LncRNAs and miRs as epigenetic signatures in diabetic cardiac fibrosis: new advances and perspectives

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Abstract

Purpose Diabetes-induced diabetic cardiomyopathy (DCM) is a serious cardiac complication of diabetes, which further lead to heart failure. It is known that diabetes-induced cardiac fibrosis is a key pathogenic factor contributing to pathological changes in DCM. However, pathogenetic mechanisms underlying diabetes cardiac fibrosis are still elusive. Recent studies have indicated that noncoding RNAs (ncRNAs) play a key role in diabetes cardiac fibrosis. The increasing complexity of epigenetic regulator poses great challenges to our conventional conceptions regarding how ncRNAs regulate diabetes cardiac fibrosis.

Methods We searched PubMed, Web of Science, and Scopus for manuscripts published prior to April 2018 using keywords "Diabetic cardiomyopathy" AND "diabetes cardiac fibrosis" OR "noncoding RNAs" OR "long noncoding RNAs" OR "microRNAs" OR "epigenetic". Manuscripts were collated, studied and carried forward for discussion where appropriate.

Results Based on the view that during diabetic cardiac fibrosis, ncRNAs are able to regulate diabetic cardiac fibrosis by targeting genes involved in epigenetic pathways. Many studies have focused on ncRNAs, an epigenetic regulator deregulating protein-coding genes in diabetic cardiac fibrosis, to identify potential therapeutic targets. Recent advances and new perspectives have found that long noncoding RNAs and microRNAs exert their own effects on the progression of diabetic cardiac fibrosis.

Conclusion We firstly examine the growing role of ncRNAs characteristics and ncRNAs-regulated genes involved in diabetic cardiac fibrosis. Then, we provide several possible therapeutic strategies and highlight the potential mechanisms in which targeting epigenetic regulators are considered as an effective means of treating diabetic cardiac fibrosis.

Keywords Diabetic cardiac fibrosis · Epigenetic · Noncoding RNA · Long noncoding RNA · MicroRNAs

Abbreviations

α-SMA α-smooth muscle actin
AGO Argonaute
RAAS Renin–angiotensin–aldosterone system
LncRNA Long noncoding RNA
ECM Extracellular matrix
miRs MicroRNAs
MI Myocardial infarction
ncRNAs noncoding RNAs
MMP Matrix metalloproteinases
DM Diabetes mellitus
TRBP TAR RNA binding protein
DCM Diabetic cardiomyopathy
EndMT Endothelial mesenchymal transition
pre-miR precursor miR
TGF-β Transforming growth factor beta
UTRs untranslated regions
pri-mRNA primary mRNA
RNase III ribonuclease III
DGCR8 DiGeorge syndrome critical region gene 8
Introduction

Diabetes mellitus (DM) is a heterogeneous group of disorders characterized by hyperglycemia and may impair numerous organs and functions of the organism [1]. There are two main forms of diabetes, type I and type II [2]. Under normal conditions, insulin stimulates the uptake of glucose into cardiac muscles, adipose tissue and other metabolic tissues to maintain glucose homeostasis [3]. However, decreased insulin signaling or insulin resistance combined with the associated diminution in glucose transport, accelerates an increase in pancreatic production of insulin that leads to hyperinsulinemia [4]. Insulin resistance and hyperinsulinemia are linked to the cardiometabolic syndrome, promoting to cardiovascular diseases [5]. Diabetic cardiomyopathy (DCM) is a serious complication of diabetic cardiovascular disease that accounts for more than half of diabetes-related morbidity and mortality cases [6]. Hyperglycemia and hyperlipidemia in DM results in cardiac dysfunction, metabolic disturbances and cardiac extracellular matrix (ECM) remodeling, which finally causes DCM [7]. Meanwhile, numerous studies have examined biopsies from patients with heart failure and noticed that diabetes was associated with the accentuation of fibrosis changes [8]. Thus, diabetes-induced cardiac fibrosis is a key pathogenic factor for pathological changes in DCM [9].

