Abstract. Diabetic cardiomyopathy (DCM) is the leading cause of death worldwide, and oxidative stress was discovered to serve an important role in the pathophysiology of the condition. An imbalance between free radicals and antioxidant defenses is known to be associated with cellular dysfunction, leading to the development of various types of cardiac disease. Nuclear factor-erythroid-2-related factor 2 (NRF2) is a transcription factor that controls the basal and inducible expression levels of various antioxidant genes and other cytoprotective phase II detoxifying enzymes, which are ubiquitously expressed in the cardiac system. Kelch-like ECH-associated protein 1 (Keap1) serves as the main intracellular regulator of NRF2. Emerging evidence has revealed that NRF2 is a critical regulator of cardiac homeostasis via the suppression of oxidative stress. The activation of NRF2 was discovered to enhance specific endogenous antioxidant defense factors, one of which is antioxidant response element (ARE), which was subsequently illustrated to detoxify and counteract oxidative stress-associated DCM. The NRF2 signaling pathway is closely associated with the development of various types of cardiac disease, including ischemic heart disease, heart failure, myocardial infarction, atrial fibrillation and myocarditis. Therefore, it is hypothesized that drugs targeting this pathway may be developed to inhibit the activation of NRF2 signaling, thereby preventing the occurrence of DCM and effectively treating the disease.

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1. Introduction

Diabetic cardiomyopathy (DCM) is widespread, as is the necrosis of the myocardium caused by diabetes mellitus (DM), and leads to cardiac microangiopathy and myocardial metabolic disorders (1). Early diastolic dysfunction is usually characterized by decreased myocardial compliance and blocked diastolic filling (2). Late diastolic dysfunction is mainly manifested as congestive heart failure (HF) (3). DCM is one of the main complications of DM, differing from hypertension and other types of cardiovascular disease, which demonstrates one of the highest incidence rates of all cardiovascular diseases with an incidence rate of 16.9% in China (4). In fact, DCM accounts for >80% of the deaths of diabetic patients (5,6).

A large number of studies have reported that the pathogenesis of DCM primarily involves mitochondrial dysfunction, impaired intracellular calcium regulation, the accumulation of advanced glycation end products in the heart, abnormal cell metabolism and endoplasmic reticulum stress (2,7). Mitochondrial dysfunction has been discovered to lead to the excessive production of reactive oxygen species (ROS), which in turn can promote the opening of mitochondrial permeability transition pores (mPTP), reduce the mitochondrial membrane potential and impede the respiratory transmission chain (8). Impaired intracellular calcium regulation has been identified to lead to impaired cardiac contractility, while the accumulation of advanced glycation end products in the heart was discovered to lead to a build up of extracellular matrix,
which in turn leads to diastolic dysfunction and eventually to functional failure (9). In addition, abnormal cell metabolism was shown to lead to the accumulation of toxic lipids in the heart, and endoplasmic reticulum stress is known to mediate cell apoptosis. It is also well known that metabolic disorders cause subcellular inflammation of the heart and inflammation is an important pathogenic feature of DM (Fig. 1) (10).

These pathologies are mainly caused by hyperglycemia, hyperlipidemia, and inflammation, which can stimulate the production of ROS or reactive nitrogen species (11). ROS are small, highly reactive molecules, also known as free radicals, which serve important roles in pathology and physiology. The role of the heart is to provide sufficient blood flow to organs and tissues to supply them with oxygen and various nutrients. The heart has high energy requirements and is prone to oxidative damage caused by physiological processes (12). The heart needs more oxygen than other organs and consumes more energy (6). It has been reported that oxidative stress served an important role in various types of cardiac disorder (13). Oxidative stress is a negative condition caused by the production of free radicals, and manifests as an imbalance of oxidation and antioxidant effects in the body (14). The higher the levels of ROS in the heart, the higher the amount of oxidative stress produced (15). ROS is considered to be responsible for systolic and endothelial dysfunction, cardiac cell apoptosis and necrosis (16). Therefore, the reduction of oxidative stress is an attractive target for the treatment of cardiac diseases.

