The diagnostic value of circulating microRNAs in heart failure (Review)

YAO-MENG HUANG1, WEI-WEI LI1, JUN WU1, MEI HAN1 and BING-HUI LI2

1Hebei Key Laboratory of Medical Biotechnology, Hebei Medical University, Shijiazhuang, Hebei 050017; 2Department of Oncological Surgery, Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei 050011, P.R. China

Received July 8, 2018; Accepted January 7, 2019

DOI: 10.3892/etm.2019.7177

Abstract. Heart failure (HF) is a complex clinical syndrome, characterized by inadequate blood perfusion of tissues and organs caused by decreased heart ejection capacity resulting from structural or functional cardiac disorders. HF is the most severe heart condition and it severely compromises human health; thus, its early diagnosis and effective management are crucial. However, given the lack of satisfactory sensitivity and specificity of the currently available biomarkers, the majority of patients with HF are not diagnosed early and do not receive timely treatment. A number of studies have demonstrated that peripheral blood circulating nucleic acids [such as microRNAs (miRs), mRNA and DNA] are important for the diagnosis and monitoring of treatment response in HF. MiRs have been attracting increasing attention as promising biomarkers, given their presence in body fluids and relative structural stability under diverse conditions of sampling. The aim of the present review was to analyze the associations between the mechanisms underlying the development of HF and the expression of miRs, and discuss the value of using circulating miRs as diagnostic biomarkers in HF management. In particular, miR-155, miR-22 and miR-133 appear to be promising for the diagnosis, prognosis and management of HF patients.

1. Introduction

The causes of heart failure (HF) include ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM), hypertension, valvular heart disease, diabetic cardiomyopathy and congenital heart disease (CHD) (1). The pathogenesis of HF is associated with myocardial hypertrophy, fibrosis or necrosis, cardiomyocyte apoptosis, renin-angiotensin-aldosterone system imbalance and collagen changes, as well as several other factors (2-7).

MicroRNAs (miRs) are small (~22 nucleotides in length), single-strand, non-coding RNA sequences derived from precursors that control gene expression in a variety of physiological and developmental processes, which are involved in post-transcriptional regulation of gene expression (8). MiR disorders are associated with a number of human diseases, including diabetes, myocardial infarction and cardiovascular disease, obesity and cancer. Several studies have demonstrated that miRs may affect different aspects of the occurrence and development of HF (9-14). The association between miRs and HF is discussed in detail below.

Circulating miRs are increasingly recognized as promising biomarkers, given their stability and resistance to endogenous RNase (15); these miRs, to some degree, may also be used as diagnostic biomarkers for angiocardiopathy. In addition, miRNAs and various types of HF have complex relationships, as described below.

2. Changes and associated mechanisms of miRs in various types of HF

miRs may be involved in several aspects of the occurrence and development of HF, such as cardiomyocyte apoptosis, hypertrophy, fibrosis, inflammation, oxidative damage and...
hypoxic damage (9-14), among others. The specific regulatory functions of miRs are indicated in Figs. 1 and 2 and are summarized in Table I (16-66).

3. Circulating miRs as diagnostic biomarkers

HF is primarily caused by cardiomyopathy, hypertension, diabetes and CHD, among other causes (15). The different etiology is associated with several miRs.

miRs associated with cardiomyopathy. The cardiomyopathies leading to HF predominantly include DCM and ICM (67-71). DCM, characterized by left ventricular dilatation, ventricular wall thinning and diffuse myocardial dysfunction, leads to congestive HF (72) and right ventricular dysfunction (73). These pathological changes result in the transition from compensatory hypertrophy to DCM (74). The heart undergoes continuous remodeling of myocardial cells through transduction of intercellular signals and activation of the transcription and transmission pathways (75). Naga Prasad et al (76) performed reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analysis on a set of samples used for miR microarray analysis, and identified that hsa-mir-378 (P<0.0055), hsa-mir-001 (P<0.0001), hsa-mir-007 (P<0.0009) and hsa-mir-29b (P<0.0087) were notably decreased in DCM compared with control samples; by contrast, hsa-mir-342 (P<0.0004), hsa-mir-214 (P<0.0001), hsa-mir-125b (P<0.0785), hsa-mir-145 (P<0.0091) and hsa-mir-181b (P<0.0047) were significantly increased in DCM compared with non-failing controls, and may be used to indicate the stage of HF development. Enes Coşkun et al (77) investigated 23 pediatric patients (aged 2-192 months) with isolated idiopathic DCM as the experimental group, and 26 age-matched healthy children with innocent murmur as the control group. Patients with fractional shortening of <25% and with a left ventricular end-diastolic diameter >112% of the predicted dimension were considered to have DCM. The results of RT-qPCR demonstrated that the expression levels of miR-454 and miR-518f were significantly higher in DCM patients compared with those in the control group. Furthermore, the expression levels of 10 miRs (miR-618, miR-875-3p, miR-205, miR-194, miR-302a, miR-147, miR-544, has-miR-99b, miR-155 and miR-218) were notably lower in patients with DCM compared with control subjects, suggesting that they may be used as potential diagnostic biomarkers. Interestingly, Miyamoto et al (78) observed that 2 miRs (hsa-miR-636 and hsa-miR-155) were upregulated and 2 miRNAs (hsa-miR-646 and hsa-miR-639) were downregulated in patients with DCM compared with patients with DCM with recovered ventricular function, which indicated that they may serve as diagnostic as well as prognostic biomarkers. However, further research is required to elucidate the specific underlying mechanisms.

Leger et al (79) and Zeng et al (80) measured left ventricular ejection fraction (LVEF) and the 6-min walk test distance (6MWTD) and CBP/p300 interacting transactivators with ED-rich termini 2 (CITED2), hypoxia-inducible factor-1 (HIF-1) in patients with ICM before and after treatment, and identified that LVEF, 6MWTD, CITED2 and HIF-1 levels were significantly lower in the ICM group compared with those in the control group prior to treatment (P<0.01). The N-terminal pro-B-type natriuretic peptide (NT-proBNP), HIF-1 and miR-182 levels in the ICM group were significantly higher compared with those in the control group (P<0.01). Following 4 months of treatment, the levels of 6MWTD, CITED2 and LVEF in the ICM group were significantly increased, whereas the levels of plasma NT-proBNP, HIF-1 and miR-182 were significantly decreased (P<0.01). Furthermore, the plasma miR-182 level was negatively correlated with CITED2, LVEF and 6MWTD (P<0.05) and positively correlated with HIF-1 (P<0.05) in the ICM group. Therefore, miR-182 is correlated with several indicators of HF, and may be considered to reflect the severity of the disease. Olson and Rooij (81) and Fichtlscherer et al (82) observed upregulation of miR-208a and miR-499 and downregulation of the circulating levels of miR-126, miR-17, miR-92a and the inflammation-associated miR-155 in patients with coronary artery disease compared with healthy controls by qPCR. Similarly, the level of miR-145 in smooth muscle was significantly reduced. By contrast, the levels of cardiac muscle-enriched miRs (miR-133a and miR-208a) tended to be higher in patients with coronary artery disease. Li et al (83) demonstrated a decrease of miR-125a, miR-20a and miR-302d levels in ICU using Deep RNA sequencing. Notably, only 55 miRs were indicated to be consistently increased in ICM and non-ischemic cardiomyopathy (NICM), including miR-21-5p, miR-125b-1-3p and miR-106b-5p, among others. However, 38 miRNAs were downregulated in both ICM and NICM (non-ischemic cardiomyopathy), including miR-20a-5p, miR-17-5p and let-7e-5 (83). The findings suggest that miR-182 appears to be a promising new biomarker for the diagnosis of ICM and DCM in clinical research.

miRs associated with hypertension. Hypertension is an independent risk factor for cardiac and cerebrovascular disease (84). It has been reported that at least 50% of patients with long-term hypertension will likely undergo cardiac remodeling, particularly left ventricular remodeling (85). Myocardial cell hypertrophy is among the primary causes underlying the occurrence of HF (86). Notably, it has been demonstrated that miR-208 can induce cardiac hypertrophy and results in the overexpression of β-myosin heavy chain in myocardial fibrosis (87). Several miRs were indicated to be differentially expressed in hypertension, including miR-296-5p, let-7e and human cytomegalovirus (HCMV)-miR-UL112, as encoded by HCMV in previous studies of the hypertension-associated miR spectrum (88-90). Interferon regulatory factor 1, which is involved in the regulation of blood pressure by acting on nitric oxide synthase and vascular angiotensin (Ang) receptor, was demonstrated to be a direct target of HCMV-miR-UL112 (91). However, in hypertension, HCMV titers are considered to reflect the expression level of HCMV-miR-UL-112 (91), which is an independent risk factor for hypertension. HCMV has been reported to inhibit vasodilation by impairing nitric oxide synthase function (92) and causing endothelial cell dysfunction (93). However, further research is warranted due to the elusive association between HCMV infection and endothelial dysfunction.
Figure 1. Association between miRs and different pathogenic mechanisms of heart failure. Solid lines represent positive regulation and dashed lines represent negative regulation. The nck of the arrow controls the tip of the arrow, for example miR-7a/b downregulates Sp1, PARP-1 and caspase-3, whereas Sp1, PARP-1 and caspase-3 promote myocardial fibrosis. Therefore, miR-7a/b protects cardiomyocytes against apoptosis. CFL2, Cofilin-2; HMGB1, high-mobility group box 1 protein; HSFB1, Heat Shock Factor Binding Protein 1; ACE2, Angiotensin-converting enzyme 2; Bcl-2, B-cell lymphoma-2; SRF, serum response factor; TAGLN2, Transgelin 2; NFATC4, Nuclear Factor Of Activated T Cells; CTGF, connective tissue growth factor; DOX, Doxorubicin; MMP-9, matrix metalloproteinase-9; β1AR and β2AR, β1- and β2-adrenoceptor; TGF-β, transforming growth factor-β; IL-1β, Interleukin-1β; MCP1, monocyte chemoattractant protein-1; PDCD4, programmed cell death 4; Sp1, specific protein 1; PARP1, poly ADP-ribose polymerase; ALDO, aldosterone; PTEN, phosphatase and tensin homolog deleted on chromosome 10; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; Akt, Protein Kinase B; Col1a1, collagen 1A1; Col1a2, collagen 1A2; Col15a1, collagen 15A1; Col III, type III collagen; Col I, type I collagen; MAPK, mitogen-activated protein kinase; VEGF, Vascular endothelial growth Factor; ERK, extracellular regulated protein kinases; MMP-2, matrix metalloproteinase-2; SPRY1, SPRY1, sprouty homolog 1.

