

Role of microRNAs in the pathogenesis of diabetic cardiomyopathy (Review)

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Abstract. The morbidity of diabetes mellitus has been increasing annually. As a progressive metabolic disorder, chronic complications occur in the late stage of diabetes. In addition, cardiovascular diseases account for the major cause of morbidity and mortality among the diabetic population worldwide. Diabetic cardiomyopathy (DCM) is a type of diabetic heart disease. Patients with DCM show symptoms and signs of heart failure while no specific cause, such as coronary disease, hypertension, alcohol consumption, or other structural heart diseases has been identified. The pathogenesis of DCM is complex and has not been well understood until recently. MicroRNAs (miRs) belong to a novel family of highly conserved, short, non-coding, single-stranded RNA molecules that regulate transcriptional and post-transcriptional gene expression. Furthermore, recent studies have demonstrated an association between miRs and DCM. In the current review, the role of miRs in the pathogenesis of DCM is summarized. It was concluded that miRs contribute to the regulation of cardiomyocyte hypertrophy, myocardial fibrosis, cardiomyocyte apoptosis, mitochondrial dysfunction, myocardial electrical remodeling, epigenetic modification and various other pathophysiological processes of DCM. These studies may provide novel insights into targets for prevention and treatment of the disease.

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1. Introduction

According to data from the International Diabetes Federation, 382 million individuals presented with diabetes mellitus in 2013 and this number is expected to rise to 592 million by 2035 (1). As a progressive metabolic disorder, chronic complications occur in the late stage of diabetes, including atherosclerosis, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy and diabetic cardiomyopathy (DCM) (2). Among the vast array of long-term complications associated with diabetes, cardiovascular diseases account for the major cause of morbidity and mortality among the diabetic population worldwide (3-7).

The Framingham Heart Study demonstrated that diabetes was an independent risk factor of cardiovascular disease, including heart failure (8). The primary causes of diabetes-associated heart failure were believed to be coronary atherosclerosis and ischemia. However, in 1972, Rubler *et al* (9) reported autopsy data of four diabetic patients with heart failure, and no specific cause, such as coronary disease, hypertension, alcohol consumption, or other structural heart disease was identified. The authors subsequently introduced the term DCM. DCM is a newly identified disease and is considered to be completely different from coronary heart disease. Coronary heart disease usually results from atherosclerosis of the coronary artery and it is regarded as a type of macrovascular complication of diabetes. Diabetes promotes the onset and development of coronary heart disease together with numerous other factors, such as obesity, smoking and hyperlipidemia. However, the distinct features of DCM are cardiac hypertrophy and myocardial fibrosis in the absence of obvious pathogenic coronary abnormalities. It appears asymptomatic until the very late stage and left ventricular diastolic dysfunction with preserved systolic function is an early sign of DCM, while systolic dysfunction eventually occurs.

The pathogenesis of DCM is complex and has not been well understood until recently. Impaired calcium handling, altered metabolism, increased oxidative stress, remodeling of extracellular matrix (ECM), endothelial dysfunction and mitochondrial dysfunction have been found to participate in the pathogenesis of DCM (2,10-14). A number of signaling proteins and pathways have been implicated in contributing to the development of DCM, including protein kinase C, nuclear

factor- κ B, peroxisome proliferator-activated receptor α , phosphatidylinositol 3-kinase (PI3K) and mitogen activated protein kinase (MAPK) signaling pathways (15,16).

In this context, microRNAs (miRs or miRNAs) are found to be important in the pathogenesis of DCM. miRs were initially described by Lee *et al* (17) in nematodes, *Caenorhabditis elegans* in 1993. As a novel family of highly conserved, short (~18-25 nucleotides), non-coding, single-stranded RNA molecules, miRs regulate transcriptional and post-transcriptional gene expression through binding to the 3'-untranslated region (3'-UTR) of their target mRNA (3). Given that miRs are crucially involved in numerous critical biological processes, including cell proliferation, apoptosis, necrosis, migration and differentiation, dysregulated miRs contribute to various human diseases, including diabetes and cardiovascular diseases (4,18-20). miR-126, miR-17, miR-92a, miR-145, miR-155, miR-133 and miR-208a were identified to be associated with coronary artery disease; miR-1, miR-21, miR-208, miR-133a/b and miR-499 were identified as important in the pathogenesis of acute cardiac infarction. In addition, miRs associated with heart failure include miR-24, miR-125b, miR-195, miR-199a and miR-214 (20-22).