Nuclear factor-erythroid-2-related factor 2 (NRF2) is expressed in a wide range of tissues and organs, including the heart, brain, liver, kidney and skin (17). A large number of reports have indicated that NRF2 signaling served important roles in processes, such as embryonic development, oxidative stress and ischemia/reperfusion injury (IRI) (14). NRF2 was also reported to regulate the clearance of free radicals and lipid homeostasis (18). Therefore, NRF2/antioxidant response element (ARE) signaling has become an attractive target for the treatment of DCM. The NRF2 signaling pathway is reportedly involved in DCM via the transcriptional regulation of other signaling pathways, including PI3K/AKT and JAK/STAT (19). The present review aimed to provide a comprehensive discussion of the current understanding of the regulation of NRF2-mediated signaling in the development of DCM.

2. The NRF2/Kelch-like ECH-associated protein 1 (Keap1)/ARE signaling pathway

Under the appropriate stimulation by physical and chemical factors, including inflammation, trauma and fever, NRF2 dissociates from Keap1, which permits the levels of NRF2 degradation to decrease and the simultaneous synthesis of NRF2 to increase, which subsequently facilitates NRF2 entering the nucleus, where it specifically recognizes and binds to the core sequence of AREs (20). As a result of this series of actions, multiple downstream antioxidants are activated, where the expression levels of inflammatory proteins and detoxification enzymes are upregulated (21). The transcription of these genes, including superoxide dismutase (SOD), GSH, GPX and heme oxygenase (HO-1), has been identified to suppress ROS production and reduce oxidative stress (Fig. 2) (22).

NRF2, which contains 589 amino acids, is a basic leucine zipper (bZIP) transcription factor belonging to the Cap ‘n’ Collar family that contains seven functional domains, Neh1-Neh7 (23). These structures serve an important role in regulating the stability of NRF2 (24). The bZIP structure of the Neh1 region can bind to the small Maf protein to form a heterodimer, which subsequently binds to the DNA molecule through the ARE (25). Neh2 is the region in which NRF2 binds to Keap1; the region involves the 69 to 84th amino acids of NRF2 (a short peptide of 16 amino acids), which contains an ETGE motif and a DLG motif binding site that binds to Keap1 (26). The Neh3 domain is located at the carboxy terminus and is highly conserved (27). The agonist chromatin helicase DNA binding protein 6 binds to the Neh3 domain and upregulates NRF2 target gene expression (Fig. 3) (28). The Neh4 and Neh5 domains, which are related to the 596 and 599 amino acids of NRF2, are involved in the transcriptional activation of the NRF2 target gene after binding to the coactivator CAMP-response element binding protein (CREB) (29). The Neh6 region contains a large number of serine residues, which form redox-insensitive regions. Under oxidative stress conditions, the degradation of Nr2f2 is associated with Neh6, such that Neh6 mediates B-TrCP-dependent ubiquitination of the NRF2 transcription factor so that NRF2 can be degraded (30). Finally, the Neh7 domain can inhibit NRF2 by binding to the retinoic X receptor α (31).

Keap1 is an important factor regulating the NRF2 response and a central regulator of cellular oxidative stress. Keap1 contains five domains: i) An N-terminal region domain; ii) a bric à brac (BTB) dimerization domain; iii) an intervening region (IVR) domain; iv) a theme containing the six Kelch motifs; and v) a C-terminal region domain (32). BTB, which is an evolutionarily conserved motif involved in protein-protein interactions found in actin-binding proteins and zinc finger transcription factors, usually forms a dimer with other BTB regions; this domain is required for Keap1 to dissociate from NRF2 and prevent phase II gene transcription (33). The IVR domain is rich in cysteine and contains the most active cysteine residue of Keap1; it is a functional regulatory region for the entire protein, which is involved in the reactions of electrophilic compounds and oxidants, and also participates in the formation of ubiquitination linkages to stabilize NRF2 (31). The DGR domain contains six bis-glycine repetitive sequences or six Kelch motifs; the repetitive Kelch motifs form six classical p-helices with multiple potential protein binding sites for Keap1 to bind to the Neh2 region, and this is where Keap1 also binds to cytoplasmic actin (34).