Figure 2. Association between miRs and different pathogenic mechanisms of heart failure. Solid lines represent positive regulation and dashed lines represent negative regulation. The nck of the arrow controls the tip of the arrow, for example miR-451 downregulates the LKB1/AMPK pathway, and the LKB1/AMPK pathway negatively regulates the tendency for cardiomyocyte hypertrophy. JUN, Jun proto-oncogene product which is a subunit of the AP-1 transcription; HOXA9, Homeobox A9; UCA1, urothelial carcinoma-associated 1; KLF13, Kruppel-like transcription factor 13; CIAPN1, cytokine-induced anti-apoptotic molecule; BDNF, brain derived neurotrophic factor; TGF-β, transforming growth factor-β; IL-6, Interleukin-6; NF-kB, Nuclear factor kappaB; TRAF3, TNF receptor associated factor 3; TNF-α, tumor necrosis factor-α; IL-1β, Interleukin-1β; MCP1, monocyte chemoattractant protein-1; PDCD4, programmed cell death 4; Sp1, specific protein 1; PARP1, poly ADP-ribose polymerase; ALDO, aldosterone; PTEN, phosphatase and tensin homolog deleted on chromosome 10; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; Akt, Protein Kinase B; Col1a1, collagen 1A1; Col1a2, collagen 1A2; Col15a1, collagen 15A1; Col III, type III collagen; Col I, type I collagen; MAPK, mitogen-activated protein kinase; VEGF, Vascular endothelial growth Factor; ERK, extracellular regulated protein kinases; MMP-2, matrix metalloproteinase-2; SPRY1, SPRY1, sprouty homolog 1.
Table I. Information on different types of miRs.

| Author, year | miRs | Relative gene protein or signaling pathways | Biological effects | Tissue, cells or experimental model | Detection means (Refs.) |
|--------------|------|---------------------------------------------|-------------------|----------------------------------|------------------------|
| Li et al, 2016 | miR-7a/b | Sp1, PARP-1 and caspase-3 | Binding activity of Sp1 may conditionally mediate the repression of miR-7a/b-regulated PARP-1 and caspase-3 expression, miR-7a/b inhibitors effectively upregulated Sp1, PARP-1 and caspase-3 expression | H9c2 cell line | Western blot, RT-qPCR, luciferase assay and ChIP (16) |
| Ball et al, 2017 | miR-21 | ALDO/SALT, TGF-β2, IL-1β, MCP-1, Colla1 and Col1a1 | miR-21 downregulation attenuated ALDO/SALT-mediated LV inflammatory marker mRNA expression, such as TGF-β2, IL-1β and MCP-1. miR-21 downregulation exacerbated ALDO/SALT-mediated LV fibrosis marker mRNA expression upregulation, such as Colla1 and Col1a1 | Left ventricle of Control, ALDO, SALT, ALDO/SALT, ALDO/SALT+Eplerenone or ALDO/SALT+AHT, ALDO (0.75 µg/h, Steraloids) | RT-qPCR and northern-blot (17) |
| Deng et al, 2016 | miR-21 | PTEN/PI3K/Akt, Caspase-3, Bax and Bcl-2 | miR-21 decreased H2O2-induced apoptosis by decreasing PTEN/PI3K/Akt signaling, miR-21 downregulated the proapoptosis protein Caspase-3 and Bax, and upregulated Bcl-2 | c-kitD CSC | RT-qPCR, western blot and confocal microscopy (18) |
| Cheng et al, 2016 | miR-21 | TGF-β1 and p-ERK/ERK | Celastrol attenuated miR-21 upregulation by TGF-β1 and decreased elevated p-ERK/ERK levels in CFs transfected with miR-21 | Cardiac fibroblasts | Western blot, RT-qPCR and luciferase reporter assay (19) |
| Xiao et al, 2016 | miR-21 | PDCD4 | miR-21 inhibited apoptosis pathway through downregulating PDCD4. Restored miR-21/PDCD4 pathway could protect myocardial cells against oxidative stress-related apoptosis | H9C2 cardiac cells | Western blot, RT-qPCR and luciferase activity assay (20) |
| Tao et al, 2016 | miR-29a | VEGF-A and p-ERK1/2 | miRNA-29a suppressed cardiac fibrosis and fibroblast proliferation via down-regulating p-ERK1/2 and VEGF-A/MAPK signal pathway | Cardiac fibroblasts | Western blot and RT-qPCR (21) |
| Liu et al, 2017 | miR-29a | APN and collagen I and III | miR-29a has a negative correlation with ANP in atherosclerosis | Blood sample | RT-qPCR and ELISA (22) |
Table I. Continued.

| Author, year | miRs     | Relative gene protein or signaling pathways | Biological effects                                                                 | Tissue, cells or experimental model                     | Detection means                                                                                     | (Refs.) |
|-------------|----------|---------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------------------------------------|---------|
| Lu et al, 2018 | miR-29b  | SPRY1, MAPK, TNF-α, ROS, NADPH oxidase, CCL2 and CCL5 | miR-29b suppressed the MAPK signaling pathway through inhibiting SPRY1 at the posttranslational level in atherosclerosis | HUVECS                                                 | Western blot, luciferase reporter assay, statistical analysis, RT-qPCR and ROS determination          | (23)    |
| Sassi et al, 2018 | miR-29  | Wnt signaling                                | miR-29 promoted cardiac hypertrophy and fibrosis via derepressing Wnt signaling   | Cardiac fibroblasts, aorta in patients with aortic valve stenosis and aorta in mice induced by TAC | RT-qPCR, immunohistochemical analyses and secretome analysis                                        | (24)    |
| Panizo et al, 2017 | miR-29b | CTGF, COL1A1 and MMP-2                      | miR-29b inhibited CTGF, COL1A1 and MMP-2                                          | Cardiomyocytes of the left ventricle                   | Western blot and RT-qPCR                                                                             | (25)    |
| Heid et al, 2017 | miR-29  | Col1a1, Col1a2 and col15a1                  | Upregulation of miR-29 decreased col1a1, col1a2 and col15a1                       | Human cardiac fibroblasts                              | Luciferase reporter assay, Masson/ immunohistochemical staining, western blot and RNA sequencing   | (26)    |
| Chen et al, 2018 | miR-30a | CTGF and collagen                            | miR-30a inhibited CTGF by directly combining with the 3'-UTR of CTGF, thereby reducing collagen and myocardial fibrosis, which improved cardiac function | Young adult and old Nfu hearts                         | RT-qPCR                                                                                             | (27)    |
| Roca-Alonso et al, 2015 | miR-30 | GATA-6, β1AR, β2AR and Gia-2                | miR-30 expression attenuates the contractile response of cardiomyocytes to βAR stimulation (β1AR, β2AR and Gia-2), which reduced cardiomyocyte contractility DOX sustained miR-30 downregulation in cardiomyocytes via improving GATA-6 | H9c2 cardiac muscle cell line                          | NanoString technology, luciferase assays, ROS detection and cAMP accumulation                       | (28)    |
| Lai et al, 2016 | miR-30e  | ACE2, caspase-3 and Beclin-1                | Silencing miR-30e reverses the heart-protective effect of ACE2 and induces primary cardiomyocyte apoptosis Overexpression of ACE2 attenuates doxorubicin-mediated pathological signaling of primary cardiomyocytes | H9C2 cardiomyocytes                                   | RT-qPCR and western blot                                                                         | (29)    |
Table I. Continued.