Although strict glycemic control appears to play a key role in the prevention and treatment of DCM, new therapeutic agents are still highly demanded, especially for drugs designed to ameliorate diabetic cardiac fibrosis [10]. Based on these findings, we undoubtedly believe that it is necessary to understand pathogenesis of diabetic cardiac fibrosis. Metabolic dysfunctions resulted from diabetes, such as hyperglycemia, hyperinsulinemia and increased cytokines, alter multiple molecular signaling pathways within the cardiomyocytes, which impair myocardial contractility and accelerate myocyte and cell dysfunction [11]. The exact mechanisms of diabetic cardiac fibrosis are still unclear. Numerous studies have revealed that lots of non-coding RNAs (ncRNAs), such as microRNAs (miRs) and long ncRNAs (LncRNAs), were identified as biologically functional ncRNAs, which had a significantly positive impact on diabetic cardiac fibrosis [12]. All ncRNAs together lead to common changes of diabetic cardiac fibrosis [13]. This review focuses on the role of ncRNAs acting as epigenetic regulators in diabetic cardiac fibrosis (Fig. 1). We furnish an outline of the recent comprehension of LncRNAs and miRs, which has been discovered to have pathological roles in diabetic cardiac fibrosis, and we show a new perspective on targeting LncRNAs and miRs as a new approach for diabetic cardiac fibrosis treatment.

Overview of diabetic cardiac fibrosis

It is well known that DCM can induce changes in cardiac structure, such as, cardiac fibrosis, hypertrophy and ECM deposition [14]. Early pathological changes in diabetic cardiac function are characterized by abnormal diastolic function and with time it will progress into a loss of contractile function [15]. Type 1 and type 2 diabetes is both related to cardiac fibrosis that may decrease cardiac compliance, and therefore promote the pathogenesis of atrial fibrillation and heart failure events [16].
fibrosis is mediated by activated cardiac fibroblasts (CFs), but may also comprise fibrogenic actions of cardiomyocytes and vascular cells [17]. The molecular mechanisms of diabetic cardiac fibrosis are still elusive.

Numerous clinical studies have indicated that the occurrence of diabetic cardiac fibrosis came independently of hypertension or coronary atherosclerosis [18]. Diabetic cardiac fibrosis is related to ECM proteins deposition, in particular collagen I and III, which exists in the left and right ventricles under both type 1 and type 2 diabetic conditions [19]. The cardiac tissue contains lots of non-cardiomyocytes, especially CFs [20]. Although CFs are the primary mediator of myocardial fibrosis in the diseased heart, other category of myocardial cells may also involve in modulating CF phenotype and functions [21].

In fibrotic cardiac tissue, CFs undergo myofibroblast transdifferentiation, increased expression of α-smooth muscle actin (α-SMA), synthesizing and remodeling newly created ECM [22]. Acute inflammation that follows the infarct induces production of inflammatory mediators, matrix-degrading activity, proliferation, migration of CFs, and fibroblasts-to-myofibroblasts transdifferentiation [23]. Therefore, exploring the potential molecular mechanisms of diabetic cardiac fibrosis is of great clinical and therapeutic significance. In this article, we offer an overview of available evidence to support the new idea that epigenetic mechanisms, such as LncRNAs and miRs, play key roles in the development of diabetic cardiac fibrosis.

Epigenetic mechanisms and roles of ncRNAs in gene regulation

In recent years, a large number of publications have focused on the area of epigenetic signatures in the gene regulation and numerous functions of a given biological system [24, 25]. Common and highly interdependent epigenetic mechanisms that are closely associated with gene expression include DNA methylation, post-transcriptional histone modifications and regulatory ncRNAs [26]. The dynamic interplay among these epigenetic mechanisms regulates chromatin remodeling and consequently can alter the expression status of large numbers of transcription factors and signal transduction molecules [27]. In this review, we focus our attention on the most extensively characterized subfamily of ncRNAs, including miRs and LncRNAs, as they have been thoroughly studied among epigenome components in the context of diabetic cardiac fibrosis.

By utilizing new high-throughput and high-resolution technologies, such as deep-transcriptome sequencing, scientists have found that complex genomes cause ncRNAs emerge [28]. NcRNAs act as key regulators of physiological programmes in biological process such as differentiation, proliferation, etc. Moreover, it has been proven that diabetic cardiac fibrosis is associated with mutation and dysregulation of ncRNAs [29]. NcRNAs are a large cluster of RNAs that do not encode proteins, but have multiple functions in controlling gene expression [30]. LncRNAs and miRs are two types of important RNA and both of them possess regulatory functions: LncRNAs (>200 nucleotides) and miRs (about 22 nucleotides) [31].

