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Review Article

The interregulatory circuit between non-coding RNA and apoptotic signaling in diabetic cardiomyopathy

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ABSTRACT

Diabetes mellitus has surged in prevalence, emerging as a prominent epidemic and assuming a foremost position among prevalent medical disorders. Diabetes constitutes a pivotal risk element for cardiovascular maladies, with diabetic cardiomyopathy (DCM) standing out as a substantial complication encountered by individuals with diabetes. Apoptosis represents a physiological phenomenon observed throughout the aging and developmental stages, giving rise to the programmed cell death, which is implicated in DCM. Non-coding RNAs assume significant functions in modulation of gene expression. Their deviant expression of ncRNAs is implicated in overseeing diverse cellular attributes such as proliferation, apoptosis, and has been postulated to play a role in the progression of DCM. Notably, ncRNAs and the process of apoptosis can mutually influence and cooperate in shaping the destiny of human cardiac tissues. Therefore, the exploration of the interplay between apoptosis and non-coding RNAs holds paramount importance in the formulation of efficacious therapeutic and preventive approaches for managing DCM. In this review, we provide a comprehensive overview of the apoptotic signaling pathways relevant to DCM and subsequently delve into the reciprocal regulation between apoptosis and ncRNAs in DCM. These insights contribute to an enhanced comprehension of DCM and the development of therapeutic strategies.

1. Introduction

Diabetes represents a worldwide pandemic, impacting approximately 463 million individuals across the globe, with projections indicating a potential surge to 700 million cases by the year 2045. The presence of diabetes plays a role in the progression of cardiovascular disease, where diabetic cardiomyopathy (DCM) arises as a notable complication within the diabetic population. Based on existing data, it is indicated that DCM impacts an estimated 12 % of individuals with a confirmed diagnosis of diabetes. Clinical investigations have elucidated that DCM stands as a prominent contributor to the occurrence of severe cardiovascular events and exacerbates the prognostic outlook for individuals with diabetes. The primary characteristics of DCM consist of impaired left ventricular contraction or diastolic dysfunction and ventricular hypertrophy, which are distinct from hypertension, coronary syndrome, and other ailments [1]. Notably, the fundamental distinction between DCM and other forms of cardiomyopathy lies in their etiology and pathogenesis. Elevated glucose levels can trigger a cascade of alterations within cardiomyocytes. The compromised handling of cardiomyocyte calcium and mitochondrial dysfunction, along with myocardial interstitial fibrosis, cardiac autonomic neuropathy, and microvascular dysfunction, have all been identified as factors contributing to the onset and advancement of DCM [2,3]. However, the presence of alternative forms of cardiomyopathy is associated with a multitude of factors, including allergic responses, ischemic conditions, endocrine disorders, metabolic irregularities, infection, and various other elements.

DCM is attributed to a complex interplay of multiple factors; however, the supporting evidence for the precise mechanistic details remains somewhat limited. Exposure of cardiomyocytes to hyperglycemic conditions can potentially result in metabolic disruptions, subsequently giving rise to insulin resistance, impaired mitochondrial function, elevated oxidative stress, increased inflammatory reactions, and apoptosis. Numerous investigations have demonstrated the involvement of apoptosis in the pathophysiological mechanisms of DCM [4,5]. Apoptosis represents a physiological phenomenon occurring throughout the aging and developmental processes, resulting in programmed cell death. The term “apoptosis" was initially introduced in a scholarly publication from 1972 by Kerr, Wyllie, and Currie [6]. It was employed

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Abbreviation

5-HD	5-hydroxydecanoate
AAVs	Adeno-associated viruses
AAV9	Adeno-associated virus serotype 9
ABCA1	ATP-binding cassette transporter A1
ADSCs	Adipose-derived mesenchymal stem cells
ARC	Apoptosis repressor with caspase recruitment domain
ATF6	Activating transcription factor-6
BMSC	Bone marrow stromal cells
cDNA	Complementary DNA
circRNAs	Circular RNAs
CTRP3	C1q/TNF-related protein-3
Cyt *c*	Cytochrome *c*
DCM	Diabetic cardiomyopathy
DD	Death domain
DISC	Death-inducing signaling complex
Dox	Doxorubicin
ERK1/2	Extracellular signal-regulated kinase 1/2
ERS	endoplasmic reticulum stress
FADD	Fas-associated death domain
FUS	Dused in sarcoma
GAS5	Growth arrest-specific 5
G-CSF	Granulocyte-colony stimulating factor
HF	Heart failure
HG	High glucose
HKL	Honokiol
HM	Hydrophobic motif
H/R	Hypoxia/reoxygenation
IGF1	Insulin-like growth factor 1
IκB	Inhibitors of NF-κB
IKK	IκB kinase
IRE1	Inositol requirement protein 1
IRE1α	Inositol-requiring kinase enzyme 1α
JNK	Jun N-terminal kinase
LAMP2	Lysosomal-associated membrane protein 2
LNAs	Locked Nucleic Acids
lncRNAs	Long noncoding RNAs
LXRα	Liver X receptor α
MAPK	Mitogen-activated protein kinase
Mcl-1	Myeloid cell leukemia 1
MI	myocardial infarction
MIAT	Myocardial infarction-associated transcript
MIRI	Myocardial ischemia-reperfusion injury
miRNAs	microRNAs
mitoKATP	Mitochondrial adenosine triphosphate-dependent potassium channels
MKPs	MAPK protein phosphatases
MOMP	Mitochondrial outer membrane permeabilization
MSCs	Mesenchymal stem cells
NAD+	Nicotinamide adenine dinucleotide
ncRNAs	Noncoding RNAs
NiDHD	Non-ischemic diabetic heart disease
NMCMs	Neonatal mouse cardiac myocytes
NRCM	Neonatal rat cardiomyocyte
Nrf2	Nuclear factor-erythroid 2-related factor 2
pAKT	Phosphorylated AKT
PI3Ks	Phosphoinositide 3-kinases
PIP2	Phosphatidylinositol 4,5-bisphosphate
PIP3	Phosphatidylinositol 3,4,5-trisphosphate
p-PERK	Phosphorylated-PERK protein kinase R (PKR)-like endoplasmic reticulum kinase
Que	Quercetin
RIP	Receptor-interacting protein
RNase III	Ribonuclease III
ROS	Reactive oxygen species
rRNAs	Ribosomal RNAs
snRNAs	Small nuclear RNAs
Sirt1	Sirtuin 1
Sirt3	sirtuin3
SOCS2	Suppressor of cytokine signaling 2
STZ	Streptozotocin
TACE	TNF-α-converting enzyme
TLR3	Toll-like receptor 3
TNF-α	Tumor necrosis factor-alpha
TNF-R1	TNF-α receptor I
TNF-R2	TNF-α receptor II
TRADD	TNF-R1-associated death domain protein
TRAF2	TNF receptor-associated factor
tRNAs	Transfer RNAs
VDAC1	Voltage-dependent anion channel 1

to delineate a homeostatic mechanism responsible for preserving cell populations by eliminating impaired and surplus cells. Apoptosis is genetically regulated and represents a universally conserved mechanism among multicellular organisms [7]. Apoptosis is orchestrated by a group of enzymes known as caspases. Caspases are intracellular proteases characterized by their enzymatic cleavage activity. They typically exist as inactive pro-enzymes within the majority of cell types. Upon activation, a caspase has the capacity to trigger the activation of additional procaspases, initiating a sequential cascade of activated caspases that ultimately culminates in cellular death [8] (Fig. 1).