| Author, year | miRs | Relative gene protein or signaling pathways | Biological effects | Tissue, cells or experimental model | Detection means (Refs.) |
|--------------|------|--------------------------------------------|-------------------|-----------------------------------|------------------------|
| van Middendorp et al, 2017 | miR-133a | CTGF | miR-133a negatively regulated CTGF expression SRF and NFATc4, as target genes of miR-133a, did not show significant relation with miR-133a in local hypertrophy | Isolated cardiomyocytes | RT-qPCR and statistical analysis (30) |
| Li et al, 2010 | miR-133a | NFATc4 | Silencing of NFATc4 by miR-133a may contribute to miR-133a-mediated anti-hypertrophy | Neonatal rat cardiomyocytes | RT-qPCR, western blot and immunostaining (31) |
| Li et al, 2015 | miR-133a | Caspase-8, caspase-9, caspase-3, Bcl-2 and TAGLN2 | miR-133a suppressed caspase-8, caspase-9, and caspase-3, but improved Bcl-2 and suppressed TAGLN2 expression via binding to 3'-UTR of TAGLN2 mRNA | Hypoxic H9c2 cells | Bioinformatics analysis and dual-luciferase reporter analysis (32) |
| Rangrez et al, 2017 | miR-301a | CFL2 | Overexpression of Cri2 or knockdown of miR-301a resulted in the activation of SRF signaling and overexpression of miR-301a reduced Cri2 expression | NRVM | RNA isolation, cDNA synthesis, RT-qPCR and microarray analysis (33) |
| Dong et al, 2016 | miR-214 | Ang-II, COL-I and COL-III | miR-214 may inhibit collagen synthesis in CFBs induced by Ang II and upregulated miR-214 can inhibit COLI and COLIII | CFBs | Masson staining, RT-qPCR and western blot (34) |
| Chaturvedi et al, 2015 | miR-455 | MMP-9 | miR-455 prevented the downstream detrimental effects of MMP9 that lead to fibrosis and myocyte uncoupling with the expression of miR-214 | Cardiosomes (exosomes from cardiomyocytes) | Western blot, RT-qPCR and IHC (35) |
| Liu et al, 2017 | miR-135a | Bcl-2 | miR-135a positively regulated H2O2-induced apoptosis in H9c2 cells via blocking Bcl-2 protein | H9c2 cells | RNA-mediated gene silencing, RNA extraction, RT-qPCR and western blot (36) |
| Wang et al, 2016 | miR-142-3p | HMGB1 and TGF-β1/Smad3 | TGF-β1/Smad3 signaling involved in the miR-142-3p/HMGB1-mediated apoptosis and fibrosis of M6200 cells miR-142-3p inhibits H/R-induced apoptosis and fibrosis by the inhibition of HMGB1 | M6200 cells | Bioinformatics analysis and dual-luciferase reporter assay (37) |
| Author, year | miRs | Relative gene protein or signaling pathways | Biological effects                                                                 | Tissue, cells or experimental model | Detection means                                                                 | (Refs.) |
|-------------|------|--------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------|---------------------------------------------------------------------------------|---------|
| Yang *et al.*, 2017 | miR-410 | HMGB1 and HSPB1                            | miR-410 may inhibit mitophagy and apoptosis following cardiac I/R injury by repressing HSPB1 activity via directly suppressing HMGB1 | HACMs                             | Dual-luciferase assay                                                           | (38)    |
| Zhang *et al.*, 2018 | miR-208a | CHD9 and Notch/NFB                         | CHD9 is a direct target of miR-208a, which was also related with Notch/NFB signal pathway during I/R injury | H9c2 cells                       | RT-qPCR, dual-luciferase activity and western blot,                              | (39)    |
| Fan *et al.*, 2018   | miR-210 | HGF                                        | Upregulation of HGF was observed among the AMI rats after receiving miR-210 agonists | HUVEC                             | RT-qPCR, immunohistochemistry, western blot and statistical analysis          | (40)    |
| Zhang *et al.*, 2018 | miR-182-5p | CIAPIN1                                   | miR-182-5p promoted apoptosis in hypoxia-induced cardiomyocytes via negative regulation of CIAPIN1 | H9c2 and 293'T cells/primary rat cardiac muscle cells | Bioinformatic analysis and dual-luciferase reporter assay                       | (41)    |
| Liu *et al.*, 2018   | miR-132 | TGF-β1 and smad3                           | miRNA-132 decreased the expression of TGF-β1 and smad3 and increased the antioxidant stress and antiapoptotic ability of H9C2 cells | HF patients' blood/H9C2 cell     | HE/Masson staining, MTT assay, RT-qPCR western blot and statistical analysis    | (42)    |
| Zhou *et al.*, 2018  | miR-184 | HOXA9 and ANP, BNP, PE and UCA1           | UCA1 promoted cardiac hypertrophy through competitively binding with miR-184 to enhance the expression of HOXA9. The overexpression of miR-184 lessened the enlarged surface area of cardiomyocytes and the elevated expression of fetal genes (ANP and BNP) induced by PE | Cardiomyocyte isolated from neonatal mice | Plasmid construction and transfection, RT-qPCR, luciferase reporter analysis and western blot | (43)    |
| Rubiš *et al.*, 2016 | miR-99 | Akt-1 and EGR-1                            | EGR-1 mediated regulation of miR-99 family that serves a key role in determining the fate of cardiac hypertrophy by regulating Akt-1 signaling | Extracellular matrix and serum    | Endomyocardial biopsy and RT-qPCR                                               | (44)    |
| Ji *et al.*, 2018    | miR-327 | ITGB3                                      | miR-327 represses integrin (ITGB)3, contributing to its effect on cardiac fibrosis | Cardiac fibroblast                | Immunohistochemistry, western blot and RT-qPCR                                  | (45)    |
| Author, year | miRs | Relative gene protein or signaling pathways | Biological effects | Tissue, cells or experimental model | Detection means (Refs.) |
|-------------|------|------------------------------------------|-------------------|-------------------------------|------------------------|
| Lu et al, 2018 | miR-672-5p | JUN | miR-672-5p had suppressive effects on cardiac hypertrophy through inhibiting the expression of Jun in cardiomyocytes | Myocardial cells | RT-qPCR, luciferase assay and western blot (46) |
| Wang et al, 2018 | miR-27b | ALK5 and Smad-2/3 pathway | miR-27b inhibited AngII-induced Smad-2/3 phosphorylation, miR-27b ameliorates AF through inactivation of Smad-2/3 pathway by inhibiting ALK5, a receptor of TGF-β | Myocardial cells | RT-qPCR, luciferase assay and western blot (47) |
| Yang et al, 2016 | miR-22 | AP-1, Bcl-2/Bax, TNF-α and IL-6 | miR-22 significantly inhibited AP-1 activity, changed Bcl-2/Bax ratio and suppressed TNF-α and IL-6 induced by H/R | Neonatal rat ventricular cardiomyocytes | RT-qPCR, western blot, ELISA and EMSA (48) |
| Zhang et al, 2018 | miR-22 | Cav3-PKCe pathway | miR-22 accelerates cardiac fibrosis through the miR-22-Cav3-PKCe pathway and inhibits angiotensin II-mediated excessive collagen deposition through protein kinase C (PKCe) inactivation | Cardiac fibroblasts from neonatal SD rats | RT-qPCR, western blot, Masson trichrome staining, luciferase reporter assay and immunofluorescence staining (49) |
| Zheng et al, 2018 | miR-26a-5p | ULK1, LC3-I and LC3-II | miR-26a-5p can reduce the expression of ULK1 and collagen I, and decrease the activation of LC3-I to LC3-II | Primary cardiac fibroblasts | Dual-luciferase reporter assay, western blot and RT-qPCR (50) |
| Gu et al, 2018 | miR-147b | KLF13 | miR-147b inhibits cell viability and promotes apoptosis of rat H9c2 cardiomyocytes via downregulating KLF13 expression | H9c2 cells | Luciferase reporter assay and RT-qPCR (51) |
| Sun et al, 2017 | miR-145 | SGK1, PI3K/AKT signaling pathway and HIF-1α | miR-145 could be upregulated by HIF-1α in cardiomyocytes under hypoxic conditions, miR-145 overexpression promoted cell viability, inhibited apoptosis and ROS activity and promoted activation of PI3K/AKT signaling pathway via SGK1 upregulation | H9c2 cell line and mouse cardiac muscle cell line | RT-qPCR, western blot and ELISA (52) |
| Chen et al, 2017 | miR-200c | GATA-4 and Bcl-2 | miR-200c significantly increased GATA-4 expression. Furthermore, downregulation of miR-200c upregulated the expression of the anti-apoptotic gene Bcl-2 | Cardiomyocyte | RT-qPCR, luciferase assay and western blot (53) |
| Author, year | miRs | Relative gene protein or signaling pathways | Biological effects | Tissue, cells or experimental model | Detection means (Refs.) |
|-------------|------|--------------------------------------------|-------------------|-----------------------------------|------------------------|
| Meng *et al*., 2017 | miR-363 | Notch1 | Inhibition of miR-363 protects cardiomyocytes against hypoxia-induced apoptosis through promotion of Notch1 expression and activation of Notch signaling | Rat myocardium-derived H9C2 and 293T cells | RT-qPCR, MTT and western blot (54) |
| Li *et al*., 2015 | miR-10a, miR-139b and miR-206 | TNF, IL-1, IL-6, Cx43 and Rho kinase | TNF, IL-1 and IL-6 downregulate the expression of miR-10a, miR-139b, miR-206 and miR-222, and upregulate the expression of Cx43 and Rho kinase in VSMCs. miR-10a, miR-139b, miR-206 and miR-222 could downregulate the expression of Cx43 and Rho kinase | Cardiomyocyte from SD rats fed with a high-fat diet | Statistical analyses, ELISA and RT-qPCR (55) |
| Gallego *et al*., 2016 | miR-10b | APAF-1 | miR-10b inhibition in HL-1 cardiomyocytes induced the overexpression of APAF-1 | Cardiomyocytes | TaqMan low density array and RT-qPCR (56) |
| Huang *et al*., 2016 | miR-195 | Bcl-2 and BDNF | miR-195 promotes ischemic apoptosis by repressing Bcl-2 and inhibits cardiac function of MI rats. BDNF abolished the pro-apoptotic role of miR-195, which was reversed by its scavenger TrkB-F | NRVMs | RNA extraction, RT-qPCR, luciferase activity assay and cell viability assay (57) |
| Blumensatt *et al*., 2017 | miR-208a | AT II | Locked-nucleic-acid-mediated inhibition of miR-208a function reversed the detrimental effects induced by AT II | Primary adult rat cardiomyocytes from Lewis rats | Statistical analysis, and histomorphological and immunohistochemical analysis (58) |
| Marchand *et al*., 2016 | miR-322 | SIRT4, IGF1R and INSR | miR-322 inhibits the insulin pathway/IGF1R and cyclin D, miR-322 downregulates SIRT4, IGF1R and INSR, which thus decreases Akt phosphorylation and insulin action | Cardiomyocytes and heart from C57BL/6 mice fed with high-fat diet (10 weeks) | RNA isolation, RT-qPCR, western blot and luciferase assay (59) |
| Zhong *et al*., 2016 | miR-19b | PTEN, a-SMS and TGFβRII | miR-19b promotes cardiac fibroblast proliferation and migration by downregulating PTEN, which decreased a-SMS expression by targeting TGFβRII | H9C2 cardiomyocytes | Western blot and RT-qPCR (60) |
| Pan *et al*., 2015 | miR-25 | Oxidative stress pathways/MCU | miR-25 protects cardiomyocytes against oxidative damage by inhibiting the MCU | H9C2 cardiomyocytes exposed to doxorubicin | FACS, TUNEL assay, immunoblotting, luciferase (61) |
| Author, year | miRs | Relative gene protein or signaling pathways | Biological effects | Tissue, cells, or experimental model | Detection means (Refs.) |
|-------------|------|--------------------------------------------|--------------------|------------------------------------|------------------------|
| Das et al, 2017 | miR-181a/b | PTEN, PI3K ROS and mt-COX1 | miR-181a/b deficiency inhibits PI3K signaling through upregulation of PTEN, miR-181a/b enhanced damage by overproduction of ROS via inhibiting mt-COX1 | H9c2 cardiomyocytes | reporter assay, western blot and RT-qPCR (62) |
| Palomer et al, 2015 | miR-146 | Fos-AP1, MMPs and collagen | Downregulation of the Fos-AP-1 pathway by miR-146a can inhibit MMP-9 activity and therefore suppresses hypertrophy of cardiomyocytes and fibrosis of the interstitial substance | AC16 cell line (cardiac muscle cells) | Immunoblot analysis, statistical analysis, electrophoretic mobility shift assay and RT-qPCR (63) |
| Khamaneh et al, 2015 | miR-155 | NF-κB inflammatory signaling pathways | Activation of inflammatory signaling pathways/NF-κB | Cardiomyocytes from diabetes mellitus type 1 model SD rats administrated with streptozotocin | RT-qPCR and statistical analysis (64) |
| Fang et al, 2015 | miR-3473b | inflammatory signaling pathways/TRAF3-NF-κB | miR-3473 negatively regulates TRAF3, a well-known negative regulator of the NF-κB pathway, to enhance NF-κB pathway | Bacterial infection model with murine macrophages | RT-qPCR and western blot (65) |
| Kuwabara et al, 2015 | miR-451 | LKB1/AMPK pathway | Induces activation of lipotoxicity through suppression of the LKB1/AMPK pathway | Neonatal cardiomyocytes from C57BL/6 mice feed with high fat diet (20 weeks)/heart | Dual luciferase reporter assay, western blot, transhoracic echocardiography and statistical analysis (66) |