MiRs is a class of small ncRNAs, which binds to the 3' or 5'-untranslated regions (UTRs) of mRNA, through complementary base pairing, and thus mediates post-transcriptional gene silencing by inhibiting protein translation or targeting mRNA degradation [32] (Fig. 2). Basically, there are two pathways involved in the miR biogenesis. First, in the canonical pathway, the genes (DNA) coding intergenic miR in the nucleus are transcribed into primary miRNA (pri-miRNA) by polymerase II and pri-miRNA is further recognized and cleaved at the distal stem portion by ribonuclease III (RNase III) endonuclease-Drosha, together with its essential cofactor DiGeorge syndrome critical region gene 8 (DGCR8) into a shorter hairpin called precursor miR (pre-miR) [33]. Pre-miR is subsequently exported into the cytoplasm from nucleus by transport factors Exportin 5 and Ran-GTP, and cleaved by RNase III endonuclease Dicer, associated with a protein activator of the interferon-induced protein kinase (PACT), double-stranded RNA binding protein and TAR RNA binding protein (TRBP) into a double-stranded miR, with only 20–22 nucleotides [33]. Subsequently, the miR duplex is loaded into argonaute (AGO) proteins such as AGO2 for the formation of the RNA-induced silencing complex (RISC)
LncRNAs have connection with diabetic cardiac fibrosis. LncRNAs affect genes on chromosomes other than the ones LncRNAs have been found to regulate epigenetic and cellular processes through various mechanisms [39]. Similar to mRNAs, most LncRNAs are transcribed by RNA polymerase II, utilize common consensus splicing signals, and are oftentimes polyadenylated [40]. Moreover, it is demonstrated that LncRNAs control RNA interactions and chromatin structure, such as the miR sponge, which increases protein expression by inhibiting the binding of miRs to their targets [41]. A number of functions caused by LncRNAs have been ascribed to their roles in decoys, guides, signals or scaffolds [42]. LncRNAs can exert cis- or trans-acting effects on gene expression [43]. Cis-acting LncRNAs silence or activate the expression of genes located on the same chromosome, whereas trans-acting LncRNAs affect genes on chromosomes other than the ones from which they are transcribed and regulate gene expression through recruiting proteins to target sites or sequestrating transcription factors away from target sites of transcription [44] (Fig. 3). Studies have revealed that LncRNAs have connection with diabetic cardiac fibrosis [45]. Role of LncRNAs and miRs is also emerging in diabetic cardiac fibrosis. In this review, we made an overview on new discoveries of the molecular functions of miRs and LncRNAs in cellular pathways associated with diabetic cardiac fibrosis, and potential therapeutic approaches to regulate ncRNAs in diabetic cardiac fibrosis.

### LncRNAs as epigenetic signature in diabetic cardiac fibrosis

LncRNAs regulate gene expression through their scaffolding activity toward chromatin-modifying proteins and recruiting these proteins to target loci by cis-regulation or trans-regulation [46]. These interactions occur via affecting the nuclear structure [47]. LncRNAs are a mechanism of epigenetics, which is a term describing the study of heritable changes in genomes and they affect gene expression independent of changes in DNA genome sequence [48].

Interleukin-17 (IL-17) plays an important role in the pathogenesis of cardiac interstitial fibrosis. Ablation of IL-17 alleviated cardiac interstitial fibrosis and improved cardiac function via inhibiting LncRNA-AK081284 in diabetic mice [49]. Moreover, LncRNA ANRIL is located on human chromosome 9 (p21.3) and transcribed in the opposite direction to the INK4b-ARF-INK4a gene cluster. ANRIL regulates functional and structural alterations in the DCM through controlling the expression levels of ECM proteins and VEGF (Vascular endothelial growth factor) [50]. What’s more, LncRNA myocardial infarction-associated transcript (MIAT) overexpression could counteract the inhibitory effect of miR-22-3p on DAPK2 [51]. Moreover, MIAT knockdown was found to reduce DAPK2 expression and inhibit apoptosis in cardiomyocytes exposed to high glucose (HG). MIAT may function as a competing endogenous RNA to upregulate DAPK2 expression by sponging miR-22-3p, which consequently leads to cardiomyocyte apoptosis involved in the pathogenesis of DCM [51].