The ARE is the core protector of cytoprotective proteins, representing an important antioxidant component of the human body (35). Under reactive chemical pressure, ARE cis-acting elements function primarily at the transcriptional level to regulate the expression levels of numerous cytoprotective enzymes, including SOD and HO-1 (36). The ARE has important structural and biological characteristics and demonstrates a unique ability to respond to oxidative stress (37). It reacts not only to H2O2, but also to specific chemical compounds, and has the ability to conduct redox cycles or produce reactive or electrophilic intermediates (38). A number of compounds have a tendency to react with the sulfhydryl groups, such as diethyl maleate,
dithiothiones and isothiocyanates, which can potently induce ARE activity (39,40).

NRF2 is a key regulator of antioxidant reactions and has been demonstrated to regulate both oxidative stress and inflammation (41,42). There are two types of antioxidant systems in the body: One is the enzyme antioxidant system, which includes superoxide, SOD, catalase and glutathione S-transferase; the other system is a non-enzymatic antioxidant system, involving, for example, glutathione (43). NRF2/Keap1 signaling serves an important role in the maintenance of intracellular redox homeostasis, in addition to serving a vital role in a variety of cell types and organs in different types of oxidative damage-related cardiac disease, including myocardial ischemic disease, HF and cardiac hypertrophy (44). Numerous NRF2 activators are plant-derived phytochemicals and natural products, such as curcumin (CUR), sulforaphane (SFN) and resveratrol (RES) compounds (45), although some synthesized NRF2 activators have been identified, including hydrogen sulfate and 4-hydroxynonenal lipoic acid (46). These chemoprotective compounds protect cells from oxidative stress by mediating the NRF2 defense response, and activating phase II detoxification enzymes, transporters and antioxidants (47).

NRF2/ARE signaling has been associated with various major pathophysiological conditions, including hypoxia, ischemia, fibrosis and apoptosis (48). It is also associated with numerous signaling pathways (49). There is increasing evidence to suggest that NRF2 and PI3K/AKT are important in oxidative stress injury, where NRF2 is involved in several signaling pathways, including the NF-κB and other cytokine signaling pathways (50). Therefore, NRF2/ARE signaling is known to serve an important role in several pathological conditions.

3. NRF2 signaling and its association with DCM complications

Ischemic heart disease. Ischemic heart disease is a serious condition, which among all patients with heart disease in China the death rate can reach 60% (51). In myocardial IR, the blood supply to the heart is blocked, following which perfusion and accompanying reoxygenation resumes (52). IR occurs
in acute coronary syndrome, cardiopulmonary resuscitation, organ transplantation thrombolysis, coronary bypass and other conditions (53). Calcium and ROS were discovered to be important molecular species involved in myocardial IRI during ischemia initiation and reperfusion. Calcium has an important electrophysiological elements, which enhances myocardial vitality and participates in heartbeat, whilst ROS plays an important regulatory role during myocardial ischemia and reperfusion (39). The mPTP opening is an important mechanism of myocardial necrosis induced by IRI (22). However, due to the complicated underlying mechanisms, there are currently no effective methods for preventing myocardial IRI.

The most critical feature of myocardial IRI formation is the production of ROS (54). During perfusion in the ischemic phase, residual oxygen can still reach the tissue and produce ROS in the myocardium (55). A small amount of ROS is formed in the early stages of myocardial ischemia, but levels were found to increase sharply after 20-25 min (56). Myocardial reperfusion is extremely sensitive to large increases in ROS, which not only damage the mitochondrial respiratory chain, but also oxidize the mitochondrial inner membrane cardiolipin and inhibit respiratory chain activity (57). When ROS levels are increased, they can also induce lipid peroxidation and cardiomyocyte oxidative damage, eventually leading to apoptosis (58).