Recent studies have demonstrated an association between miRs and DCM (23-25). The expression level of miR in the hearts of patients with DCM was found to be different when compared with that of healthy individuals (25,26). Furthermore, analysis of miR expression levels in the hearts of various rat and mouse diabetic models also indicated the abnormal expression of miRNA. Further studies demonstrated that miRs contribute to numerous important pathophysiological processes of DCM, including cardiomyocyte hypertrophy, myocardial fibrosis, cardiomyocyte apoptosis, mitochondrial dysfunction, myocardial electrical remodeling and epigenetic modification (27-32). The present review discusses the possible role of miRs in the pathogenesis of DCM regarding the above-mentioned processes.

2. miR involvement in the pathogenesis of DCM

miRs in cardiomyocyte hypertrophy. Cardiomyocyte hypertrophy is one of the distinct structural features of DCM. Studies have shown that various miRs were dysregulated and contributed to the pathogenesis of cardiomyocyte hypertrophy in DCM (29,33-36). miR-30c, miR-133a, miR-150 and miR-373 were found to be downregulated in the heart of DCM, while miR-451 was found to be upregulated (29,33-36).

miR-133 is abundantly expressed in heart tissue, and is known to regulate various physiological and pathophysiological events, including non-diabetic cardiac hypertrophy (37-39). Hyperglycemia results in cardiac hypertrophy. A recent study reported that the expression level of miR-133a was reduced in cardiomyocytes treated with high levels of glucose, as well as in hypertrophic cardiac tissue samples from streptozotocin (STZ)-induced diabetic mice, and transfection of miR-133a mimics prevented altered gene expression and hypertrophic changes (33). Therefore, it was concluded that miR-133a participated in mediating glucose-induced cardiomyocyte hypertrophy in diabetes. Additionally, another study demonstrated that serum and glucocorticoid-regulated kinase 1 and insulin-like growth

factor-1 (IGF-1) receptor may be involved in this process as potential targets of miR-133a (33).

Various anti- and pro-growth signaling pathways have been demonstrated to participate in cardiomyocyte hypertrophy, including the PI3K/AKT signaling pathway. p21-activated kinases (PAKs) and cell division control protein 42 homolog (Cdc42) are components of the PI3K/AKT signaling pathway, and PAKs are effectors of Cdc42. Myocardial *Cdc42* and *Pak1* mRNA and protein expression levels were found to be significantly increased in DCM rats with cardiac hypertrophy and in high glucose (HG)-treated cardiomyocytes, which was accompanied by a significant decrease in cardiac miR-30c expression levels in DCM rats (3.73-fold), patients with DCM (2.9-fold) and in HG-treated cardiomyocytes (3.5-fold) (35). Further investigation indicated that miR-30c possessed binding sites for the 3'-UTR and open reading frame (ORF) regions of *Cdc42* and *Pak1*, and modulated *Cdc42* and *Pak1* expression levels in cardiomyocytes. In addition, miR-30c overexpression decreased HG-induced upregulation of *Cdc42* and *Pak1* and resulted in decreased expression levels of hypertrophic marker, atrial natriuretic peptide and a reduction in HG-treated cardiomyocyte cell size (35). These findings indicate that miR-30c exerts an anti-hypertrophic effect by inhibiting *Cdc42* and *Pak1* gene expression levels in DCM.

As a type of histone acetyl transferase, transcriptional co-activator, p300 has been confirmed to participate in the cardiomyocyte hypertrophy that is induced by pro-hypertrophic stimuli, particularly hyperglycemia (29). Further investigations found that the expression level of miR-150 was significantly reduced, whereas the expression level of p300 was markedly elevated, concomitant with cardiomyocyte hypertrophy, in the hypertrophic hearts of diabetic rats and in neonatal rat cardiomyocytes exposed to high levels of glucose (29). In addition, a luciferase reporter activity assay indicated that miR-150 functioned directly with the 3'-UTR of p300 and miR-150 mimics prevented glucose-induced cardiomyocyte hypertrophy (29). Thus, it was concluded that miR-150 was important in p300-mediated cardiomyocyte hypertrophy in response to hyperglycemia.