Noncoding RNAs (ncRNAs) constitute a substantial category of RNA molecules that lack the capacity to encode proteins. NcRNAs encompass various subclasses, such as miRNAs (microRNAs), lncRNAs (long noncoding RNAs), circRNAs (circular RNAs), and snRNAs (small nuclear RNAs), and have garnered recognition for their roles in the regulation of diabetes-related conditions [9,10]. NcRNAs could directly or indirectly impact a wide array of molecular targets, governing *cis*-acting elements, *trans*-acting factors, and pre-mRNA transcription at various hierarchical levels [11]. Recent research has demonstrated the significant regulatory influence of ncRNAs in instigating the process of apoptosis. In this context, Long et al. examined the potential involvement of the lncRNA FTX/miR-29b-1-5p axis in the context of cardiomyocyte apoptosis. Their results illustrate that lncRNA FTX overexpression mitigated the occurrence of cardiomyocyte apoptosis in cultured cardiomyocytes when exposed to hydrogen peroxide treatment. Furthermore, they observed that miR-29b-1-5p facilitated cardiomyocyte apoptosis by suppressing the expression of Bcl2l2 protein levels. Therefore, FTX acts as a sponge for miR-29b-1-5p, modulating the post-transcriptional function of miR-29b-1-5p, and ultimately governing the expression of Bcl2l2 [12]. In the current paper, we firstly describe apoptosis signaling pathway in cardiomyocyte, and subsequently described the impact of lncRNAs and miRNAs on cell apoptosis in DCM. As well, in the final section we demonstrated that targeting ncRNAs/apoptosis axis could be implemented in the treatment of DCM.

2. An overview on intrinsic and extrinsic pathway of apoptosis

The process of apoptosis predominantly encompasses two fundamental pathways: the intrinsic pathway and the extrinsic pathway. The intrinsic pathway entails the disruption of mitochondrial function triggered by cellular stressors or cytotoxic stimuli. In cells experiencing stress, proapoptotic members of the BCL-2 family, such as Bax and Bid,

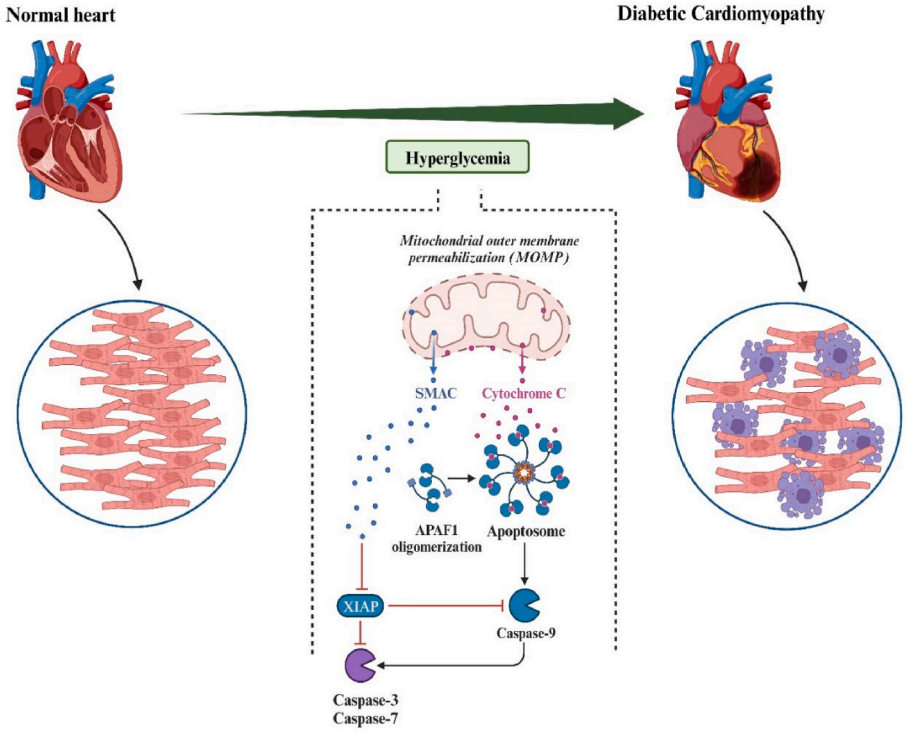

Fig. 1. Illustration depicting the impact of hyperglycemia on cardiomyocyte apoptosis and the development of DCM. Hyperglycemia-induced pathways leading to increased oxidative stress, inflammation, and mitochondrial dysfunction contribute to cardiomyocyte apoptosis, ultimately leading to the progression of DCM.

facilitate mitochondrial outer membrane permeabilization (MOMP), resulting in the release of cytochrome *c* (cyt *c*) into the cytoplasm. Subsequently, cyt *c* in the cytoplasm promotes the assembly of the 'apoptosome' [13]. Cysteine protease caspase-9, and the adaptor protein apoptotic protease-activating factor-1 (Apaf-1) are the main constituent of this multimeric complex. Sequentially, caspase-3, the effector enzyme, is mobilized to the apoptosome, where it undergoes activation by caspase-9. Caspase-3 subsequently cleaves essential cellular substrates, initiating numerous cellular and biochemical processes associated with apoptosis [14]. On the other hand, extrinsic pathway activation occur upon engagement of cell-surface death receptors such as Fas by their respective ligands. Following activation, death-inducing signaling complex (DISC) formation by each receptor is accomplished via recruitment of procaspases 8 and 10, and adapter Fas-associated death domain (FADD) [15,16]. This recruitment is associated with caspases 8 and 10 activation through proximity-based mechanisms, subsequently triggering their auto-cleavage and the release of active caspase molecules within the cytoplasm. These enzymes subsequently undergo cleavage, thereby activating the effector caspases 3, 6, and 7, leading to the execution of apoptosis [17](Fig. 1).