Activated CFs play key roles in diabetic cardiac fibrosis [52]. LncRNA H19 and miR-455 on cardiac fibrosis-associated ECM protein are synthesized in CFs [53]. Among these aberrantly expressed miRs, miR-455 was significantly downregulated in diabetic mouse myocardium and Ang II-induced CFs [53]. Loss- and gain-of-function experiments demonstrated that the expression of miR-455 level was negatively correlated with collagen I and III expression in Ang II-induced CFs [53]. MiR-455 targeted connective tissue growth factor (CTGF) and H19 with complementary binding sites at the 3’-UTR. Moreover, H19 knockdown could enhance the antifibrotic role of miR-455 and attenuate the CTGF expression, and then further decrease fibrosis-associated protein synthesis (collagen I, III and α-SMA) [53]. Keshervani et al. found that H19 LncRNA was
Apoptosis and improves left ventricular function [60]. LncRNA MALAT1 decreases diabetic rats cardiomyocyte end-diastolic volume ratio [58]. LncRNA MALAT1 is directly associated with LV (Left ventricular) mass to LV enriched differentiation-associated LncRNA (SENCR) were related to grade I diastolic dysfunction [58]. MIAT, smooth muscle and endothelial cell- 

Increased but LncRNA Neat1 was decreased in Akita mice DCM [54]. Moreover, LncRNA H19 inhibits apoptosis by epigenetically silencing of DIRAS3 in DCM [55]. Furthermore, LncRNA H19/miR-675 axis regulates cardiomyocyte apoptosis by targeting VDAC1 in DCM [56].

Contractile dysfunction is a feature of DCM [57]. LncRNAs are regarded as a biomarker of subclinical cardiac abnormalities in type 2 diabetes. It has been shown that long intergenic ncRNA predicting cardiac remodeling (LIPCAR) was inversely associated with diastolic function. LIPCAR was positively related to grade I diastolic dysfunction [58]. In addition, MIAT, smooth muscle and endothelial cell-enriched differentiation-associated LncRNA (SENCR) were directly associated with LV (Left ventricular) mass to LV end-diastolic volume ratio [58]. LncRNA MALAT1 is involved in DCM development [59]. Downregulation of LncRNA MALAT1 decreases diabetic rats cardiomyocyte apoptosis and improves left ventricular function [60].

Therefore, studies have demonstrated that LncRNAs may act as key regulators of diabetic cardiac fibrosis signaling pathways (Fig. 4). LncRNAs may sustain cell function and enhance their viability and motility, which are linked to clinically relevant fibrosis that could be used to predict diabetic cardiac fibrosis behavior (Table 1).

### MiRs as epigenetic signature in diabetic cardiac fibrosis

MiRs are a large class of noncoding, single-stranded, small RNA molecules [61]. MiRs, DNA methylation and histone modifications are the general mechanisms of epigenetic, which is a term describing the study of heritable changes in genomes, and they affect gene expression independently of changes in DNA genome sequence [62]. More than one-third of the genes can be regulated by miRs. MiRs bind to the 3'-UTR of its mRNA target, in view of a partial base-pairing complementarity [63]. Translation of mRNA is ultimately prevented either by transcript degradation or the inhibition of translation, thus leading to the decrement of proteins [64]. Cardiac miRs are a recently discovered key modulator of gene expression in hearts and they have been shown to contribute to both transcriptional and post-transcriptional regulation in DCM and cardiac fibrosis [65]. Both alterations in the synthesis of miR and levels of specific miR have been shown to play critical roles in cardiac remodeling and the progression of diabetic cardiac fibrosis.

In addition, miRs can affect other epigenetic changes and result in modulating gene modification and expression [66]. Under HG condition, miR-mediated signals can be transferred to other cells or tissues. MiR-155 has been determined as a regulatory factor in fibrosis diseases [67]. Significantly, miR-155, a potent promoter of M1 polarization, can be enhanced in macrophages and hearts by ovarietomy [68]. Through tail vein injection of miR-155-AuNP, in which thiol-modified antago-miR-155 was covalently conjugated with gold nanoparticle (AuNP), it was discovered that nucleic acids were preferentially delivered into macrophages via phagocytosis [68]. In vivo, delivery of antago-miR-155 reduced cell apoptosis and restored the cardiac function accompanied with an increased M2 ratio and a reduced inflammation. The restoration efficacy of miR-155-AuNP was much better than general macrophage depletion by clodrosome [68]. Moreover, miR-155 deficiency could protect diabetic cardiac fibrosis in mice and attenuate collagen synthesis in CFs [69]. MiR-155 exerts its regulatory effects on cardiac fibrosis through the transforming growth factor beta 1 (TGF-β1)/(SMAD family member 2, Smad2) signaling pathway [69]. Furthermore, intramyocardial delivery of BMPCs (Bone marrow progenitor cells) in infarcted diabetic db/db mice significantly

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**Table 1** Molecular alterations of LncRNAs in DCM