miR-373 has also been demonstrated to be involved in the pathogenesis of hyperglycemia-induced cardiac hypertrophy. It was found to be downregulated in heart samples of STZ-induced diabetic mice, and exposure of neonatal rat cardiomyocytes to glucose and transfection with miR-373 mimic demonstrated increased expression levels of miR-373 and cell size, indicating a strong involvement of miR-373 in glucose-induced cardiomyocyte hypertrophy (36). In addition, the study revealed that miR-373 was transcriptionally regulated by p38 MAPK and that its anti-hypertrophic effects may be mediated by targeting the hypertrophic protein, myocyte enhancer factor 2C (36).

Triglyceride accumulation and excess supply of saturated fatty acids, such as palmitic acid, have been implicated in the induction of cardiac hypertrophy in diabetes. miR-451 expression levels were observed to be significantly elevated in diet-induced obesity (DIO) mouse hearts with hypertrophy and in neonatal rat cardiomyocytes stimulated with palmitate (34). In addition, high-fat diet-induced cardiac hypertrophy and contractile reserves were ameliorated in cardiomyocyte-specific miR-451 knockout mice compared

Table I. miRs that are dysregulated in DCM and their roles.

Author, year	miRs	Expression	Type of model investigated	Potential targets	Role in DCM	Refs.
Chavali <i>et al.</i> , 2012; Chen <i>et al.</i> , 2014; and Feng <i>et al.</i> , 2010	miR-133a	Downregulated	Cardiac tissues of STZ-induced and Ins2 ^{+/-} Akita diabetic mice; neonatal rat myocytes exposed to high levels of glucose	SGK1 and IGF1R; TGFβ1, FGF1, CTGF	Antihypertrophic effect; regulating DNA methylation; protection against myocardial fibrosis	(27,28,33)
Duan <i>et al.</i> , 2013	miR-150	Downregulated	Hearts of STZ diabetic SD rats; HG-treated primary neonatal rat cardiomyocytes	p300	Antihypertrophic effect	(29)
Li <i>et al.</i> , 2014	miR-30d	Upregulated	Hearts of STZ-induced diabetic rats and high glucose-treated cardiomyocytes	Foxo3a	Promoting pyroptosis	(30)
Panguluri <i>et al.</i> , 2013	miR-301	Upregulated	Right ventricle and left ventricle of db/db mice	Kv4-2	Inducing depletion of repolarization reserve	(31)
Kuwabara <i>et al.</i> , 2015	miR-451	Upregulated	DIO mouse hearts; neonatal rat cardiomyocytes stimulated with palmitate	Cab39	Prohypertrophic effect	(34)
Raut <i>et al.</i> , 2015	miR-30c	Downregulated	Hearts of Wistar rats fed with HFD and low-dose STZ; cardiac tissue samples from patients with DCM; HG-treated rat cardiomyocyte cell line (H9C2)	Cdc42 and Pak1	Antihypertrophic effect	(35)
Shen <i>et al.</i> , 2011	miR-373	Downregulated	Heart samples of STZ-induced diabetic mice	MEF2C	Antihypertrophic effect	(36)
Liu <i>et al.</i> , 2014	miR-21	Upregulated	Rat cardiac fibroblasts treated with a high level of glucose	DUSP8	Promoting myocardial fibrosis	(41)
Zhao <i>et al.</i> , 2013	miR-34a	Upregulated	High glucose-treated rat cardiomyocyte H9C2 cell line	Bcl-2	Promoting apoptosis	(42)
Shan <i>et al.</i> , 2010	miR-1 and miR-206	Upregulated	Myocardium of STZ-induced diabetic rat and high glucose-treated neonatal rat ventricular cardiomyocytes	Hsp60	Promoting apoptosis	(43)
Yu <i>et al.</i> , 2008	miR-1	Upregulated	H9C2 cells exposed to high glucose	IGF-1	Inducing mitochondrial dysfunction, cytochrome c release and apoptosis	(44)
Zheng <i>et al.</i> , 2015	miR-195	Upregulated	Hearts of STZ-induced type 1 and db/db type 2 diabetic mice; high glucose-treated rat cardiomyocytes	Bcl-2 and sirtuin 1	Promoting oxidative stress, apoptosis, myocardial hypertrophy and dysfunction	(45)
Baseler <i>et al.</i> , 2012	miR-141	Upregulated	Hearts of STZ-induced diabetic Friend Virus B mice	Slc25a3	Decreasing mitochondrial ATP production	(47)