3. Major signaling molecules in cardiomyocyte apoptosis

3.1. PI3K/Akt pathway

The phosphoinositide 3-kinases (PI3Ks) constitute a family of heterodimeric lipid kinases, categorized into class I, II, and III isoforms. The Class IA subset of PI3Ks, which is stimulated by receptor tyrosine kinases, comprises a p110 catalytic subunit (p110α, PIK3CA; p110β, PIK3CB; p110δ, PIK3CD) along with one of five regulatory subunits similar to p85 (p85α, p55α, p50α, PIK3R1; p85β, PIK3R2; p55γ, PIK3R3) [18–20]. The Class IB category of PI3Ks, triggered by G protein-coupled receptors, includes the catalytic subunit (p110γ, PIK3CG) in conjunction with regulatory subunits (p101, PIK3R5; p87, PIK3R6). Class II PI3Ks encompass PI3K–C2α (PIK3C2A), β (PIK3C2B), and γ (PIK3C2G). On the other hand, the sole member of the class III PI3Ks is hVPS34 (PIK3C3). As well, AKT is a serine protein kinase, evolutionarily conserved, and part of the AGC subfamily of protein kinases. It consists of three structurally conserved domains: an N-terminal PH domain, a short C-terminal tail that includes a regulatory hydrophobic motif (HM), and a connecting region housing a central kinase catalytic domain. Upon activation, Class I PI3K phosphorylates the substrate phosphatidylinositol 4, 5-bisphosphate (PIP2), leading to the production of phosphatidylinositol 3,4,5-trisphosphate (PIP3) on intracellular membranes. This, in turn, facilitates the recruitment of signaling proteins, including AKT [21]. AKT regulates a multitude of downstream effectors, encompassing protein and lipid kinases, transcription factors, modulators of small G proteins, elements involved in vesicle trafficking, metabolic enzymes, cell cycle control factors, E3 ubiquitin ligases, and a diverse array of other effector molecules, primarily through serine and/or threonine phosphorylation. These effectors collectively possess a shared minimal sequence motif, characterized as Arg-Xaa-Arg-Yaa-Zaa-Ser-Hyd. via its effectors, AKT plays crucial roles in numerous cellular processes, including apoptosis [22]. In this context, Song et al. explored the molecular mechanisms involved in hypoxia-induced cardiomyocyte apoptosis through the PI3K-AKT pathway. Their investigation revealed that the PI3K-AKT pathway became activated in cardiomyocytes subjected to hypoxic conditions. As well, in their study, Phosphorylated AKT (pAKT) was observed to relocate from the cytosol to the mitochondria through mitochondrial adenosine triphosphate-dependent potassium channels (mitoKATP). This translocation resulted in an elevation of cytochrome *c* oxidase activity, leading to the inhibition of apoptosis. Furthermore, their observations indicated that the use of the mitoKATP-specific inhibitor, 5-hydroxydecanoate (5-HD), or the silencing of cytochrome *c* oxidase with siRNA, hindered the mitochondrial translocation of pAKT. This intervention preserved cytochrome *c* oxidase activity, thereby leading to mitochondrial dysfunction and the onset of hypoxia-induced cellular apoptosis. Thereby, PI3K-AKT pathway's anti-apoptotic influence, achieved by pAKT migration to mitochondria via mitoKATP, appears to involve the modulation of

cytochrome *c* oxidase activity [23]. Furthermore, Zheng et al. investigated the mechanistic aspects associated with cardiomyocyte apoptosis induced by oxidative stress, with particular attention to the signaling pathway involving Akt and p53. Their findings revealed that cardiomyocyte apoptosis exhibited a dose-dependent response to oxidative stress. Their mechanistic investigation revealed that oxidative stress hindered cardiomyocyte glucose metabolism, leading to an accumulation of lactic acid, while also inducing calcium overload in cardiomyocytes. Ultimately, they observed that oxidative stress suppressed Akt pathway while concurrently activating the p53 signaling pathway. Additionally, they discovered that genetic silencing of p53 negated the cardiomyocyte injury and mortality induced by oxidative stress by modulating the expressions and functions of Bax and caspase-3. Altogether, there is an association between oxidative stress and cardiomyocyte apoptosis via a mechanism characterized by perturbations in the Akt/p53 signaling pathway [2].

3.2. MAPK pathway

Extracellular signal-regulated kinase 1/2 (ERK) is a member of the mitogen-activated protein kinase (MAPK) family, responsible for participating in signaling cascades that transmit external signals to intracellular targets. The initiation of a MAPK cascade takes place within a series of successive phosphorylation events. In this process, following an initial stimulus, each MAPK undergoes phosphorylation by upstream MAPKs [24]. A MAPK module consists of a MAP3K responsible for triggering the activation of a MAP2K, which subsequently initiates the activation of a MAPK. Phosphorylation events within the MAPK pathway can be counteracted by MAPK protein phosphatases (MKPs), which engage in the dephosphorylation of both phosphotyrosine and phosphothreonine residues on MAPKs [25]. Based on the constituents within the MAPK layer, four distinct MAPK cascades have been delineated: ERK1/2, c-Jun N-terminal kinase (JNK), p38 MAPK, and ERK5 [26]. ERK1/2 is triggered in reaction to growth factors, hormonal, and proinflammatory agents, whereas JNK and p38 MAPK are activated by internal and external stressors, alongside proinflammatory triggers [27]. Research has demonstrated that the p38 MAPK and JNK pathways are primarily associated with cellular stress and apoptosis, whereas the ERK/MAPK signaling pathway, recognized as the most extensively investigated MAPK signaling pathway, is intimately linked to cell proliferation and differentiation, serving a central role in the cellular signal transduction network [28,29]. Clinical observations have provided evidence that elevated expression levels of JNK MAPKs and p38 are linked to cardiomyocyte apoptosis. In this context, Zhang et al. investigated the involvement of the MAPK signaling pathway in cardiomyocyte apoptosis in a murine model of post-infarction heart failure (HF). In their study, the group with myocardial infarction (MI) displayed an enlarged left ventricle and reduced cardiac function. They observed a substantial rise in the protein expressions of CHOP and GRP78 in myocardial tissues, particularly within the subgroup treated with SB203580, a specific inhibitor targeting the MAPK pathway. They also revealed a significant upregulation in the expressions of cleaved caspase 12 proteins and p-JNK, particularly within the subgroup treated with SB203580. They finally revealed a notably increased susceptibility to apoptosis in the cardiomyocytes of the MI group, with the SB203580 subgroup displaying a more pronounced effect. Thereby, myocardial infarction (MI) is concomitant with endoplasmic reticulum stress (ERS), likely mediated through the MAPK signaling pathway. Furthermore, SB203580, a dedicated inhibitor of this pathway, was shown to mitigate cardiomyocyte apoptosis and safeguard the myocardium by alleviating this stress [3]. Notably, Li et al. explored the potential protective effects of Quercetin (Que) on cardiomyocytes subjected to *in vitro* hypoxia/reoxygenation (H/R) and sought to elucidate its underlying cardioprotective mechanisms. Their *in vitro* experiments demonstrated that pre-treatment with Quercetin (Que) augmented H9c2 cardiomyocytes viability and mitigated the apoptosis induced by hypoxia/reoxygenation (H/R) in these cardiomyocytes. They observed that Quercetin (Que) effectively mitigated the hypoxia/reoxygenation (H/R)-induced phosphorylation of p38 and JNK, subsequently elevating Bcl-2 expression, and either indirectly or directly inhibiting caspase-3 and Bax activation. In this manner, Quercetin (Que) can confer cardioprotective effects by suppressing the p38 MAPK and JNK signaling pathways and regulating the expression of Bax and Bcl-2 proteins. These findings offer a novel empirical basis for potential therapeutic interventions in myocardial ischemic disease [4].