NRF2 regulates a series of antioxidant enzymes and cell oxidative stress, and it has been reported that the overexpression of NRF2 protected against IRI (59). The myocardial infarction (MI) area was demonstrated to increase, while the degree of cardioprotection decreased in NRF2 knockout mice following IR (60). Notably, following the activation of the NRF2 signaling pathway, a large number of compounds can protect the heart from IR damage (61). Similarly, reduced NRF2 activity in H9C2 cardiomyoblasts led to a decrease in cell survival under hypoxic conditions, irrelevant of whether reoxygenation occurred (62).

It has been suggested that NRF2 activity may be linked to mitochondrial function (63). NRF2 signaling controlled mitochondrial ROS production by regulating mitochondrial function, which indicated that the NRF2 signaling pathway may serve a vital role in cellular redox homeostasis (64). In clinical terms, this may lead to improved ischemic tolerance and make organs more resistant to ischemia (65). Following ischemic injury, organ transplantation and IR are beneficial for restoring blood flow (66). Although it is also worthy to note that several drugs can also be used to prevent IRI (67), as it is important to remove ROS from cardiomyocytes, the manipulation of the NRF2/Keap1 signaling pathway may represent a novel strategy for the treatment of IRI (68).

HF. HF is a pathological process in which the cardiac pump function is reduced due to myocardial contraction and/or diastolic dysfunction, resulting in a decrease in cardiac output and an inability of the heart to meet the metabolic needs of the body tissues (69). HF is considered the end point of numerous types of cardiovascular disease. Persistent, abnormal neuro-hormonal and mechanical stresses can lead to HF (70); such pathological stresses include, hypertension, cardiac fibrosis, cardiac hypertrophy and cardiomyocyte apoptosis (71). These stresses can alter the microvascular structure and ventricular dilation, ultimately leading to cardiac dysfunction and HF (12,38). However, it is common that the heart remains within the normal range of ejection fraction (72).

It was previously reported that oxidative stress accelerated the progression of HF (73). In fact, there is some experimental evidence to suggest that ROS-induced changes in the structure and function of the heart can lead to HF, which highlights that oxidative stress and myocardial function are closely related.

Figure 3. Domain structure of NRF2 and Keap1. NRF2, nuclear factor-erythroid-2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; β-TrCP, β-transducin repeat containing; NTR, N-terminal region; BTB, bric á brac; IVR, intervening region; C-terminal region; RXRα, retinoid X receptor α; Cul3, cullin 3.
NRF2 is known to be associated with the inducible expression of various antioxidant genes and other cytoprotective phase II detoxifying enzymes, and it was previously reported that NRF2 participated in the mechanism of HF (74-76). In addition, several clinical studies have identified that microRNA (miRNA/miR)-27a expression levels were upregulated in human HF (63,67,77). This is interesting as miR-27a was one of the microRNAs predicted to be a target of NRF2; however, its mechanism of action remains unknown (69,78). Therefore, it is important to further investigate the specific role of NRF2 during HF.

Cardiac remodeling. Cardiac remodeling is an adaptive process of cardiomyocytes to repeated stress in order to maintain homeostasis (79). Cardiac remodeling frequently impairs function at the level of molecules, cells, tissues and organs (80). Numerous animal and clinical studies have revealed that cardiac hypertrophy, myocardial apoptosis and interstitial collagen deposition eventually led to systolic dysfunction (81-83).

During cardiac remodeling, the loss of cardiomyocytes has been widely ascribed to necrosis, apoptosis or autophagy (80); however, fibrosis can also occur through fibroblast proliferation and extracellular matrix reorganization (84). Mitochondrial dysfunction and metabolic abnormalities were also discovered to contribute to the process of cardiac remodeling (85,86). In fatigued cardiomyocytes, calcium uptake is impaired, where calcium efflux becomes dysregulated and involves components such as sarco/endoplasmic reticulum calcium-ATPase-2a and the lysine receptor (87). Morphological changes also occur in the heart, with the shape morphing from elliptical to spherical (82). Cardiac remodeling also damages the systolic function of the heart (88).