STZ, streptozotocin; SGK1, serum and glucocorticoid-regulated kinase 1; IGF1R, insulin-like growth factor-1 receptor; TGFβ1, transforming growth factor-β1; FGF1, fibroblast growth factor 1; CTGF, connective tissue growth factor; HFD, high fat diet; DCM, diabetic cardiomyopathy; Cdc42, cell division control protein 42 homolog; Pak1, p21-activated kinase 1; HG, high glucose; p300, transcriptional co-activator p300; DIO, diet-induced obesity; Cab39, calcium-binding protein 39; MEF2C, myocyte enhancer factor 2C; DUSP8, dual specific phosphatase 8; Bcl-2, B cell leukemia/lymphoma 2; Hsp60, heat shock protein 60; IGF-1, insulin-like growth factor 1; Foxo3a, forkhead box O3; Slc25a3, solute carrier family 25 member 3; Kv4.2, voltage gate potassium channel 4.2.

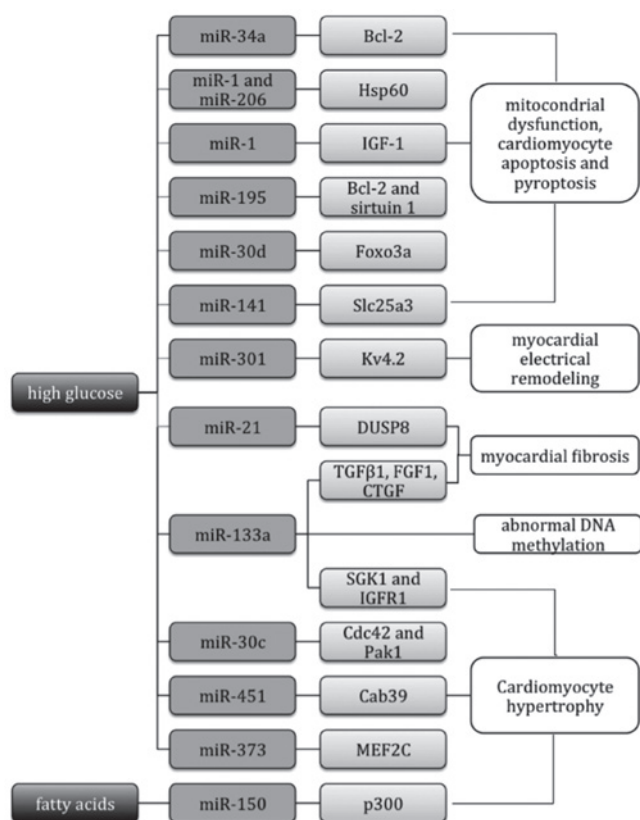


Figure 1. miRs involved in the pathogenesis of DCM. miRs participate in regulating cardiomyocyte hypertrophy, myocardial fibrosis, cardiomyocyte apoptosis, mitochondrial dysfunction, myocardial electrical remodeling and epigenetic modification via their target genes. miRs, microRNAs; Bcl-2, B-cell lymphoma 2; Hsp60, heat shock protein 60; IGF-1, insulin-like growth factor-1; Foxo3a, forkhead box O3; Slc25a3, solute carrier family 25 member 3; Kv4.2, voltage gate potassium channel 4.2; DUSP8, dual specificity phosphatase 8; TGFβ1, transforming growth factor-β1; FGF1, fibroblast growth factor 1; CTGF, connective tissue growth factor; SGK1, serum and glucocorticoid-regulated kinase 1; IGF1R, IGF-1 receptor; Cdc42, cell division control protein 42 homolog; Pak1, p21-activated kinase 1; Cab39, calcium-binding protein 39; MEF2C, myocyte enhancer factor 2C; p300, transcriptional co-activator p300.

with the control (34). As an important component of the liver kinase B1 (LKB1)/adenosine monophosphate activated protein kinase (AMPK) signaling pathway, calcium-binding protein 39 (Cab39) was identified to be a direct miR-451 target in neonatal rat cardiac myocytes. Further experiments indicated that protein expression levels of Cab39 and phosphorylated AMPK were increased and phosphorylated mammalian target of rapamycin (mTOR) was reduced in cardiomyocyte-specific miR-451 knockout mouse hearts compared with control mouse hearts, demonstrating that miR-451 was involved in DCM via suppression of the LKB1/AMPK signaling pathway (34).

miRs in myocardial fibrosis. Myocardial fibrosis is another main cause of DCM. Abnormally elevated ECM deposition, in particular collagen deposition, increases myocardial stiffness, leads to irreversible tissue damage and finally results in myocardial fibrosis (16).