3.3. TNF-α/NF-κB

Tumor necrosis factor-alpha (TNF-α) is initially produced as a transmembrane protein possessing a molecular weight of 26 kDa, and the pro-peptide becomes released in its soluble form as a 17-kDa entity following cleavage facilitated by TNF-α-converting enzyme (TACE) [30]. TNF-α exerts its influence via two distinct receptors, namely TNF-α receptor I (TNF-R1; also known as p55 or p60) and TNF-α receptor II (TNF-R2; alternatively referred to as p75 or p80) [31,32]. TNF-R1 and TNF-R2 are members of the TNF superfamily receptors, which are characterized by structurally akin extracellular domains enriched with cysteine residues. TNF-R2 expression is limited to immune and endothelial cells [33]. Despite evidence indicating that TNF-R2 is involved in signaling pathways conducive to tissue healing and angiogenesis, the precise functional outcomes of TNF-R2 signaling remain inadequately defined. TNF-R1 is ubiquitously expressed on all cell types and exhibits a more expansive function in NF-κB activation compared to TNF-R2 [34]. Ligation of TNF-R1 initiates the dimerization of the receptor and the recruitment of the adaptor protein known as TNF-R1-associated death domain protein (TRADD), which interacts with a distinct death domain (DD) within the cytoplasmic domain of TNF-R1. The TNF-R1-associated death domain protein additionally serves to enlist TNF receptor-associated factor (TRAF2) and initiate the activation of IκB kinase (IKK) via the involvement of receptor-interacting protein (RIP). RIP1 undergoes ubiquitination in a process dependent on TRAF2 during the activation of TNF-R1 and plays a crucial role in facilitating TNF-α-induced IKK and NF-κB activation [35]. NF-κB proteins represent a group of transcription factors that play a pivotal role in the regulation of inflammatory and immune responses. Within the mammalian system, the NF-κB proteins encompass three members of the Rel family (RelA or p65, RelB, and cRel), along with p50 and p52. In resting cells, the function of NF-κB is regulated by its retention in the cytoplasm, a process facilitated by a group of proteins known as inhibitors of NF-κB (IκB). Upon encountering external stimuli, the activation of IκB kinase (IKK) ensues, leading to the phosphorylation of IκB. Subsequently, phosphorylated IκB is marked for ubiquitination and subsequent degradation through the proteasome-dependent pathway. The NF-κB that has been released translocates to the nucleus, thereby initiating the transcription of a specific group of genes. Recent experimental research has revealed that oxidative stress induced by TNF-α in cardiomyocytes results in apoptosis through the activation of the NFκB pathway [36]. In this regard, Yu et al. explored the potential protective influence of leptin on cardiomyocytes subjected to TNF-α, along with an exploration of the underlying mechanisms. They exposed neonatal rat cardiomyocytes to TNF-α, either with or without the presence of leptin. Through Western blot analysis and FITC/Annexin V flow cytometry, they observed that TNF-α elevated Annexin V binding and induced cleavage of caspase-3/PARP. These effects were mitigated by prior treatment with leptin. Moreover, their observations indicated that leptin shielded cardiomyocytes from mitochondrial apoptosis by restraining the increase in cytochrome C levels and the reduction in Bcl-2. In their study, leptin supplementation effectively nullified the TNF-α-induced activation of P38 MAPK and NF-κB. Moreover, the application of inhibitors targeting P38 (SB203580) and NF-κB (Bay117082) substantially alleviated the apoptotic impact of TNF-α. These findings suggest that the activation of P38 MAPK and NF-κB might underlie the apoptotic processes in

cardiomyocytes exposed to TNF-α. Therefore, leptin appeared to impart an anti-apoptotic influence on cardiomyocytes subjected to TNF-α, potentially through the suppression of the P38 MAPK and NF-κB pathways activated by TNF-α [37].

3.4. SIRT1

Sirtuin 1 (Sirt1), belonging to the class III histone deacetylases, is a histone deacetylase that relies on nicotinamide adenine dinucleotide (NAD+) for its enzymatic activity [38]. Recently, it has become evident that Sirt1 engages in deacetylating both non-histone and histone proteins, contributing to a wide array of cellular processes, among them apoptosis. In this context, Luo et al. examined the potential regulatory role of Sirt1 in apoptosis and autophagy within hypoxic H9C2 cardiomyocytes and in an experimental mouse model subjected to hypoxia. In their study, heart tissue specimens obtained from cyanotic patients displayed heightened levels of both apoptosis and autophagy, in conjunction with increased Sirt1 expression, in comparison to the non-cyanotic control samples. Their results from the Western blot analysis demonstrated that Sirt1 facilitated autophagic flux while diminishing apoptosis in hypoxic H9C2 cells. Upon further investigation, they unveiled that Sirt1 shields hypoxic cardiomyocytes from apoptosis, at least partially, by involving inositol-requiring kinase enzyme 1α (IRE1α). So, Sirt1 through IRE1α pathway mitigated apoptosis induced by hypoxia, thereby protecting cardiomyocytes from the detrimental effects of hypoxic stress [39] (Fig. 2).