<table>
<thead>
<tr>
<th>DCM pathogenesis</th>
<th>Relevant molecular target</th>
<th>Target cells</th>
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<td></td>
<td>H19</td>
<td>Cardiomyocytes</td>
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![Fig. 4 LncRNA-mediated diabetic cardiac fibrosis through epigenetic mechanisms. LncRNAs are at the diabetic heart of developmental regulation, determining the epigenetic status and transcriptional network. Important alterations are encompassing epigenetic changes controlled by LncRNAs, and interfere with epigenetic processes in a targeted manner in the treatment of diabetic cardiac fibrosis](image-url)
downregulated pro-fibrotic miR-155 in myocardium and improved cardiac remodeling and its function [70]. Apart from that, inhibition of paracrine factor hepatocyte growth factor (HGF) signaling in vivo suppressed the BMPC-mediated inhibition of miR-155 expression and the associated protective effect on cardiac fibrosis and function [70]. In vitro studies confirmed that the conditioned medium of BMPC inhibited miR-155 expression and pro-fibrotic signaling in mouse CFs under diabetic conditions [70].

Hyperglycemia plays a crucial role in the pathogenesis of diabetic complications [71]. Endothelial cells are known to contribute to cardiac fibrosis through endothelial–mesenchymal transition (EndMT) under HG stimulation [72]. By using HAVECs (Human aortic valvular endothelial cells), we revealed that miR-18a-5p regulated HG-induced EndMT [73]. Moreover, HG levels induced Notch2 expression, which would promote EndMT [73]. Furthermore, Notch2 was identified as a target of miR-18a-5p. Therefore, the upregulation of miR-18a-5p could decrease Notch2 expression and subsequently suppress EndMT [73].

CircRNAs (Circular RNAs) plays multiple roles in the pathogenesis of cardiovascular diseases, including diabetic cardiac fibrosis. CircRNA_010567 was significantly increased in diabetic mice myocardium and Ang II-induced CFs [74]. CircRNA_010567, sponge miR-141 and miR-141 directly targeted TGF-β1 [74]. Therefore, circRNA_010567 silencing could increase miR-141, reduce TGF-β1 expression, and suppress cardiac fibrosis-associated ECM protein deposition in CFs [74].

Interestingly, downregulation of miR-15a/b preceded the development of diastolic dysfunction and fibrosis in type 2 diabetic mouse hearts [75]. Therapeutic restoration of miR-15a and -15b in HL-1 cardiomyocytes reduced the activation of pro-fibrotic TGF-βR1, CTGF and the expression of pro-senescence p53 protein, which confirmed causal regulation of these fibrosis and senescence mediators by miR-15a/b [75]. Moreover, conditioned medium (CM) collected from cardiomyocytes treated with miR-15a/b markedly diminished the differentiation of diabetic human CFs [75].

To analyze the role of endothelial miR-146a in mediating fibrosis and inflammation in DCM. The expression of ECM proteins and inflammatory markers were increased in hearts of diabetes wild-type mice [76]. In vitro studies showed that glucose promoted the expression levels of the inflammatory cytokines and specific NF-κB (Nuclear factor-kappa B) regulators IRAK1 (Interleukin-1 receptor-associated kinase 1) and TRAF6 (TNF receptorBCL-2 associated factor 6). Such changes were corrected in the HCMECs (Human cerebral microvascular endothelial cell) transfection with miR-146a mimic [76].

Type 2 diabetes in ovariectomized rats maBCL-2kdely reduced the expression of miR-133, IGFl-1, miR-29, BCL-2 genes and proteins, increased caspase 3 activity and decreased collagen deposition and fibroblast [77]. Therefore, type 2 diabetes and menopause may synergically boost cardiac fibrosis due to dysregulation of miR-133, miR-29, IGF-1, Bcl-2 genes and proteins, and increased caspase 3 activity [77].

Interleukin-6 (IL-6) is an important regulator of cardiac fibrosis [78]. Cardiac function was significantly improved and fibrosis was apparently alleviated in streptozotocin-induced diabetic mice with IL-6 knockout. Treatment with IL-6 significantly contributed to CFs proliferation and collagen production [79]. HG treatment increased collagen production whereas it was mitigated in CFs from IL-6 KO mice. Moreover, knockout of IL-6 alleviated the upregulation of TGF-β1 in diabetic hearts of mice and cultured CFs treated with HG or IL-6 [79]. Furthermore, the expression of miR-29 reduced after IL-6 treatment, whereas it was increased in IL-6 KO hearts. Overexpression of miR-29 blocked pro-fibrotic effects of IL-6 on cultured CFs [79].