In addition to cardiac hypertrophy, miR-133a was identified to be involved in the pathogenesis of diabetes-induced myocardial fibrosis. The expression level of miR-133a was decreased in the hearts of STZ-induced diabetic mice,

accompanied by an increase in the transcriptional co-activator, p300 and in major markers of fibrosis (transforming growth factor-β1, connective tissue growth factor, fibronectin and collagen 1 α1V), as well as increased focal cardiac fibrosis, as measured by Masson's trichrome stain (28). Furthermore, miR-133a overexpression prominently alleviates cardiac fibrosis as observed by assessment of major fibrosis markers and microscopic examination, indicating miR-133a as a potential therapeutic target for combatting cardiac fibrosis (28).

The peripheral blood level of miR-21 has been demonstrated as a biomarker for myocardial fibrosis (40). A recent study showed that miR-21 was upregulated in rat cardiac fibroblasts in response to high levels of glucose, accompanied by promoted fibroblast proliferation and collagen synthesis (41). In addition, dual specific phosphatase 8 (DUSP8) was identified to be a direct target of miR-21; the expression of DUSP8 was suppressed by miR-21, which promoted HG-induced cardiac fibrosis by affecting the activity of the c-Jun N-terminal kinase/stress activated protein kinase and p38 signaling pathways (41).

Thus, miR-133a and miR-21 are dysregulated by HG stimulation, leading to myocardial fibrosis in DCM. Interventions focusing on the expression levels of these miRs may result in novel concepts for improving DCM remodeling.

miRs in cardiomyocyte apoptosis and mitochondrial dysfunction. Various miRs have been demonstrated to be involved in DCM-associated cardiomyocyte apoptosis and mitochondrial dysfunction, including miR-34a, miR-1, miR-206, mi-195 and mi-30d.

High levels of glucose may induce cardiomyocyte apoptosis and thus contribute to the pathogenesis of DCM; miR-34a was found to be involved in this process. Upregulation of miR-34a expression levels and a decrease in the B cell leukemia/lymphoma 2 (*Bcl-2*) expression level were observed in the rat H9C2 cardiomyocyte cell line when exposed to HG, while apoptosis of H9C2 cells was significantly increased (42). Furthermore, treatment with miR-34a mimics significantly decreased the *Bcl-2* expression level and promoted HG-induced apoptotic changes in H9C2 cells, whereas treatment with an miR-34a inhibitor markedly increased the *Bcl-2* expression level and prevented H9C2 cell apoptosis, indicating that miR-34a was critical in the HG-induced decrease of the pro-apoptosis protein, *Bcl-2* expression level and subsequent cardiomyocyte apoptosis (42).

The molecular chaperone heat shock protein 60 (Hsp60) is an important anti-apoptotic protein, which may regulate the *Bcl-2* family. Reduced expression levels of the Hsp60 protein were observed in the diabetic rat myocardium and HG-treated neonatal rat ventricular cardiomyocytes, which was accompanied by significant upregulation of miR-1 and miR-206 (43). Further studies then demonstrated that rat miR-1 and miR-206 negatively regulated Hsp60 expression by directly targeting the 3'-UTR of Hsp60 mRNA, and miR-1 and miR-206 mediated their effects on H9C2 cell apoptosis via Hsp60 (43). These findings indicated that miR-1 and miR-206 modulate the expression of their common target, Hsp60 and consequently mediated HG-induced apoptosis of cardiomyocytes.

In addition, miR-1 was found to mediate apoptosis of HG-treated H9C2 cells through regulating another potential

target, IGF-1, which is proposed to be an anti-apoptosis factor (44). It was observed that H9C2 cells exposed to HG levels exhibited increased miR-1 expression levels, decreased mitochondrial membrane potential, increased cytochrome c release and increased apoptosis; however, these consequences were detected to be blocked by IGF-1 (44).