4. Non-coding RNA: from biological features to functioning

Roughly 2 % of the genome is transcribed into RNAs that encode proteins, whereas the remaining 70–90 % of the genome is transcribed into RNAs that do not code for proteins, also known as non-coding RNAs (ncRNAs) [40]. Non-coding RNAs including spliceosomal RNA, ribosomal RNAs (rRNAs), and transfer RNAs (tRNAs), are indispensable components of diverse cellular machinery, fulfilling crucial functions [41]. In addition to the classical ncRNAs, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are now acknowledged as significant modulators of gene expression [42]. MiRNAs comprise single-stranded non-coding RNAs that are highly conserved, with a length ranging from 16 to 27 nucleotides. Their initial discovery occurred in the nematode *Caenorhabditis elegans* [43]. The production of miRNAs is governed by two nuclear ribonuclease III (RNase III) proteins, namely Dicer and Drosha. On a transcriptional level, the biogenesis of miRNAs is under the control of Drosha, resulting in the release of roughly 70–100 nucleotides of precursor miRNAs. Drosha regulates the biogenesis of miRNAs by cleaving the pre-miRNA at the transcriptional level, leading to the liberation of approximately 70–100 nucleotides of precursor miRNAs. Following its translocation to the cytoplasm, Dicer cleaves the precursor, giving rise to the formation of a mature miRNA [44]. A vital role of miRNAs is to regulate transcription and translation processes [45]. LncRNAs, exceeding a length of 200 nucleotides, represent a newly identified category of functional RNAs that lack the capacity to encode proteins [46]. However, various lncRNAs that are associated with ribosomes have been found to possess a coding region capable of translating a peptide [47]. LncRNAs control the expression of multiple genes through their interaction with specific DNA/RNA or protein

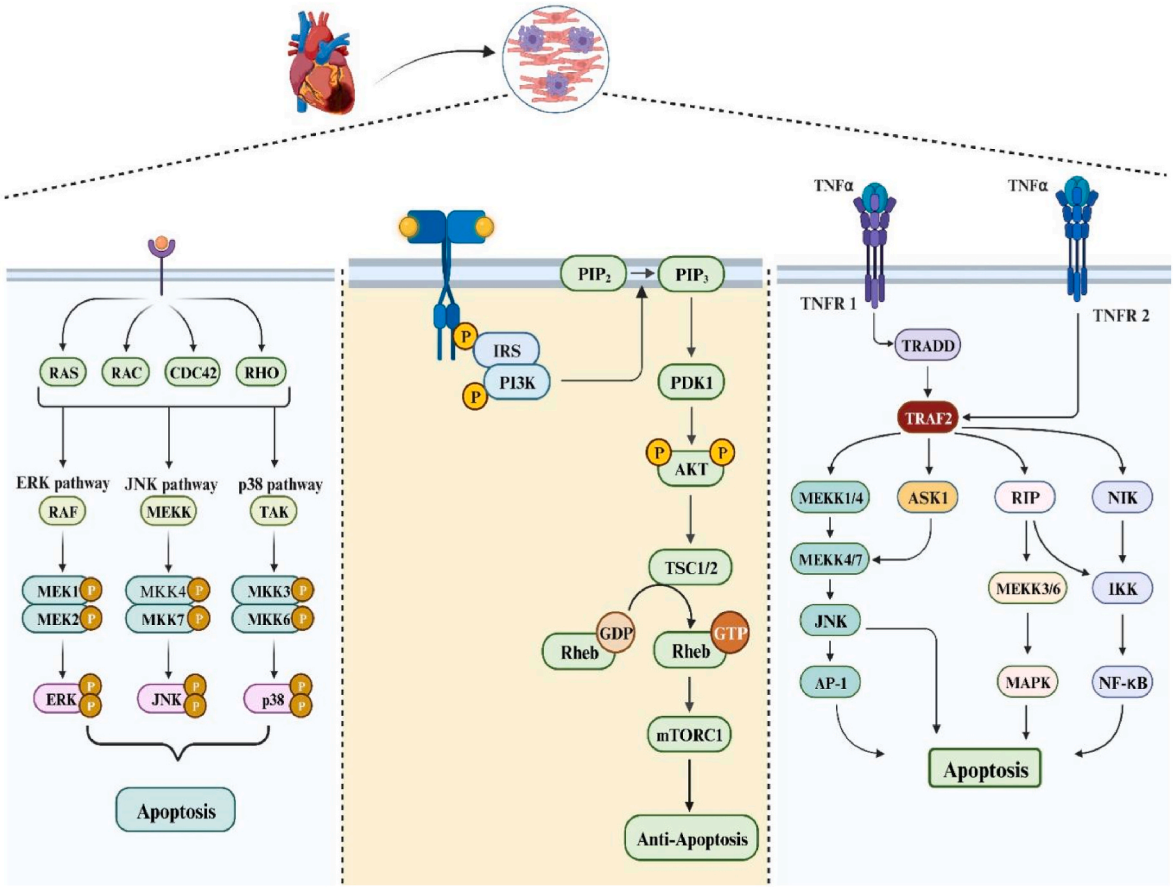

Fig. 2. A schematic representation of major signaling pathway in DCM. This diagram depicting the impact of signaling pathways-PI3K fostering anti-apoptotic responses, while MAPK and TNF-α/NF-κB induce apoptotic effects—in DCM. This visual representation highlights the pivotal role of these pathways in regulating cardiomyocyte apoptosis and underscores their significance in the context of diabetic heart complications.