Cardiac remodeling usually leads to left ventricular mass hypertrophy and a reduction of ejection fraction (89). It has been previously reported that ROS activated NRF2 signaling to facilitate different cardiac remodeling processes (90). Notably, the activation of the NRF2 pathway using allicin treatment was observed to prevent the development of cardiac remodeling to cardiac dysfunction (91). Oxidative stress was also discovered to be closely related to cardiac remodeling (92). In addition, antioxidants have been found to prevent cardiac remodeling and several studies have revealed that oxidative stress served a regulatory role in myocardial fibrosis (86,88,93). Therefore, NRF2 may serve as a good potential target for cardiac remodeling.

MI. MI is a type of myocardial necrosis caused by the acute and persistent ischemia and hypoxia of the coronary arteries, which occurs due to an imbalance between the oxygenated blood supply and demand (92). Every year, ~10% of patients with symptoms of acute coronary syndrome are diagnosed with acute MI worldwide (94). Necrosis was considered to be the main cause of cardiomyocyte death; however, cell apoptosis also serves an important role in the process of cell death (95). Although rapid reperfusion therapy was discovered to reduce infarct size and improve left ventricular function, reperfusion itself resulted in cell necrosis (96). IRI was also revealed to serve an important role in oxidative stress and myocardial infarction (97). During oxidative stress, large amounts of ROS are produced, which was identified to induce lipid peroxidation and convert oxidizing proteins to an inactive state, resulting in DNA damage and the exacerbation of IRI (11). Therefore, excess ROS should be eliminated as soon as possible. NRF2 is a well-known antioxidant and has been discovered to be closely related to MI (51). NRF2/Keap1 pathway is an important antioxidant defense mechanism, which is closely related to DCM heart remodeling mediated by oxidative stress (98). It has been reported that after myocardial infarction (MI), the NRF2 protein in the heart is downregulated, which leads to a decrease in the antioxidant enzymes targeted by NRF2 (91). At this stage, the human body will protect the heart tissue from further damage, so it will trigger a series of reactions to downregulate NRF2 (96). As the heart tissue continues to undergo irreversible damage, DCM will increase the transcription and activation of NRF2 (14). Therefore, if a gene target that blocks NRF2 is found, it may provide a new method for the treatment of DCM (96,98).

Cardiac hypertrophy. Cardiac hypertrophy is a relatively slow, but effective, compensatory function, which occurs mainly under long-term stress overload (99). Cardiac hypertrophy includes physiological hypertrophy and pathological hypertrophy (100). Physiological hypertrophy occurs mainly in healthy individuals, pregnant women and individuals pursuing long-term high intensity training and it is a reversible condition; however, pathological hypertrophy is a compensatory response (101). Different stimuli can provoke different types of cardiac hypertrophy, including persistent stress overload (hypertension), excessive volume overload (arteriovenous shunt) and genetic mutations (cardiomyopathic hypertrophy) (102).

Cardiomyocytes can enhance myocardial contractility to a certain extent under the stimulus of various outside factors, including myocardial ischemia and septic shock (103). When a stimulus persists, the compensatory mechanisms of the myocardial cells become decompensated, and eventually HF develops (80). Cardiac hypertrophy has been strongly linked to HF and cardiac death, indicating that preventing cardiac hypertrophy may be of utmost importance (53). Previous studies revealed that oxidative stress activated cardiac hypertrophy and other pathways including PI3K/AKT, NRF2/ARE signaling (104). Notably, upon the knockdown of NRF2 expression, angiotensin II-induced cardiac hypertrophy was exaggerated and the degree of oxidative stress in the heart was exacerbated (105). Other previous studies have indicated that endogenous antioxidants, such as HO-1, protected against cardiac hypertrophy (22,68). For example, in hypertension model rats, an increase in HO-1 effectively reduced left ventricular hypertrophy (106-108).