PDCD4, programmed cell death 4; TGFβ-2, transforming growth factor β-2; MCP-1, monocyte chemoattractant protein-1; CSCs, cardiac stem cells; CFs, cardiac fibroblasts; APN, adiponectin; HUVECs, human umbilical vein endothelial cells; TAC, transverse aortic constriction; coll1a1, collagen 1A1; colla2, collagen 1A2; coll15a1, collagen 15A1; ARVCs, adult rat ventricular cardiomyocytes; DOX, doxorubicin; b1AR and b2AR, b1- and b2-adrenoceptor; NRVM, neonatal rat ventricular cardiomyocytes; CFBS, cardiac fibroblasts; H/R, hypoxia/reoxygenation; I/R, ischemia-reperfusion; HMGB1, high-mobility group box 1 protein; HUVECs, human umbilical vein endothelial cells; CIAPIN1, cytokine-induced anti-apoptotic molecule; PE, phenylephrine; HOXA9, homeobox A9; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; EGR-1, early growth response protein 1; ITGB3, integrin β3; JUN, Jun proto-oncogene; AP-1, activator protein 1; AF, atrial fibrosis; Bcl-2, B-cell lymphoma-2; Cav3, Caveolin 3; ULK, Unc-51 like autophagy activating kinase; Cx43, connexin 43; APAF-1, apoptotic protease activating factor-1; BDNF, brain derived neurotrophic factor; IGFR1, insulin-like growth factor 1 receptor; PTEN, phosphatase and tensin homolog deleted on chromosome 10; MCU, mitochondrial calcium uptake; MMP-3, matrix metalloproteinase-3; NF-kB, nuclear factor-kB; TRAFs, TNF receptor associated factors; AMPK, adenosine monophosphate-activated protein kinase; TTC, 2,3,5-triphenyltetrazolium chloride; TUNEL, TdT-mediated dUTP nick-end labeling; ELISA, enzyme linked immunosorbent assay; ROS, reactive oxygen species; CCL2, collagen-2; IHC, immunohistochemistry; HF, heart failure; UCA1, urothelial carcinoma-associated 1; AT, angiotensin; EMSA, electrophoretic mobility shift assay; TNF, tumor necrosis factor; SD, Sprague-Dawley; PKC, protein kinase C; FACS, fluorescence-activated cell sorting; western blot, western blotting analysis; ALDO, aldosterone; SALT, 1.0% NaCl; AHT, triple antihypertensive therapy (240 mg/kg hydralazine + 75 mg/kg hydrochlorothiazide + 1.5 mg/kg reserpine); KLF, Kruppel-like transcription factor; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; SGK, serum and glucocorticoid induced kinase; ChIP, chromatin immunoprecipitation assay; COL-I, type I collagen; COL-III, type III collagen.
Kontaraki et al (94,95) reported that upregulated miRs included miR-1 and miR-21, whereas downregulated miRs included miR-9, miR-126, miR-133, miR-143 and miR-145 in the hypertension group compared with the healthy control group. In addition, miR-21, miR-143 and miR-145 were negatively correlated and miR-133 was positively correlated with 24-h ambulatory mean blood pressure, mean diastolic blood pressure and mean pulse pressure in the hypertension group. Furthermore, miR-9 and miR-126 were positively correlated with mean pulse pressure, but the association between miR-9 and left ventricular hypertrophy index was positively correlated with the 24-h ambulatory mean blood pressure and mean diastolic blood pressure. Therefore, this miR may reflect the severity of hypertensive HF.

Dickinson et al (96) reported that the circulating levels of miR-423-5p, miR-106b, miR-20b, miR-223, miR-16 and miR-93 were markedly increased in hypertension-induced HF, which was confirmed via RT-qPCR analysis of plasma RNA from hypertensive rats. These results indicate that several miRs can reflect disease progression to a certain extent, and may be used as biomarkers of hypertensive HF. This suggests that miRs should be detected pre- and post-treatment to reduce the effects of medication on the results of the experiment. Hou et al (97) randomly divided 16 spontaneously hypertensive rats (SHR) into the SHR control (distilled water) and intervention SHR (captopril 10 mg/kg/day) groups. An additional 8 Wistar male rats comprised the normal control groups (captopril 10 mg/kg/day or distilled water for 8 weeks). The expression of miR-137 was detected by RT-qPCR and western blot analysis in rat hearts, and miR-137, Ang II, transforming growth factor (TGF)-β1, Smad3, collagen (Col)-I and Col-III were identified to be more highly expressed in the SHR treatment and SHR control groups than the normal control group (P<0.01 and P<0.05, respectively); by contrast, the levels of miR-137, Ang II, TGF-β1, Smad3, Col-I and Col-III were significantly lower in the normal control groups compared with the SHR control group (P<0.01 and P<0.05, respectively). Thus, miR-137 may promote cardiac remodeling in SHR by upregulation of Ang II and the TGF-β1/Smad3 signaling pathway; in addition, captopril intervention can inhibit miR-137 expression. Therefore, miR-137 not only indicates the presence of high blood pressure, it may also reflect its severity.

Li et al (98) reported that insulin-like growth factor (IGF)-1 prevented diabetes-induced cardiomyopathy via marked anti-apoptotic and anti-fibrotic effects, which are mediated by miR-1. These findings provide a new paradigm for the endocrine effects of IGF-1 in the heart, and suggest that cardiac-specific miR-1 may be a useful biomarker and therapeutic target for diabetes-induced cardiomyopathy. Yang et al (99) observed that miR-505 interfered with the migration of cultured endothelial cells through targeting fibroblast growth factor 18, suggesting that miR-505 may be involved in vascular regeneration. In addition, a group of miRs (miR-92a, miR-130a and miR-195) were demonstrated to be abnormally expressed in hypertensive patients with metabolic syndrome. Notably, miR-92a is differentially expressed in the blood of hypertensive and non-hypertensive patients (100) and may promote miR-mediated intercellular communication (101). Kontaraki et al (94,95) confirmed several types of differentially expressed miRs in an animal model: Myocardial hypertrophy was induced by miR-21, miR-208b and miR-499; the anti-myocardial hypertrophy miRs comprised miR-1, miR-26b and miR-133a, of which miR-1, miR-21, miR-208b and miR-499 were upregulated, whereas miR-26b and miR-133a were downregulated in peripheral blood mononuclear cells from patients with hypertension compared with healthy controls. In patients with hypertension, the degree of left ventricular hypertrophy was negatively correlated with the miR-1 and miR-133 indices, whereas the miR-21, miR-26b, miR-208b and miR-499 indices were positively associated with left ventricular hypertrophy.