components. In contrast to other small non-protein coding RNAs (ncRNAs), lncRNAs display limited conservation and exert their functions through a wide array of diverse mechanisms. LncRNAs can serve various roles, including (i) acting as architectural scaffolds that facilitate the assembly of protein complexes, (ii) functioning as decoys that sequester microRNAs, (iii) hosting microRNAs, (iv) governing mRNA degradation, sequestering transcription factors within DNA, and participating in epigenetic regulation of chromatin structure, and (v) stabilizing mRNA by masking miRNA binding sites [48]. Importantly, recent advancements in genome annotations and transcriptomics research have revealed a wide array of regulatory ncRNAs that possess the capability to impact various biochemical processes in eukaryotic organisms, including apoptosis. A mounting body of evidence exists, illustrating the role of lncRNAs as regulators of apoptosis in the context of cellular differentiation and organ development. In this context, Yu et al. employed RNA sequencing to identify lncRNAs that exhibited differential expression patterns in response to oxidative stress and apoptosis induced by HG in cardiomyocyte. They discovered a total of 306 out of 400 lncRNAs with altered expression levels, comprising 156 out of 198 lncRNAs displaying increased expression and 150 out of 202 lncRNAs exhibiting decreased expression at both 24 h and 48 h following HG stimulation, respectively. To explore their functional roles in oxidative stress-induced apoptosis, they subsequently opted to investigate three lncRNAs with increased expression, namely NONRATT002486.2, NONRATT007560.2, and NONRATT029805.2. It was indicated that NONRATT007560.2 silencing had the capacity to mitigate ROS formation and diminish apoptosis, implying that NONRATT007560.2 may hold significant implications in the progression of cardiomyopathy. Therefore, lncRNAs exhibiting abnormal expression levels may be involved in the regulation of oxidative stress and apoptosis in cardiomyocytes [49]. In addition, Wang et al. investigated the impact of lncRNAH19 on DCM and its influence on endoplasmic reticulum stress (ERS)-related cardiomyocyte apoptosis. Their *in vivo* findings revealed that H19 ameliorated left ventricular dysfunction in diabetic individuals, leading to a reduction in cardiomyocyte apoptosis and improved fibrosis. They revealed that H19 could diminish the levels of p-PERK, p-IRE1α, ATF6, CHOP, cleaved caspase-3, cleaved caspase-9, cleaved caspase-12, and BAX proteins in cardiac tissues. Furthermore, they provided evidence that *in vitro*, H19 suppressed oxidative stress, ERS, and apoptosis. In their final revelation, they indicated that the impact of H19 on apoptosis associated with ERS could potentially be counteracted through the use of LY294002, a specific inhibitor of AKT and PI3K. Therefore, H19 mitigates DCM in individuals with DM by reducing ROS and apoptosis in cardiomyocytes induced by ERS. This effect appears to be associated with the PI3K/AKT/mTOR signaling pathway activation [50]. As well, a mounting body of evidence suggests that miRNAs are involved in the regulation of apoptosis. For example, miR-21 can directly suppress FasL, leading to an increase in apoptosis, while miR-130a can diminish TRAIL resistance by influencing other miRNAs, thereby enhancing apoptosis [51]. In addition, Zhang et al. sought to elucidate the function of miR-144-3p in the context of heart failure (HF). In their study, Doxorubicin (Dox) induced cardiac dysfunction, exacerbated cardiac injury, reduced cardiomyocyte viability, and led to decreased expression levels of miR-144-3p, Bcl-2, phosphorylated PI3K, and AKT. However, it increased the expression of Bax and cleaved caspase-3. These effects were reversed when miR-144-3p was increased, and conversely, they were exacerbated when miR-144-3p was decreased. As well, increased expression of miR-144-3p mitigated cardiac dysfunction and cell apoptosis induced by Doxorubicin through the regulation of SOCS2. This study provides novel evidence regarding the role of miR-144-3p in heart failure. Therefore, miR-144, acting through the SOCS2/PI3K/AKT axis, exerts a pivotal influence on the process of apoptosis in cardiomyocytes [52].

5. Non-coding RNA: a new player in DCM

Recent studies have reported the involvement of ncRNAs in the development of various human disorders, including complications associated with DM [53]. Also, ncRNAs hold significant promise as a valuable resource for advancing the formulation of therapeutic approaches and enhancing the clinical care of individuals afflicted with cardiomyopathy [54]. In this context, Chen et al. explored the involvement of lncRNA TINCR in DCM. Their research revealed that the expression of TINCR was notably reduced in both myocardial biopsy samples and serum of individuals suffering from DCM when compared to diabetic patients without cardiomyopathy and a healthy control group. Additionally, their investigation indicated that exposure to HG had no substantial impact on the expression of TINCR in human cardiomyocyte cells. Moreover, they observed that upregulation of TINCR effectively suppressed apoptosis in cardiomyocytes subjected to HG treatment. So, lncRNA TINCR experiences a downregulation in the context of DCM, and furthermore, it possesses the capability to impede apoptosis in cardiomyocytes [55]. Additionally, Zhang et al. investigated the function of lncRNA lncDACH1 in DCM and sought to elucidate the molecular mechanisms that underlie its involvement. Their findings indicated an upregulation in the expression of lncDACH1 in hearts affected by DCM as well as in cardiomyocytes subjected to HG treatment. They further observed that the lncDACH1 silencing resulted in a reduction of mitochondrial oxidative stress, cellular apoptosis, cardiac fibrosis, and hypertrophy. This, in turn, led to an improvement in cardiac function in DCM mice. Furthermore, their investigation uncovered that the lncDACH1 overexpression increased the levels of mitochondria-derived ROS and apoptosis. Additionally, it led to a reduction in the activity of manganese superoxide dismutase (Mn-SOD) in cardiomyocytes exposed to HG. In their mechanistic analysis, they unveiled that lncDACH1 directly interacted with sirtuin3 (SIRT3) and, through ubiquitination, expedited its degradation, consequently enhancing mitochondrial oxidative damage and cellular apoptosis in mouse hearts. Their subsequent experiments revealed that the protective benefits of lncDACH1 silencing in cardiomyocytes were nullified when SIRT3 was silenced. Therefore, lncDACH1 exacerbates DCM by enhancing mitochondrial oxidative stress and cellular apoptosis, a process facilitated through the increase in ubiquitination-mediated SIRT3 degradation in mouse hearts. So, lncDACH1 silencing presents a fresh and innovative therapeutic approach for mitigating DCM [56]. Importantly, miRNAs could regulate the response to oxidative stress, impact inflammatory pathways, and affect the survival of cardiomyocytes. Hence, these miRNAs may have a pivotal role in DCM. In this regard, Ahmed et al. set out to pinpoint the specific miRNA responsible for the initiation of DCM, employing a combination of in silico and *in vitro* methodologies. Their *in vitro* and in silico investigations revealed that miR-17 exhibited increased expression, while miR-320a, miR-214, miR-199a, miR-150, and miR-24 displayed decreased expression in patients with DCM in comparison to healthy individuals. Thereby, aberrant expression and interaction of target genes and miRNAs could be significant contributors to the development of DCM [57]. Furthermore, Kumar et al. investigated the function of miR-21, specifically in cardiac fibroblasts, concerning its involvement in cardiac fibrosis associated with DCM. They detected a substantial 15-fold elevation in the expression of miR-21 within the DCM group when contrasted with the control group. In their study, the levels of mRNA associated with fibrosis-promoting genes in the myocardium were notably elevated within the DCM group, and these elevations exhibited a positive correlation with the expression of miR-21. Furthermore, they revealed that cardiac fibroblasts exposed to HG (25 mM) for 72 h exhibited a tenfold upregulation in miR-21 expression. This HG environment also led to elevated expression of genes associated with fibrosis when compared to cells incubated under normal glucose conditions. They finally detected a significant increase in the myocardial mRNA levels of PTEN, a possible target of miR-21, in the DCM group (with a fivefold rise) and in fibroblasts subjected to high

glucose (with a fourfold increase) relative to their corresponding control groups. The heightened expression of miR-21 specifically in fibroblasts may potentially facilitate cardiac fibrosis through the modulation of PTEN in DCM [58].

6. Non-coding RNA and DCM: insight into their role in apoptosis

6.1. Apoptosis-related miRNA in DCM

Given the dysregulation of both apoptosis and miRNAs in DCM, it is imperative to comprehend the interplay between these two processes. Accumulated empirical findings indicate a bidirectional relationship between the processes of apoptosis and microRNA pathways. Notably, given the direct regulatory capacity of microRNAs over approximately 30 % of cellular genes, their participation in essential cellular functions, including apoptosis, is an unsurprising observation. In the following section, we will highlight literatures regarding how miRNAs regulate apoptosis in DCM (Fig. 3).

