. Mol Med Rep [Internet]. 2019 May 1 [cited 2022 Jun 13];49(5):3823–30. Available from: http://www.spandidos-publications.com/10.3892/mmr.2019.10053/abstract
97. Hulin A, Hego A, Lancellotti P, Oury C. Advances in Pathophysiology of Calcific Aortic Valve Disease Propose Novel Molecular Therapeutic Targets. Front Cardiovasc Med [Internet]. 2018 Mar 14 [cited 2022 Jun 17];5. Available from: https://doaj.org/article/3996787908b445c98e9a5d2b480c4dc2
98. Lerman DA, Prasad S, Alotti N. Calcific aortic valve disease: Molecular mechanisms and therapeutic approaches. Eur Cardiol Rev. 2015;10(2):108–12.
99. Avolio E, Meloni M, Spencer HL, Riu F, Katare R, Mangialardi G, *et al.,* Combined intramyocardial delivery of human pericytes and cardiac stem cells additively improves the healing of mouse infarcted hearts through stimulation of vascular and muscular repair. Circ Res [Internet]. 2015 May 8 [cited 2022 Jun 17];116(10):e81–94. Available from: https://www.ahajournals.org/doi/abs/10.1161/CIRCRESAHA.115.306146
100. Campagnolo P, Cesselli D, Al Haj Zen A, Beltrami AP, Kränkel N, Katare R, *et al.,* Human adult vena saphena contains perivascular progenitor cells endowed with clonogenic and proangiogenic potential. Circulation [Internet]. 2010 Apr [cited 2022 Jun 17];121(15):1735–45. Available from: https://pubmed.ncbi.nlm.nih.gov/20368523/
101. Ma T, Chen Y, Chen Y, Meng Q, Sun J, Shao L, *et al.,* MicroRNA-132, delivered by mesenchymal stem cell-derived exosomes, promote angiogenesis in myocardial infarction. Stem Cells Int. 2018;2018.
102. Chen X, Ba Y, Ma L, Cai X, Yin Y, Wang K, *et al.,* Characterization of microRNAs in serum: A novel class of biomarkers for diagnosis of cancer and other diseases. Cell Res [Internet]. 2008 Oct [cited 2022 Jun 1];18(10):997–1006. Available from: https://pubmed.ncbi.nlm.nih.gov/18766170/
103. Ishikawa H, Yamada H, Taromaru N, Kondo K, Nagura A, Yamazaki M, *et al.,* Stability of serum high-density lipoprotein-microRNAs for preanalytical conditions. Ann Clin Biochem [Internet]. 2017 Jan 1 [cited 2022 Aug 7];54(1):134–42. Available from: https://pubmed.ncbi.nlm.nih.gov/27166305/
104. Creemers EE, Tijsen AJ, Pinto YM. Circulating MicroRNAs: Novel biomarkers and extracellular communicators in cardiovascular disease? [Internet]. Vol. 110, Circulation Research. Circ Res; 2012 [cited 2022 Jun 1]. p. 483–95. Available from: https://pubmed.ncbi.nlm.nih.gov/22302755/
105. Lavenniah A, Luu TDA, Li YP, Lim TB, Jiang J, Ackers-Johnson M, *et al.,* Engineered Circular RNA Sponges Act as miRNA Inhibitors to Attenuate Pressure Overload-Induced Cardiac Hypertrophy. Mol Ther. 2020 Jun 3;28(6):1506–17.
106. Täubel J, Hauke W, Rump S, Viereck J, Batkai S, Poetzsch J, *et al.,* Novel antisense therapy targeting microRNA-132 in patients with heart failure: results of a first-in-human Phase 1b randomized, double-blind, placebo-controlled study. Eur Heart J [Internet]. 2021 Jan 7 [cited 2022 Jun 24];42(2):178–88. Available from: https://pubmed.ncbi.nlm.nih.gov/33245749/
107. Robson A. Inhibition of miR-132 prevents the progression of heart failure. Nat Rev Cardiol [Internet]. 2021 Sep 1 [cited 2022 Jun 24];18(9):612. Available from: https://pubmed.ncbi.nlm.nih.gov/34155375/
108. Condorelli G, Ferrante G. MicroRNA-132 Inhibition Prevents Myocardial Hypertrophy and Heart Failure in Pigs: Making Sense Out of Antisense. J Am Coll Cardiol. 2021 Jun 15;77(23):2936–8.
109. Herkt M, Foinquinos A, Batkai S, Thum T, Pich A. Pharmacokinetic Studies of Antisense Oligonucleotides Using MALDI-TOF Mass Spectrometry. Front Pharmacol. 2020 Mar 25;11:220.
110. Baker AH, Giacca M. Antagonism of miRNA in heart failure: first evidence in human. Eur Heart J [Internet]. 2021 Jan 7 [cited 2022 Jun 24];42(2):189–91. Available from: https://pubmed.ncbi.nlm.nih.gov/33338200/
111. Gupta SK, Garg A, Avramopoulos P, Engelhardt S, Streckfuss-Bömeke K, Batkai S, *et al.,* miR-212/132 Cluster Modulation Prevents Doxorubicin-Mediated Atrophy and Cardiotoxicity. Mol Ther [Internet].

2018 Nov 13 [cited 2022 Jun 25];27(1):17–28. Available from: https://europepmc.org/articles/PMC6319305

112. Jover E, Fagnano M, Cathery W, Slater S, Pisanu E, Gu Y, *et al.,* Human adventitial pericytes provide a unique source of anti-calcific cells for cardiac valve engineering: Role of microRNA-132-3p. Free Radic Biol Med [Internet]. 2021 Dec 23 [cited 2022 Jun 25];165:137–51. Available from: https://research-information.bris.ac.uk/en/publications/human-adventitial-pericytes-provide-a-unique-source-of-anti-calci

113. Qin J, Ke J, Xu J, Wang F, Zhou Y, Jiang Y, *et al.,* Downregulation of microRNA-132 by DNA hypermethylation is associated with cell invasion in colorectal cancer. Onco Targets Ther [Internet]. 2015 Dec 7 [cited 2022 Aug 8];8:3639–48. Available from: https://pubmed.ncbi.nlm.nih.gov/26675712/

114. El Fatimy R, Li S, Chen Z, Mushannen T, Gongala S, Wei Z, *et al.,* MicroRNA-132 provides neuroprotection for tauopathies via multiple signaling pathways. Acta Neuropathol 2018 1364 [Internet]. 2018 Jul 7 [cited 2022 Jul 27];136(4):537–55. Available from: https://link.springer.com/article/10.1007/s00401-018-1880-5