miRs associated with diabetic HF. Dickstein (102) reported that the occurrence and development of insulin resistance in HF was correlated with overactivation of the renin-angiotensin-aldosterone system (103,104), disturbance of energy metabolism in the myocardium (105), liver pathology, as well as other factors. It was previously demonstrated that the expression of miR-133 and miR-1 increased significantly in myocardial cells following hyperglycemic injury (106). IGF-1 and IGF-1 receptor are the two target genes of miR-1 (107). Previous studies demonstrated an increasing level of miR-133 and decreasing levels of miR-650, miR-222 and miR-338 in hyperglycemic cardiomyocyte injury (108,109). Greco et al (110) collected biopsies from the peri-infarctual area (border zone) and the non-ischemic remote zone from patients with diabetic HF (D-HF), non-diabetic HF (ND-HF) and the control group. miR expression was measured using RT-qPCR in left ventricular biopsies from 10 patients with D-HF and 19 patients with ND-HF affected by non-end-stage ischemic cardiomyopathy. A total of 17 miRs were revealed to be differentially expressed in patients with D-HF and/or ND-HF when compared with control subjects; in particular, miR-34b, miR-34c, miR-210, miR-199b and miR-372 were upregulated, whereas miR-650 and miR-223 were downregulated. Therefore, miRs may not only be obtained from the blood or serum, but also from tissue biopsies, when the content in the body fluids is low. Nandi et al (111) and Deng et al (112) reported that attenuation of miR-133a in diabetic hearts is associated with the induction of autophagy and hypertrophy. In conclusion, attenuation of miR-133a appears to serve a key role in D-HF and contributes to the exacerbation of diabetes-mediated cardiac autophagy and hypertrophy in patients with HF undergoing left ventricular assist device implantation. Chavali et al (113) used multiplex RT-qPCR in insulin 2 mutant Akita mouse hearts (a diabetic mouse model with heart disease) and observed marked downregulation of miR-744, miR-142-3p, miR-384-3p, miR-494, let-7a, miR-450, miR-338, miR-130, miR-142-3p, miR-148, miR-338, miR-345-3p, miR-433, miR-451, miR-455, miR-500, miR-542-3p and miR-872. By contrast, miR-295 was upregulated in Akita mouse hearts. Therefore, miR-295 may be used as a mammalian-specific miR in early embryonic stages. Increased miR-295 expression was associated with pathological changes in Akita mouse hearts. miR-223, as an anti-inflammatory miR, may reflect the progression of diabetic Ins2−/− Akita heart.
Table II. Expression of miRs in different types of heart failure.

| Author, year | Heart failure type | miR expression level | Detection means | Source | (Refs.) |
|-------------|-------------------|----------------------|----------------|--------|--------|
| Leger et al, 2013 | ICM | miR-361 ↑ in ICM group | RT-qPCR | Serum | (79) |
| Zeng et al, 2017 | ICM | miR-182 ↑ in coronary artery disease group compared with the healthy control group | RT-qPCR | Plasma/serum | (80) |
| Olson and Rooij, 2014 | ICM | miR-208 and miR-499 ↑ in ICM group | RT-qPCR | Serum | (81) |
| Fichtlscherer et al, 2010 | ICM | miR-126, miR-17, miR-92 and miR-155 ↓ in ICM | RT-qPCR | Serum and blood | (82) |
| Li et al, 2018 | ICM | miR-125a, miR-20a and miR-302d only in ICM | RT-qPCR and deep RNA sequencing | Serum | (83) |
| Li et al, 2018 | ICM | miR-20a-5p, miR-17-5p and let-7e-5 ↓ in ICM and NICM | RT-qPCR and deep RNA sequencing | Serum | (83) |
| Li et al, 2018 | ICM | miR-21-5p, miR-125b-1-3p and miR-106b-5p ↑ in ICM and NICM | RT-qPCR and deep RNA sequencing | Serum | (83) |
| Naga et al, 2017 | DCM | hsa-miR-214, hsa-miR-342, hsa-miR-125b, hsa-miR-181b and hsa-miR-145 ↑ in the DCM compared with controls | RT-qPCR | Serum | (76) |
| Naga Prasad et al, 2017 | DCM | hsa-miR-1, hsa-miR-29b, hsa-miRNA-7, hsa-miR-378 ↓ in the DCM compared with controls | RT-qPCR | Serum | (76) |
| Enes Coşkun et al, 2016 | DCM | miR-454 and miR-518f ↑ in DCM | RT-qPCR | Serum | (77) |
| Enes Coşkun et al, 2016 | DCM | miR-636 and miR-637 in the DCM | RT-qPCR | Serum | (78) |
| Miyamoto et al, 2015 | DCM | miR-137 ↑ in SHR treatment group vs. SHR control | RT-qPCR | Serum | (97) |
| Hou et al, 2016 | Diabetic heart failure | miR-137 ↑ in SHR treatment group vs. SHR control group compared with the normal control group | RT-qPCR | Serum | (98) |
| Latronico et al, 2007 | Diabetic heart failure | miR-133 ↑ in diabetic heart failure compared with control | RT-qPCR | Serum | (109) |
| Author, year       | Heart failure type | miR expression level                                                                 | Detection means | Source                                | (Refs.) |
|-------------------|-------------------|---------------------------------------------------------------------------------------|----------------|---------------------------------------|---------|
| Latronico et al., 2007 | Diabetic heart failure | Level of miR-650, miR-222 and miR-338 ↓ in diabetic heart failure | RT-qPCR         | Serum                                 | (109)   |
| Greco et al., 2012 | Diabetic heart failure | miR-650 and miR-223 ↓ in diabetic heart failure | RT-qPCR         | Body tissue                           | (110)   |
| Greco et al., 2012 | Diabetic heart failure | miR-34b-34c, miR-210, miR-199b and miR-372 ↑ in D-HF and ND-HF compared with control group | RT-qPCR         | Body tissue                           | (110)   |
| Nandi et al., 2015 | Diabetic heart failure | miR-133a ↓ in diabetic heart failure introduced by insulin2 mutant (Ins2+/61) Akita heart disease | RT-qPCR         | Serum                                 | (111)   |
| Deng et al., 2017 | Diabetic heart failure | miR-24 ↓ in diabetic heart failure | RT-qPCR         | Serum                                 | (112)   |
| Chavali et al., 2014 | Diabetic heart failure | miR-295 ↑ in Akita | RT-qPCR         | Serum                                 | (113)   |
| Chavali et al., 2014 | Diabetic heart failure | miR-126, miR-222, miR-130a, miR-142-3p, miR-148, miR-338, miR-345-3p, -miR-384-3p, miR-433, miR-450, miR-451, miR-455, miR-499, miR-500, miR-542-3p, miR-744 and miR-872 ↓ in diabetic heart failure | RT-qPCR         | Serum                                 | (113)   |
| van Solingen et al., 2012 | Diabetic heart failure | miR-126 ↓ in diabetic microvascular tissues | RT-qPCR         | Diabetic microvascular tissues | (116)   |
| Fichtlscherer et al, 2010 | Diabetic heart failure | miR-126 ↑ in patients with coronary atherosclerosis | RT-qPCR         | Serum                                 | (117)   |
| Škrha et al., 2015 | Diabetic heart failure | miR-29a, miR-1, miR-373, miR-143 and miR-20a ↓ in diabetic heart failure | RT-qPCR         | Serum                                 | (118)   |
| Škrha et al., 2015 | Diabetic heart failure | miR-195, miR-199a-3p, miR-700, miR-142-3p, miR-24, miR-21, miR-22, miR-499-3p, miR-208a and miR-705 ↑ in diabetic heart failure | RT-qPCR         | Serum                                 | (118)   |
| Li et al., 2018    | CHD                | miR-29 ↑ in patients with CHD | RT-qPCR         | Serum                                 | (83)    |
| Mukai et al., 2017 | CHD                | miR-486-3p, miR-155-5p and miR-486-5p ↑ in congenital cyanotic heart disease | RT-qPCR         | Serum                                 | (125)   |
| Mukai et al., 2017 | CHD                | miR-133a-2, let-7e-5p and miR-1260a ↓ in congenital cyanotic heart disease | RT-qPCR and microarrays | Serum                                | (125)   |
| Chen and Li, 2017 | CHD                | miR-19a, miR-198, miR-130a and miR-27b ↑ in patients with CHD | RT-qPCR         | Serum                                 | (129)   |

miR, microRNA; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; HHF, hypertensive heart failure; DCM, dilated cardiomyopathy; CHD, congenital heart disease; ICM, ischemic cardiomyopathy; NICM, nonischemic cardiomyopathy; SHR, spontaneously hypertensive rats; D-HF, diabetic heart failure; ND-HF, nondiabetic heart failure; ↓, downregulation; ↑, upregulation.
miR-1 are present in the same transcription unit (in CHD via specific protein regulation. miR-133 and abnormalities (resulting from structural or functional cardiovascular types were almost normal with deletion of either miR-133a-1 to CHD (115). The decrease of miR-126 in diabetic microvascular tissues may indicate the severity of diabetic vascular complications (116); however, the expression of miR-126 did not decrease, but was rather significantly increased in patients with coronary atherosclerosis (117). In a mouse model of type 1 diabetes mellitus established by streptozotocin (118), 15 miRs were differentially expressed in the myocardium, among which 10 miRs (miR-195, miR-199a-3P, miR-700, miR-142-3p, miR-24, miR-21, miR-22, miR-499-3p, miR-208a and miR-705) were upregulated, whereas 5 miRs (miR-29a, miR-1, miR-373, miR-143 and miR-20a) were notably downregulated. Histological examination revealed hypertrophy of the myocardial cells in type 1 diabetes mellitus group mice compared with the control group, with a disorderly arrangement and enlarged nuclei. Notably, the prediction of associated target genes primarily involves cell growth, differentiation, proliferation, collagen fiber growth, apoptosis and angiogenesis.

miRs of HF in CHD. CHD is a multi-gene genetic disease resulting from structural or functional cardiovascular abnormalities present at birth that are caused by congenital abnormalities (119). Disrupted miR expression may result in CHD via specific protein regulation. miR-133 and miR-1 are present in the same transcription unit (120); miR-1 is the most abundant miR and is highly conserved in human myocardial cells (121). Mature miR-1-1 and miR-1-2 have the same gene sequence; the miR-13 family includes miR-133a-1, miR-133a-2 and miR-133b (122,123). During heart development, the deletion or mutation of the essential gene Hand2 of muscle precursor cells in early embryonic development may lead to cardiac hypoplasia and even cardiac arrest (124). Mukai et al (125) revealed that miR-486-3p, miR-155-5p and miR-486-5p were increased in patients with cyanotic heart disease compared with those without heart disease. Furthermore, let-7e-5p and miR-1260a were decreased in patients with early-stage acyanotic heart disease compared with those without heart disease, suggesting that these miRs may be used for early diagnosis.