6.2. MiR-144

The miR-144/451 gene locus is characterized as a bicistronic genetic element residing on chromosome 17 in the human genome and chromosome 11 in the mouse genome. The miR-144/451 locus contains two exceptionally conserved miRNAs: miR-144-3p and miR-451a [59]. Tao et al. examined the function of miR-144 in cell injury induced by HG in H9c2 and neonatal rat cardiomyocyte (NRCM) models. In their study, HG significantly hindered mitochondrial biogenesis, as indicated by disrupted mitochondrial morphology, decreased mitochondrial DNA quantities, altered expression of genes associated with biogenesis, and a concurrent increase in cellular apoptosis. As well, the downregulation of miR-144 expression was noted in cardiomyocytes subjected to HG conditions, as well as in cardiac tissue samples exposed to streptozotocin (STZ) challenge. Importantly, they presented compelling evidence demonstrating that the intravenous administration of a miR-144 agomir through the tail vein effectively alleviated mitochondrial dysfunction and cardiac impairment induced by streptozotocin (STZ) in adult mice. Furthermore, it attenuated cardiac fibrosis and apoptosis. Conversely, the inhibition of miR-144 resulted in contrasting outcomes. They discovered that Rac-1 is a target gene of miR-144 and demonstrated that the reduction in Rac-1 levels triggered AMPK phosphorylation and PGC-1α deacetylation. This cascade of events resulted in enhanced mitochondrial biogenesis and decreased cell apoptosis. Therefore, miR-144 plays a protective role in shielding the heart from hyperglycemia-induced damage. This protective effect is achieved through enhancing mitochondrial biogenesis and reducing cell apoptosis, which is attributed to the direct targeting of Rac-1 by miR-144. Hence, the enforced expression of miR-144 could potentially serve as a protective therapeutic approach for addressing cardiac dysfunction induced by hyperglycemia [60]. Furthermore, Yu et al. examine the impact of miR-144 on the regulation of oxidative stress and apoptosis in cardiomyocytes subjected to HG conditions in *in vitro* experiments, as well as in a DCM model induced by STZ in *in vivo* settings. They noted a decrease in miR-144 levels in the heart tissues of diabetic mice induced by STZ, and HG exposure similarly led to decreased miR-144 levels in cultured cardiomyocytes. They revealed that miR-144 regulated the oxidative stress induced HG in cultured cardiomyocytes by directly acting on nuclear factor-erythroid 2-related factor 2 (Nrf2), a key modulator of the cellular response to oxidative stress. As well, the introduction of miR-144 mimics exacerbated the formation of ROS and

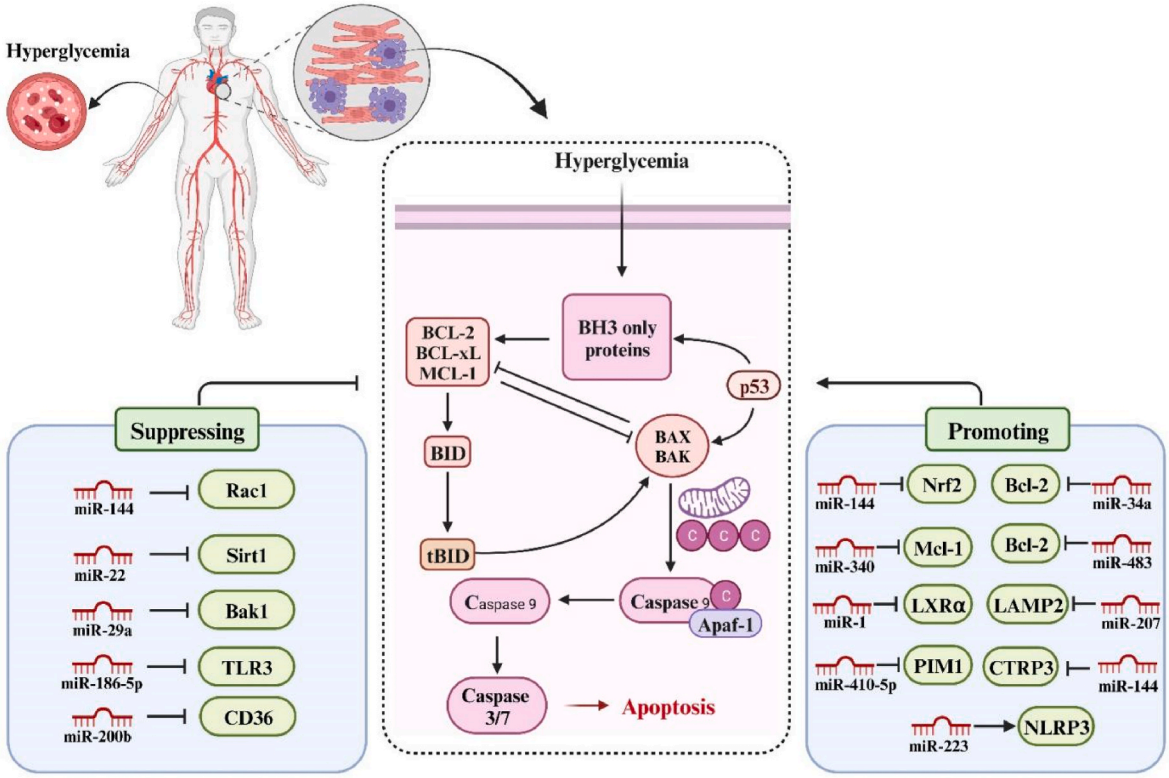

Fig. 3. The Role of Hyperglycemia-Induced Apoptosis in Cardiomyocytes Leading to DCM and the Crucial Role of miRNAs. Hyperglycemia triggers a cascade of molecular events leading to mitochondrial dysfunction, which collectively promote apoptosis in cardiomyocytes. Additionally, this figure illustrates the categorization of miRNAs based on their roles in regulating apoptosis in cardiomyocytes under hyperglycemic conditions, contributing to DCM. miRNAs such as miR-186-5p, miR-22, and miR-29a are shown to suppress apoptosis, thereby potentially offering protective effects against cardiomyocyte death. In contrast, miRNAs like miR-34a, miR-483, and miR-207 promote apoptosis, exacerbating cardiomyocyte loss. Notably, miR-144 exhibits a dual role by targeting different mRNAs, thereby both promoting and suppressing apoptosis depending on the specific context within hyperglycemic environments.