Diabetic cardiomyocyte hypertrophy increased the ratio of heart-to-body weight. MiR-30c was found to target Pak1 and Cdc42 genes, and cardiac miR-30c expression was found to be reduced in DCM rats, patients with DCM, and HG-treated cardiomyocytes [80]. MiR-30c overexpression decreased Cdc42 and Pak1 genes and attenuated HG-induced cardiomyocyte hypertrophy, whereas miR-30c inhibition increased Cdc42 and Pak1 gene expression and myocyte hypertrophy in HG-treated cardiomyocytes [80]. HG promoted the proliferation and collagen synthesis of rat CFs, which was accompanied by an increase of miR-21 [81]. Gain-of-function and loss-of-function assays confirmed that miR-21 mediated these outcomes, suggesting a crucial role of miR-21 in DCM. The suppressed expression of DUSP8 mediated by miR-21 through JNK/SAPK (c-Jun NH2 terminal kinases/stress activated protein kinases) and p38 signaling pathways promoted HG-induced cardiac fibrosis [81].

MiR-133a has been shown to be associated with cardiac fibrosis [82]. Interestingly, in diabetic mice with cardiac-specific miR-133a overexpression, cardiac fibrosis was significantly decreased [83]. Cardiac miR-133a overexpression prevented ERK1/2 (Extracellular regulated protein kinases1/2) and Smad-2 (SMAD family member 2) phosphorylation [83] (Fig. 5). Therefore, studies have indicated that miRs may regulate cardiac fibrosis in DCM via their targets, and provide insights into the pathogenesis of diabetic cardiac fibrosis (Table 2).

**Novel ncRNA-based therapies in diabetic cardiac fibrosis**

Diabetic cardiac fibrosis involves multiple cellular processes, including proliferation, apoptosis, and so on [84]. In view of the studies, ncRNAs play an essential role in cell
apoptosis and proliferation in diabetic cardiac fibrosis, which exhibits a promising potential to treat diabetic cardiac fibrosis in clinical applications. Studies have indicated that inhibiting proliferation or apoptosis may be a good therapeutic strategy for diabetic cardiac fibrosis. Due to ncRNA mimics or inhibitors can be easily synthesized, ncRNAs provide promising therapeutic targets to treat diabetic cardiac fibrosis. The ncRNAs may represent an important therapeutic target in diabetic cardiac fibrosis. NcRNAs inhibitors should be effective in diabetic cardiac fibrosis which ncRNAs components are mutated such as CFs activation. An important question to be answered is what is the most efficient cellular target of compounds that target the ncRNAs. And in cardiac fibrosis, ncRNAs inhibitors may become the first use drug in future clinical life. Moreover, these advantages of ncRNA applications led to the definition of a new class of drug targets and introduced ncRNA therapy as the future challenge for clinical applications. Viral vehicles show higher efficiency of incorporating ncRNAs, as they have been designed to provide improved transfection efficiency for ncRNA mimics or anti-ncRNAs. However, they are characterized by increased cytotoxicity and immune response. On the other hand, non-viral ncRNA delivery systems are characterized by lower toxicity and immunogenicity, increased cellular uptake, water solubility, resistance to endonucleases and phagocytosis. Several non-viral delivery strategies, including lipid-based, polymer-based and inorganic ncRNA vesicles, have been designed and are widely used in targeting approaches. However, appropriate combination therapy may be required for effective therapy. Therefore, large populations of challenges remain to be solved in the development of ncBCL-2RNA-based therapy. Further studies are still required to probe the complex mechanisms connecting ncRNAs and different mode of diabetic cardiac fibrosis pathological conditions.

**Table 2** Molecular alterations of microRNAs in DCM

<table>
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**Concluding remarks and perspectives**

With a growing epidemic of DM and associated cardiac complications, the value of perceiving ncRNAs as a new therapeutic target for DCM has garnered enormous interest among the scientific community. Based on the article, we explained the roles of ncRNAs and analyzed the diabetic cardiac fibrosis clinical implications of ncRNAs in future. Studies have shown that the epigenetic regulation of gene expression levels in diabetic cardiac fibrosis. In particular, given that CFs are dynamic in response to extracellular signals, the plastic epigenetic control of gene expression plays a central role in CFs adaptation to stimulus. In summary, ncRNA pathways and other epigenetic mechanisms...
in CFs will hopefully offer new therapeutic strategies for diabetic cardiac fibrosis.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**References**