Zhao et al (126) reported that the expression of miR-1-2 was upregulated in myocardial and skeletal muscle cells. Overexpression of miR-1 during cardiac development may inhibit ventricular myocyte dilatation. It was also demonstrated that miR-1-2 targets the Hand2 gene, which may block Hand2 protein synthesis and regulate cardiac morphogenesis (127); its abnormal expression may even lead to CHD (127). Another study reported that the mouse phenotypes were almost normal with deletion of either miR-133a-1 or miR-133a-2, but the synchronous lack of these two miRs led to a fatal ventricular septal defect in approximately half of the mice during the embryonic period (128). Thus, miR-133 can promote myoblast proliferation, and miR-1 can stimulate myogenic differentiation. Therefore, miR-1 and miR-133 exhibit a dialectical association, and abnormalities may lead to the development of CHD.

Chen and Li (129) quantified the levels of miR-19a by RT-qPCR in the plasma of 30 patients with CHD, and changes in the levels of miR-19a, miR-130a and miR-27b were also confirmed using RT-qPCR. The levels of miR-19a, miR-198, miR-130a and miR-27b were significantly increased in patients suffering from pulmonary arterial hypertension induced by CHD. These observations suggest that circulating miR-19a may be a novel biomarker for the diagnosis of pulmonary arterial hypertension induced by CHD.

The abovementioned data summarize the differences in expression of miRs in patients with HF (including cardiomyopathy, hypertension, D-HF and CHD). Their clinical significance as HF biomarkers were analyzed (Table II).

Limitations of miRs as biomarkers of HF. Establishing an accurate, reliable circulating miR system for HF diagnosis, prognosis and prediction of response to treatment is challenging, from sample collection and processing to data analysis. First, overlapping between various failure mechanisms leads to difficulties in assessing which mechanisms underlie the expression changes in circulating miRs. Second, serum or plasma are the first choices for sample selection and handling, but the level of circulating biomarker miRs was low, which to some degree impedes the detection of miRs (130). Serum hemolysis may result in waste of samples (131). Furthermore, the serum level of miRs was higher than for circulating plasma, indicating that serum samples can prevent potential interference caused by platelets and leukocytes during sample preparation (132). Therefore, use of the same type of material and synchronous sampling is important for the patient and control groups, as well as a standard scheme to avoid sample hemolysis, minimizing differences between patient selection and classification. Third, some studies have reported fluctuation of miR levels in patients with HF following treatment (133,134). Blood samples were collected at three stages, namely prior to, during and following treatment. A fourth factor was the choice of measurement platform for miR. As indicated in Fig. 2, all research techniques have advantages and disadvantages, but the most commonly used method is RT-qPCR. This method is more sensitive and more cost-effective compared with other methods, but its primary limitation is the inability to detect new miRs. In addition, the standardization of miR expression level may be difficult, as the expression levels of miRs fluctuate with changes in physiological and pathological conditions. Therefore, standard methods are commonly used for the experiments, including the use of equal amounts of starting material (such as serum or plasma), which is more reliable for endogenous miRs for data normalization.

As observed in the present study, the clinical manifestations of HF caused by expression changes of different miRs are similar, and the changes in miR expression caused by
different types of HF may also be similar, reflecting the complexity of miR biology.

4. Conclusion

As described in Fig. 3, the expression of miR-145 was upregulated and the expression of miR-147 and miR-7 was downregulated in DCM, ultimately inhibiting cardiomyocyte apoptosis. The upregulation of miR-181 inhibited oxidative stress. Furthermore, upregulation of miR-214 and downregulation of miR-29b attenuated cardiomyocyte fibrosis, which may be a late regulatory mechanism. By contrast, upregulation of miR-155 promotes cardiomyocyte inflammation, which may be an early regulatory mechanism. The above-mentioned miRs appear to be promising potential candidate markers associated with DCM.

In ischemic HF, upregulation of miR-155 intensified cardiomyocyte inflammation and upregulation of miR-182 promoted apoptosis, which may be an early indicator of this condition. Upregulation of miR-21 alleviated apoptosis via negative feedback regulation. Thus, miR-21 may be a late-age indicator in ischemic HF.

In hypertensive HF, downregulation of miR-133 inhibited cardiomyocyte hypertrophy and promoted cardiomyocyte apoptosis, which may be a late-stage decompensation.

In D-HF, upregulation of miR-22 reduced cardiomyocyte fibrosis, apoptosis and inflammation, and downregulation of miR-455 restrained cell fibrosis, which may be a late indicator of diabetic heart failure, whereas the upregulation of miR-195 and miR-142 aggravated apoptosis and miR-451 downregulation exacerbated cardiomyocyte hypertrophy, which may be an early indicator.

In conclusion, miR-155, miR-22 and miR-133 appear to be promising markers of the development, diagnosis and prognosis of HF. However, further research is required to determine whether there is an efficient miR template for application in clinical oncology practice.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 81372150 to BHL and grant nos. nos. 91739301 and 91849102 to MH).

Availability of data and materials

Not applicable.

Authors’ contributions

MH and BHL designed and conceived the study. YMH, WWL and JW provided advice and assistance. YMH wrote the manuscript. All the authors have contributed to and approved the final version of the manuscript.
The authors declare that they have no competing interests.