Myocarditis. Myocarditis can be caused by viral, bacterial or parasitic infections, or by noninfectious factors, including trauma and drugs (41). Therefore, myocarditis is a common infectious or non-infectious myocardial immunopathological process (109). Acute viral myocardial inflammatory injury without clinical symptoms and chronic myocarditis were discovered to lead to immune-mediated myocardial damage and dysfunction (110). Importantly, myocarditis is a precursor lesion of DCM and may develop into DCM. It has been
reported that ROS and oxidative stress were involved in the pathogenesis of myocarditis (78). ROS and oxidative stress are associated with innate and adaptive immunity and tissue repair (73).

Persistent myocardial inflammation causes myocardial remodeling, which eventually develops into DCM. This leads to the release of cytokines, causing an inflammatory response. Histamine was discovered to increase the susceptibility of mice to autoimmune myocarditis (111). In addition, the activation of cytokines, such as TGFs, activated the intracellular signaling protein SMAD cascade, increased probiotic factors, pathological fibrosis and myocardial remodeling, and decreased cardiac function, all of which lead to progressive HF (112). ROS was also identified to directly alter cardiac contractility; it has also been associated with cardiac depression in acute inflammation other than chronic myocarditis (113).

NRF2 is an important regulator of antioxidant reactions, which regulate oxidative stress (12). Several natural compounds, such as CUR, have antioxidant properties (53). CUR was discovered to regulate specific transcription factors, such as NRF2, which subsequently regulated free radical scavenging and the expression of lipid homeostasis (102). The induction of the activity of antioxidative enzymes has been attempted using gene therapies and nanotechnologies (39). However, there is a lack of clinical evidence for this effect (71,114). The clinical efficacy has not been established in human myocarditis, therefore, further research remains to be undertaken. Although additional studies are required, NRF2 may serve a vital role in myocarditis.

4. Natural substance therapies for DCM

Oxidative stress, and hence antioxidants, have been illustrated to serve an important role in the pathogenesis of DCM (82). NRF2 and its downstream signaling pathways have been reported to have a key role in preventing DCM and other cardiovascular events induced by high glucose (69). In addition, it was demonstrated that natural or synthetic NRF2 activators had a therapeutic role in DCM model animals (54). Therefore, NRF2 is considered to be a target for the treatment of DCM.

CUR. CUR is a naturally occurring polyphenol isolated from the turmeric plant (115); it has been discovered to contain antioxidants, anti-inflammatory agents and anti-cancer agents, in addition to exerting anti-diabetic activity (65). In streptozocin (STZ)-induced diabetic model mice, CUR intervention was identified to reduce blood glucose levels (116). Using malondialdehyde and NAD(P)H quinone dehydrogenase 1 (NQO1) as indicators, CUR was also reported to inhibit myocardial oxidative stress by upregulating NRF2 in type 1 DM (T1DM) model rats (45). The upregulation of the endogenous antioxidant gene NRF2 also inhibited hyperglycemia-induced inflammation, macrophage infiltration, diabetic-induced cardiac dysfunction, endoplasmic reticulum stress, oxidative stress injury and apoptosis (117).

SFN. As an isothiocyanate, SFN is widely found in cruciferous vegetables, especially broccoli (118). SFN was discovered to be an activator of the transcription factor NRF2, and it was observed to reduce the oxidative damage caused by DCM and improved cardiac function in T1DM model mice (119). SFN was also identified to effectively prevent cardiac enlargement and cardiac dysfunction in type 2 DM model mice by upregulating the expression levels of NRF2 and the subsequent expression levels of the downstream genes, HO-1 and NQO1, and significantly reducing the myocardial inflammatory response, fibrosis and oxidative damage (120).