Another study demonstrated that the level of miR-195 expression was increased and expression levels of its target proteins (Bcl-2 and sirtuin 1) were decreased in STZ-induced type 1 and db/db type 2 diabetic mouse hearts (45). Upregulation of miR-195 in diabetic hearts was associated with oxidative stress, apoptosis, myocardial hypertrophy and dysfunction, as well as a reduction in coronary blood flow while silencing of miR-195 reduces oxidative damage, apoptosis and hypertrophy, and restores coronary blood flow in diabetic hearts, with a concurrent upregulation of Bcl-2 and *sirtuin 1*, leading to an improvement in myocardial function (45). This study validated the role of miR-195 in promoting apoptosis in the DCM heart, as well as in other pathophysiological changes (45).

Pyroptosis is pro-inflammatory programmed cell death and it is another type of cell death that is different from apoptosis or necrosis (46). HG may induce cardiomyocyte pyroptosis and miR-30d was observed to be involved in this process. It was revealed that miR-30d expression was substantially increased in STZ-induced diabetic rats, as well as in HG-treated cardiomyocytes (30). Furthermore, upregulation of miR-30d promoted cardiomyocyte pyroptosis in DCM by directly targeting forkhead box O3, which resulted in suppression of the expression of its downstream protein, apoptosis repressor with caspase recruitment domain and upregulated expression of inflammatory molecules, including caspase-1, interleukin (IL)-1 β and IL-18, and finally led to pyroptosis of cardiomyocyte (30).

Dysfunction of mitochondria also contributes to the pathogenesis of DCM and miR-141 was found to participate in this process. The expression level of miR-141 was significantly upregulated in the hearts of STZ-induced diabetic mice. Furthermore, through regulating its potential target, solute carrier family 25 member 3, which provides inorganic phosphate to the mitochondrial matrix and is essential for ATP production as an inner mitochondrial membrane phosphate transporter, overexpression of miR-141 was indicated to decrease inorganic phosphate transport and exert functional implications for mitochondrial ATP production (47).

miRs and other pathophysiological processes of DCM. miRs are also involved in the pathogenesis of DCM through participating in various pathophysiological processes, such as myocardial electrical remodeling and epigenetic modification (27,31).

A significant increase in the level of miR-301 expression and reduction of the voltage gated potassium channel, Kv4.2 expression level were observed in the diabetic (db/db mice) ventricles and miR-301 was validated to modulate Kv4.2 by direct binding on its 3'-UTR (31). Kv4.2 is important in maintaining the cardiac repolarization reserve, and the depletion of repolarization reserve was further identified in the diabetic hearts, elucidating that miR-301 mediated DCM by regulating myocardial electrical remodeling (31).

DNA methylation is an important aspect of epigenetic modification. In addition to its role in mediating myocardial hypertrophy and fibrosis, miR-133a was found to contribute to hyperglycemia-mediated DNA hypermethylation by regulating the expression levels of DNA methyl transferases, which catalyze DNA methylation. It was observed that the expression of miR-133a was attenuated while DNA methyl transferase (*Dnmt*)-1 and -3b were induced in *Ins2^{+/-}* Akita hearts, and overexpression of miR-133a inhibits, but silencing of miR-133a induces, *Dnmt*-1, -3a and -3b, demonstrating the involvement of miR-133a in the regulation of DNA methylation (27).

3. Conclusion

In conclusion, miRs are crucial in the pathogenesis of DCM by regulating cardiomyocyte hypertrophy, myocardial fibrosis, cardiomyocyte apoptosis, mitochondrial dysfunction, myocardial electrical remodeling, epigenetic modification and various other pathophysiological processes, as shown in Table I and Fig. 1. Furthermore, numerous studies have demonstrated that interventions with the expression levels of associated miRNAs may improve the pathophysiological process of DCM, providing novel insights into targets for the prevention and treatment of DCM (28,29,34,35,45). However, those studies were limited to the expression changes of miRs in heart tissue samples. To the best of our knowledge, circulating miRNAs have not yet been identified to be specifically dysregulated in DCM. Further studies and clinical observations are required to identify circulating miRs as biomarkers for early prediction and diagnosis of DCM.

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