Patient consent for publication
Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Cordes KR and Srivastava D: MicroRNA regulation of cardiovascular development. Circ Res 104: 724-732, 2009.
2. Anderson ME, Brown JH and Bers DM: CaMKII in myocardial hypertrophy and heart failure. J Mol Cell Cardiol 51: 468-473, 2011.
3. Yang J, Savvatis K, Kang JS, Fan P, Zhong H, Schwarz K, Barry V, Mikels-Vidal A, Karpinski S, Korneyev D, et al: Targeting LOXL2 for cardiac interstitial fibrosis and heart failure treatment. Nat Commun 7: 13710, 2016.
4. Kawakami H, Kubota Y, Takeno S, Miyazaki Y, Wada T, Hamada R and Nanashima A: Gastrointestinal: Severe congestive heart failure and acute gastric mucosal necrosis. J Gastroenterol Hepatol 32: 949, 2017.
5. Petrovic D: Cytopathological basis of heart failure-cardiomyocyte apoptosis, interstitial fibrosis and inflammatory cell response. Folia Biol (Praha) 50: 58-62, 2004.
6. Orsborne C, Chaggar PS, Shaw SM and Williams SG: The renin-angiotensin-aldosterone system in heart failure for the non-specialist: The past, the present and the future. Postgrad Med J 93: 29-37, 2017.
7. Polyakova V, Loeffler I, Hein S, Miyagawa S, Piotrowska I, Dammer S, Risteli J, Schaper J and Kostin S: Fibrosis in endstage human heart failure: Severe changes in collagen metabolism and MMP/TIMP profiles. Int J Cardiol 151: 18-33, 2011.
8. Romaine SP, Tomaszewski M, Condorelli G and Samani NJ: MicroRNAs in cardiovascular disease: An introduction for clinicians. Heart 101: 921-928, 2015.
9. Liu X, Tong Z, Chen K, Hu X, Jin H and Hou M: The role of miRNA-132 against apoptosis and oxidative stress in heart failure. Biomed Res Int 2018: 3452748, 2018.
10. Gómez AM, Valdivia HH, Cheng H, Lederer MR, Santanael LF, Cannel MC, McCune SA, Altschuld RA and Lederer WJ: Defective excitation-contraction coupling in experimental cardiac hypertrophy and heart failure. Science 276: 800-806, 1997.
11. Kumar R, Woo MA, Birrer BV, Macey PM, Fanoraw GC, Hamilton MA and Harper RM: Mammaryl bodies and fornix fibers are injured in heart failure. Neurobiol Dis 33: 236-242, 2009.
12. Neupane B, Zhou Q, Gawaz M and Gramlich M: Personalized medicine in inflammatory cardiomyopathy. Per Med 15: 127-136, 2018.
13. Diluca PV, Dias SC, Obonye N, Johnson R, Louw J and Nkambule BB: A systematic review on the protective effect of N-acetyl cysteine against diabetes-associated cardiovascular complications. Am J Cardiovasc Drugs 18: 283-298, 2018.
14. Güven Baglia A, Iğkin Gülen M, Erkan F, Ağgün F, Erkan E and Bakar C: Changes in kidney tissue and effects of erythropoietin after acute heart failure. Biotech Histochem 93: 340-353, 2018.
15. Lindner K, Haier J, Wang Z, Watson DJ, Hussey DJ and Hummel R: Circulating microRNAs: Emerging biomarkers for diagnosis and prognosis in patients with gastrointestinal cancers. Clin Sci (Lond) 128: 1-15, 2015.
16. Li R, Geng HH, Xiao J, Qin XT, Wang F, Xing JH, Xia YF, Mao Y, Liang JW and Jia XP: miR-7a/b attenuates post-myocardial infarction remodeling and protects H9c2 cardiomyoblasts against hypoxia-induced apoptosis involving Sp1 and PARP-1. Sci Rep 6: 29082, 2016.
17. Ball JP, Syed M, Maramon RO, Hall ME, Kc R, Reckelhoff JF, Yanes Cardozo LL and Romero DG: Role and regulation of MicroRNAs in aldosterone-mediated cardiac injury and dysfunction in male rats. Endocrinology 158: 1859-1871, 2017.
18. Deng W, Wang Y, Long X, Zhao R, Wang Z, Liu Z, Cao S and Shi B: miR-21 reduces hydrogen peroxide-induced apoptosis in c-kit+ cardiac stem cells in vitro through PTEF/P3K/Akt signaling. Oxid Med Cell Longev 2016: 5389181, 2016.
19. Cheng M, Wu G, Song Y, Wang L, Tu L, Zhang L and Zhang C: Cell-culture-induced suppression of the MR-21/ERK1 signaling pathway attenuates cardiac fibrosis and dysfunction. Cell Physiol Biochem 38: 1928-1938, 2016.
20. Xiao J, Pan Y, Li XH, Yang XY, Feng YL, Tan HH, Jiang L, Feng J and Yu XY: Cardiac progenitor cell-derived exosomes prevent cardiomyocytes apoptosis through exosomal miR-21 by targeting PDCD4. Cell Death Dis 7: e2277, 2016.
21. Tao H, Chen ZW, Yang JH and Shi KH: MicroRNA-29a suppresses cardiac fibroblasts proliferation via targeting VEGF-A/MAPK signal pathway. Int J Biol Macromol 88: 414-423, 2016.
22. Liu CZ, Zhong Q and Huang YQ: Elevated plasma miR-29a level are associated with increased carotid intima-media thickness in atherosclerosis patients. Tohoku J Exp Med 241: 183-188, 2017.
23. Lu Z, Wang F, Yu P, Wang X, Wang Y, Tang ST and Zhu HQ: Inhibition of miR-29b suppresses MAPK signaling pathway through targeting SPRY1 in atherosclerotic. Vascul Pharmacol 102: 29-36, 2018.
24. Sassi Y, Avramopoulou P, Ramanujam D, Grüter L, Werfel S, Giesecke S, Brunner A, Esfandaryi D, Papadopoulos AS, De Strooper B, et al: Cardiac myocyte miR-29 promotes pathology remodeling of the heart by activating Wnt signaling. Nat Commun 8: 1614, 2017.
25. Panizo S, Carrillo-López N, Naves-Díaz M, Solache-Berrocal G, Martínez-Arias L, Rodrigues-Diez RR, Fernández-Vázquez A, Martinez-Salgado C, Ruiz-Ortega M, Dusso A, et al: Regulation of miR-29b and miR-29a by vitD in myocytes. Acta Diabetologica 55: 1751-1759, 2018.
26. Heid J, Cencioni C, Ripa R, Baumgart M, Atlante S, Milano G, Scopece A, Kuenne C, Guenther E, Azzimato V, et al: Age-dependent increase of oxidative stress regulates microRNA-29 family preserving cardiac health. Sci Rep 7: 16839, 2017.
27. Chen L, Ji Q, Zhu H, Ren Y, Fan Z and Tian N: miR-30a attenuates cardiac fibrosis in rats with myocardial infarction by inhibiting CTGF. Exp Ther Med 15: 4318-4324, 2018.
28. Rosa-Afonso L, Castellano L, Mills A, Dabrowska AF, Sikkel MB, Pellegrino L, Jacob J, Frankton AE, Krell J, Coombes RC, et al: Myocardial MiR-30 downregulation triggered by doxorubicin drives alterations in β-adrenergic signaling and enhances apoptosis. Cell Death Dis 6: e1754, 2015.
29. Li J, Chen J, Zhu G, Duan X and Liu B: MicroRNA-30e mediated cardioprotection of ACE2 in rats with Doxorubicin-induced heart failure through inhibiting cardiomyocytes autophagy. Life Sci 169: 69-75, 2017.
30. van Middendorp LB, Kuiper M, Munts C, Wouters P, Maessen JG, van Nieuwenhoven FA and Prinzen FW: Local microRNA-133a downregulation is associated with hypertrophy in the dysynchronous heart. ESC Heart Fail 4: 241-251, 2017.
31. Li Q, Lin X, Yang X and Chang J: NFA1C4 is negatively regulated in miR-133a-mediated cardiomyocyte hypertrophic repression. Am J Physiol Heart Circ Physiol 298: H1340-H1347, 2010.
32. Li AY, Yang Q and Yang K: miR-133a mediates the hypoxia-induced apoptosis by inhibiting TAGLN2 expression in cardiac myocytes. Mol Cell Biochem 400: 173-181, 2015.
33. Rangrez AY, Hoppe P, Kuhn C, Zille E, Frank J, Frey N and Frank D: MicroRNA miR-199a targets a novel cardiac regulator of Cofilin-2. PLoS One 12: e0183901, 2017.
34. Dong H, Dong S, Zhang L, Gao X, Lv G, Chen W and Shao S: MicroRNA-214 exerts a Cardio-protective effect by inhibition of fibrosis. Anat Rec (Hoboken) 299: 1348-1357, 2016.
35. Chaturvedi P, Kanali A, Medina I, Fitalessa A and Tyagi SC: Cardiome mediating regulation of MMP9 in diabetic heart: Role of miR-29b and miR55 in exercise. J Cell Mol Med 19: 2153-2161, 2015.
36. Liu N, Shi YF, Diao HY, Li XY, Cui Y, Song XJ, Tian X, Li TY and Xue B: MicroRNA-15a3a regulates apoptosis induced by hydrogen peroxide in rat cardiomyoblast cells. J Int Biol Sci 13: 13-21, 2017.
Rubiś P, Totoń‑Żurańska J, Wiśniowska‑Śmiałek S, Holcman K, Moreno MU, Valencia F, de Teresa E, Díez J and González A: Relations between circulatory, J Cell Mol Med: 2018.

Meng X, Ji Y, Wan Z, Zhao B, Feng C, Zhao J, Li H and Chen: Apoptosis via regulating SGK1 in simulated myocardial infarction. Mol Med Rep 17: 2016.

Zheng L, Lin S and Lv C: MiR‑26a‑5p regulates cardiac fibroblasts proliferation and migration. J Cell Mol Med 20: 2016.

Pan L, Huang BJ, Ma XE, Wang SY, Feng J, Lv F, Liu Y, Liu Y, Li CM, Liao BD, et al: MiR-25 protects cardiomyocytes against oxidative damage by targeting the mitochondrial calcium uniporter. J Int J Mol Sci 16: 2015.

Dass S, Kohr M, Dunkerly‑Eyring B, Lee DI, Bedja D, Kent OA, Leung AK, Henao‑Mejia J, Flavell RA and Steenbergen C: Divergent effects of miR‑181 family members on myocardial function. Circ Res 117: 2015.

Khanameh AM, Alipour MR, Sheikhzadeh Hesari F and Ghadirí Soufi F: A signature of microRNA‑155 in the pathogenesis of diabetic complications. J Physiol Biochem 71: 2015.

Fang Y, Chen H, Hu Y, Li Q, Hu Z, Ma T and Mao X: Burkholleria pseudomallei‑derived miR‑3473 enhances NF‑κB via targeting TRAF3 and is associated with different inflammatory responses compared to Burkholderia thailandensis. J Hypertens 34: 2016.

Kuwabara Y, Horie T, Baba O, Watanabe S, Nishiga M, Usami S, Izuhara M, Nakao T, Nishino T, Otsu K, Izuhara M, Nakao T, Nishino T, Otsu K, et al: MicroRNA‑451 exacerbates lipotoxicity in cardiac myocytes and high‑fat diet‑induced cardiac hypertrophy in mice through suppression of the LKB1/AMPK Pathway. Circ Res 116: 2015.

Cohen‑Solal A, Beauvais F and Logeart D: Heart failure and diabetes mellitus: Epidemiology and management of an alarming association. J Card Fail 14: 615‑625, 2008.

Nargesi AA, Esteghamati S, Heidari B, Hafezi‑Nejad N, Sheikhbahaeti S, Pajouhi A, Nakjavan M and Esteghamati A: Nonlinear relation between use of cardiovascular medications and coronary heart disease in patients with type 2 diabetes or hypertension. J Hypertens 34: 974‑980, 2016.

Puntmann VO, Carr‑White G, Jabbour A, Yu CY, Gebker R, Kelle S, Hinojara R, Doltra A, Varma N, Child N, et al: T1‑mapping and outcome in nonsnomic cardiomyopathy: All‑cause mortality and heart failure. JACC Cardiovasc Imaging 9: 40‑50, 2016.

Cahill TJ, Ashrafian H and Watkins H: Genetic cardiomyopathies causing heart failure. Circ Res 113: 660‑675, 2013.

Ortega A, Roselló‑Lletí E, Tarazón E, Molina‑Navarro MM, Márquez‑Delgado C, Li J and Samper‑Gago E, Montoro‑Mateos JD, Salvador A, Rivera M and Portolés M: Endoplasmic reticulum stress induces different molecular structural alterations in human dilated and ischemic cardiomyopathy. PLoS One 9: e017635, 2014.

Yeung F, Chung E, Gowing M, Bell ML and Leinwand LA: Myh7b/mir‑499 gene expression is transcriptionally regulated by MRFs and Esos. Nucleic Acids Res 40: 7303‑7318, 2012.

Abraityte A, Lunde IG, Askevold ET, Michelsen AE, Christensen G, Aukrust P, Yndestad A, Fiane A, Andreasen A, Aukrust S, et al: Wnt5a is associated with right ventricular dysfunction and adverse outcome in dilated cardiomyopathy. Sci Rep 7: 3490, 2017.

Yamamoto S, Yamauchi T, Ikenaga O, Shimizu H, Nakajima A, Sato A, Sugiyama K, Tanaka J, et al: Apoptosis‑dependent myocardial damage by activating apoptosis without compensatory ventricular myocyte hypertrophy. J Clin Invest 111: 1463‑1474, 2003.
Changes in BNP in asymptomatic hypertensive patients reflects sub-clinical hypertrophy.

Ledwidge P, Phelan M: RNA sequencing elucidates microRNA-regulated molecular mechanisms of cardiac myopathy.