RES. RES is a polyphenolic substance widely present in plants, including grape skins, nuts and knotweed (121). It was shown to have antioxidative stress and antihypertensive effects in T1DM model rats (122). RES was found to attenuate cardiac dysfunction, cardiac hypertrophy and myocardial fibrosis (123). By detecting various indicators of oxidative stress in the heart, it was also illustrated that RES significantly reduced the degree of oxidative stress damage caused by DM (124). RES also reduced oxidative stress and inhibited the cardiac hypertrophy and vascular fibrosis caused by connective tissue growth factor by upregulating NRF2 expression levels and the transcriptional activity of its downstream target genes (125).

DMF. DMF is an oral drug used for the treatment of adult multiple sclerosis and in Europe for the treatment of psoriasis (126). In both human and animal experiments, it was demonstrated that DMF effectively activated NRF2 and promoted its downstream antioxidative stress activity (127). In mice with T1DM, the measurements of the antioxidant enzymes, SOD, HO-1 and other indicators, suggested that DMF significantly inhibited the levels of oxidative stress in the DCM myocardium by reducing the source of free radicals and increasing the expression of enzymes and proteins involved in oxidative stress (128). Another previous study also revealed that the protective effect of DMF on DCM was related to the upregulation of NRF2 and the expression of downstream antioxidant genes in the cardiomyocytes of T1DM model mice (129).

Rutin. Rutin is a medicinally active ingredient of a flavonoid plant that exerts strong pharmacological activity and low toxicity (130). Rutin reportedly promoted vasodilation, the antagonization of platelet activating factor, anti-inflammatory and anti-oxidative processes, and the protection of the pancreas (131). It was reported that rutin may also reverse diabetic myocardial injury (78). In STZ-induced diabetic model mice, the levels of serum myocardial enzymes and other indicated were recorded, and hematoxylin and eosin and Masson's trichrome staining were performed, and rutin was illustrated to reduce the serum myocardial enzyme content, improve the pathological morphology of myocardial cells, reduce the degree of fibrosis and alleviate myocardial injury in mice with DCM (132).

5. miRNAs as a novel drug therapy for DCM

miRNA is a type of endogenous, non-coding single-stranded RNA, which participates in numerous physiological processes, including angiogenesis, metabolism, cell growth, survival and death, proliferation and differentiation (133). miRNA can negatively regulate gene expression by
promoting the degradation, and inhibiting the translation, of target RNA (134). Notably, the dysregulation of miRNA biological mechanisms has been shown to promote a variety of diseases, including DCM (135). For example, miR-1 was found to be abundant in the diabetic myocardium, where it promoted ROS production and the decline in mitochondrial membrane potential, whilst upregulating Bax expression levels and inhibiting Bcl-2 expression levels, thereby promoting cardiomyocyte apoptosis (136). Similarly, Dludla et al (137) suggested that inhibiting the expression levels of miR-1 had a protective effect on the myocardium in patients with diabetes.

As one of the important downstream components of p53-mediated cell signal transduction pathways, miR-34b was discovered to serve a proapoptotic role in patients with DM complicated with HF (138,139). It has been reported that p53 is a target of miR-30c and miE-181a (124). In addition, in another previous study, the downregulation of miR-30c and miR-181a in DCM was closely related to the activation of the p53 pathway in cardiomyocyte apoptosis (140).

During the course of DM, miRNAs have been discovered to be involved in numerous aspects of DCM pathogenesis, including apoptosis, fibrosis, hypertrophy, mitochondrial dysfunction and epigenetic modifications (141). Therefore, it is hypothesized that miRNAs may serve an important role in the pathophysiological processes of DCM. Further research into miRNAs has the potential to provide new perspectives into the prevention and treatment of DCM.

6. Conclusions

Oxidative stress is known to serve a significant role in DCM. Therefore, signaling via the NRF2/Keap1/ARE pathway may represent a novel drug target for the treatment of DCM. In addition, research into the relationship between miRNA and DCM has far-reaching clinical significance. Thus, the role of miRNA in the pathophysiology of DCM must be further clarified to be applied in clinical practice.

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Authors’ contributions

XW and JL wrote the manuscript, reviewed the draft; and LH was responsible for analyzing the literature and reviewing drafts of the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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