Fichtlscherer S, Markham DW, Leger KJ, Singh S, Canseco D, VonGrote EC, Karim-Ud-Din S, Miyamoto SD, Karimpour-Fard A, Peterson V, Auerbach SR, cardiomyopathy.

Ergün E, Enes Coşkun M, One 12: e0170456, 2017.

alterations in specific cardiovascular signaling networks. PLoS One 10684-10693, 2015.

Zhang Y, Kanter EM and Yamada KA: Remodeling of cardiac immune endothelial cell damage. Lupus 24: 419-432, 2015.

and cyclooxygenase inhibition is greater in women: Contributions of nitric oxide synthase activation.

miRNAs in plasma from oral lichen planus patients associate with white coat hypertension.

Kirat E, Karter Y and Ozen M: Differential expression of miRNAs in patients with coronary artery disease.

Maleszewski JJ and Redfield MM: Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation 131: 550-559, 2015.

rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation 131: 550-559, 2015.

Choi J: Is substantial renal dysfunction in patients with heart failure no longer a contraindication for RAS inhibition? The power of a large, high-quality registry to illuminate major clinical issues. Eur Heart J 36: 2279-2280, 2015.

Zhang F, Wang SC, Hsu CY, Miao Y, Martin M, Yin Y, Wu CC, Wang YT, Wu G, Chien S, et al: MicroRNA-92a mediates endothelial dysfunction in diabetic nephropathy. Am J Physiol Nephrol 29: 3251-3261, 2017.

Valdasi E, Kloter K, Bossios A, Sjöstrand M, Lee JJ and Lötjoll JO: Exosomes-mediated transfer of miRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 9: 654-659, 2007.

Wang C, Fan F, Cao Q, Shen C, Zhu H, Wang P, Zhao X, Sun X, Dong Z, Ma X, et al: Mitochondrial aldehyde dehydrogenase 2 deficiency aggravates energy metabolism disturbance and diastolic dysfunction in diabetic mice. J Mol Med (Berlin) 94: 1243-1250, 2016.

Wong TK, AlZajadi MA, Choy AM and Lang CC: Insulin resistance: A potential new target for therapy in patients with heart failure. Cardiovasc Ther 26: 203-213, 2008.

Yu XY, Song YH, Geng YJ, Lin QX, Shan ZX, Lin SG and Li Y: Glucose induces apoptosis of cardiomyocytes via microRNA-1 and IGF-1. Biochem Biophys Res Commun 376: 548-552, 2008.

Horie T, Ono K, Nishii H, Iwanaga Y, Nagao K, Kinoshita M, Kuwabara Y, Takakabe R, Hasegawa K, Kita T and Kimura T: MicroRNA-153 regulates the expression of GLUT4 by targeting KLF15 and involved in myocardial fibrosis of diabetic myocytes. Biochem Biophys Res Commun 389: 315-320, 2009.

Latronico MV, Catalucci D and Condorelli G: Emerging role of microRNAs in cardiovascular biology. Circ Res 101: 1225-1236, 2007.

Greco S, Fasanò P, Castelvecchio S, D'Alessandra Y, Arcelli D, Di Noato M, Malavazos A, Capogrossi MC, Menicanti L and Martelli F: MicroRNA dysregulation in diabetic ischemic heart failure patients. Diabetes 61: 1633-1641, 2012.

Nandi SS, Duryee MJ, Shahshah HR, Theile GM, Anderson DR and Mishra PK: Induction of angiotensin II mediates myocardial injury is associated with attenuation of miR-133a in diabetic heart failure patients undergoing mechanical unloading. Am J Transplant 7: 683-696, 2015.

Deng X, Liu Y, Luo M, Wu J, Ma R, Wao Q and Wu J: Circulating miR-199a-3p targets miR-199a-3p, miR-199a-3p and miR-199a-3p in diabetic patients with coronary heart disease and type 2 diabetes mellitus. Oncotarget 8: 63038-63046, 2017.
113. Chavali V, Tyagi SC and Mishra PK: Differential expression of dicer, miRNAs, and inflammatory markers in diabetic Ins2/-Akita hearts. Cell Biochem Biophys 68: 25-35, 2014.

114. Izarra A, Moscoso J, Cañón S, Carreiro C, Fondevila D, Martín-Caballero J, Blanca V, Valiente I, Díez-Juan A and Bernad A: miRNA-1 and miRNA-133a are involved in early commitment of pluripotent stem cells and demonstrate antiangiostatic roles in the regulation of cardiac differentiation. J Tissue Eng Regen Med 11: 787-799, 2017.

115. Liu H, Yang L, Chen KH, Sun HY, Jin MW, Xiao GS, Wang Y and Li GR: SKF-96365 blocks human ether-a-go-go-related gene potassium channels stably expressed in HEK 293 cells. Pharmacol Res 104: 61-69, 2016.

116. van Solingen C, Bijkerk R, de Boer HC, Rabelink TJ and van Zonneveld AJ: The Role of microRNA-126 in vascular homeostasis. Curr Vasc Pharmacol 13: 341-351, 2015.

117. Fichtlscherer S, De Rosa S, Fox H, Schwietz T, Fischer A, Liebetrau C, Weber M, Hamm CW, Röxe T, Müller-Ardogan M, et al: Circulating microRNAs in patients with coronary artery disease. Circ Res 107: 677-684, 2010.

118. Ľskra P, Hajer J, Anděl M, Hořínek A and Korabečná M: miRNA as a new marker of diabetes mellitus and pancreatic carcinoma progression. Cas Lek Cesk 154: 122-126, 2015 (In Czech).

119. Talmud PJ: How to identify gene-environment interactions in a multilociorial disease: CHD as an example. Proc Nutr Soc 63: 5-10, 2004.

120. Carè A, Catalucci D, Felicetti F, Bonci D, Addario A, Gallo P, Bang ML, Segnalini P, Gu Y, Dalton ND, et al: MicroRNA-133 controls cardiac hypertrophy. Nat Med 13: 613-618, 2007.

121. Wang L, Tian D, Hu J, Xing H, Sun M, Wang J, Jian Q and Yang H: MiRNA-145 regulates the development of congenital heart disease through targeting FXN. Pediatr Cardiol 37: 629-636, 2016.

122. Fang Y, Niu LL, Wei W, Zhang WY, Li XY, Cao JH and Zhao SH: A feedback circuit between miR-133 and the ERK1/2 pathway involving an exquisite mechanism for regulating myoblast proliferation and differentiation. Cell Death Dis 4: e934, 2013.

123. Liu N, Bezprozvannaya S, Williams AH, Qi X, Richardson JA, Bassel-Duby R and Olson EN: microRNA-133a regulates cardiomyocyte proliferation and suppresses smooth muscle gene expression in the heart. Genes Dev 22: 3242-3254, 2008.

124. Shan ZX, Lin QX, Deng CY, Zhou ZL, Zhang XC, Fu YH and Yu XY: Plasmid-mediated miRNA-1-2 specifically inhibits Hand2 protein expression in H9C2 cells. Nan Fang Yi Ke Da Xue Xue Bao 28: 1559-1561, 2008 (In Chinese).

125. Mukai N, Nakayama Y, Murakami S, Tanahashi T, Sessler DI, Ishii S, Ogawa S, Tokuhira N, Mizobe T, Sawa T and Nakajima Y: Potential contribution of erythrocyte microRNA to secondary erythrocytosis and thrombocytopenia in congenital heart disease. Pediatr Res 83: 866-873, 2018.

126. Zhao Y, Samal E and Srivastava D: Serum response factor regulates a muscle-specific microRNA that targets Hand2 during cardiogenesis. Nature 436: 214-220, 2005.

127. Lu CX, Gong HR, Liu XY, Wang J, Zhao CM, Huang RT, Xue S and Yang YQ: A novel HAND2 loss-of-function mutation responsible for tetralogy of Fallot. Int J Mol Med 37: 445-451, 2016.

128. Ferreira LR, Frade AF, Santos RH, Teixeira PC, Baron MA, Navarro IC, Benvenuti LA, Fiorelli AI, Bocchi EA, Stolf NA, et al: MicroRNAs miR-1, miR-133a, miR-133b, miR-208a and miR-208b are dysregulated in chronic chagas disease cardiomyopathy. Int J Cardiol 175: 409-417, 2014.

129. Chen W and Li S: Circulating microRNA as a novel biomarker for pulmonary arterial hypertension due to congenital heart disease. Pediatr Cardiol 38: 86-94, 2017.

130. Patrick DM, Montgomery RL, Qi X, Obad S, Kauppinen S, Hill JA, van Rooij E and Olson EN: Stress-dependent cardiac remodeling occurs in the absence of microRNA-21 in mice. J Clin Invest 120: 3912-3916, 2010.

131. Wang Y, Gu J, Roth JA, Hildebrandt MA, Lippman SM, Ye Y, Minna JD and Wu X: Pathway-based serum microRNA profiling and survival in patients with advanced-stage non-small cell lung cancer. Cancer Res 73: 4801-4809, 2013.

132. Hamam D, Alsaleh KA, Kassem M, Zaher W, Alfayez M, Aldahmash A and Alajez NM: Circulating microRNAs in breast cancer: Novel diagnostic and prognostic biomarkers. Cell Death Dis 8: e3045, 2017.

133. Duttagupta R, Jiang R, Gollub J, Getts RC and Jones KW: Impact of cellular miRNAs on circulating miRNA biomarker signatures. PLoS One 6: e20769, 2011.

134. Sassi Y, Avramopoulos P, Ramanujam D, Grüter L, Werfel S, Giosele S, Brunner AD, Esfandyari D, Papadopoulou AS, De Strooper B, et al: Cardiac myocyte miR-29 promotes pathological remodeling of the heart by activating Wnt signaling. Nat Commun 8: 1614, 2017.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.