apoptosis in cardiomyocytes subjected to HG. Dihydro-CDDO-trifluoroethyl amide (dh404) is a novel Nrf2 activator that by suppressing oxidative stress exert therapeutic potential for cardiac diseases. The administration of Dh404, an activator of Nrf2, was effective in reducing these effects. They additionally illustrated that the miR-144 silencing resulted in the suppression of ROS generation and the reduction of apoptosis induced by HG in cultured cardiomyocytes. Notably, they observed decreased oxidative stress and apoptosis in cardiac tissues, leading to an improvement in cardiac function in diabetic mice induced by STZ after administering the miR-144 antagomir. Thereby, miR-144 silencing holds promise as a clinical strategy to mitigate oxidative stress, diminish cardiomyocyte apoptosis, and enhance cardiac function in the context of DCM [61,62]. In addition, Song and colleagues investigated the CTRP3 and miR-144 expression levels in AC16 cardiomyocytes exposed to HG. Their findings revealed an increased expression of miR-144 and a decreased expression of CTRP3 in AC16 cardiomyocytes exposed to HG. As well, it was observed that the suppression of miR-144 or the CTRP3 upregulation significantly enhanced cell proliferation and decreased apoptosis in AC16 cardiomyocytes exposed to HG. They also observed that the suppression of miR-144 substantially reduced *p*-JNK and Bax protein levels while increasing the expression of Bcl-2 in AC16 cardiomyocytes exposed to HG. Moreover, in their study, CTRP3 was identified as a direct target of miR-144, and its inhibition reversed the influences of miR-144 knockdown on apoptosis and cell proliferation in AC16 cardiomyocytes exposed to HG. Thereby, miR-144 plays a regulatory role in the apoptosis and proliferation of AC16 cardiomyocytes exposed to HG by targeting the CTRP3/JNK signaling pathway, offering a novel potential approach for addressing DCM [63]. These findings demonstrated that miR-144 play a dual role in cardiomyocyte apoptosis.

6.3. MiR-34a

Among the three constituents of the miR-34 family, miR-34a exhibits widespread expression in healthy human tissues. In contrast, miR-34b/c expression displays tissue-specific patterns predominantly in the testicles, brain, lungs, and fallopian tubes. In the human genome, miR-34a is situated within chromosome 1p36, whereas miR-34c and miR-34b are co-expressed from a shared transcript located on chromosome 11q23 [64]. Zhao et al. explored the potential of a HG environment in triggering apoptosis within the H9c2 rat cardiomyocyte cell line, specifically examining the involvement of microRNA-mediated modulation of the Bcl-2 signaling pathway. Their findings demonstrated a substantial upregulation in the expression of miR-34a, a noteworthy reduction in Bcl-2 expression, and a conspicuous increase in cardiomyocyte apoptosis in H9c2 cells exposed to HG levels, as compared to the control group treated with normal glucose concentrations. As well, their investigation revealed a direct targeting of the Bcl-2 gene by miR-34a, where the use of miR-34a mimics resulted in diminished Bcl-2 expression and an augmented glucose-induced apoptosis, while conversely, miR-34a inhibitors exhibited opposing effects. Their dataset also provides evidence of miR-34a playing a role in the reduction of Bcl-2 expression induced by elevated glucose levels, ultimately leading to cardiomyocyte apoptosis [65]. Granulocyte-colony stimulating factor (G-CSF) is a peptide growth factor involved in the neutrophilic granulocyte production and also function in proliferation of hematopoietic progenitor cells [66]. Notably, Park et al. postulated that cardiac miRNAs might play a regulatory role in the mechanism underlying the anti-apoptotic effects of G-CSF in a rat model of DCM. Their findings revealed that G-CSF treatment led to a notable reduction in apoptosis and a decrease in miR-34a expression in both diabetic myocardium and H9c2 cells exposed to HG conditions. They also revealed that G-CSF treatment significantly elevated the expression of Bcl-2 protein, which is targeted by miR-34a. Finally, through a transfection assay, they demonstrated that the miR-34a mimic markedly enhanced apoptosis and reduced Bcl-2 luciferase activity in H9c2 cells. Their findings suggest that in a DCM rat model, G-CSF could exert an anti-apoptotic effect by reducing the expression of miR-34a [67].

6.4. MiR-340-5p

The human miR-340 is categorized as an intragenic miRNA and can be found within the intronic region of the host gene RNF130, situated on chromosome 5q35.3. MiR-340 exhibits a high degree of conservation among mammals, and its expression pattern closely mirrors that of the host gene [68]. Zhu and colleagues sought to clarify the mechanism behind the potential involvement of miR-340-5p in DCM within the context of db/db mice. Initially, they established that the expression of miR-340-5p exhibited a significant increase in both cardiac tissues of mice and cardiomyocytes under diabetic conditions. As well, they found that elevating the levels of miR-340-5p worsened DCM, leading to more pronounced myocardial fibrosis and increased dysfunction in db/db mice. This exacerbation was evident through higher numbers of apoptotic cardiomyocytes, increased ROS production, and compromised mitochondrial function. Furthermore, they revealed that the use of a robust decoy (TUD) vector effectively inhibited miR-340-5p, resulting in the prevention of ROS generation and apoptosis. This intervention demonstrated promise in mitigating the effects of DCM. They pinpointed myeloid cell leukemia 1 (Mcl-1) as a primary target gene affected by miR-340-5p and demonstrated that Mcl-1 silencing was responsible for heightened functional impairment of mitochondria, elevated oxidative stress, and cardiomyocyte apoptosis. This, in turn, contributed to cardiac dysfunction in diabetic mice. Thereby, miR-340-5p, through its anti-apoptotic effect, plays a pivotal role in the progression of DCM and could be a viable target for therapeutic strategies in this context [69].

6.5. MiR-22

miR-22 exhibits a high degree of conservation among vertebrates and is broadly expressed in multiple organs. The miR-22 gene resides on chromosome 17p13, and its complementary DNA (cDNA) synthesized by RNA polymerase II is approximately 1.3 kilobase in length [70]. Tang and colleagues explored the protective function of miR-22 in the context of DCM. They noted that H9c2 cells exposed to HG conditions exhibited oxidative stress-induced damage and apoptosis, both of which were mitigated by miR-22. As well, Sirtuin 1 (Sirt1) expression markedly decreased in diabetic mice and H9c2 cells treated with HG, but its levels were reinstated through miR-22 upregulation. Their bioinformatic analysis and subsequent luciferase reporter assay confirmed that Sirt1 was a plausible target gene of miR-22. They additionally confirmed that miR-22 enhanced the expression of Sirt1 by directly binding to the 3′-UTR of the Sirt1 gene. The increased expression of Sirt1 led to improved cell viability and a reduction in both oxidative stress-induced injury and apoptosis in H9c2 cells treated with HG, akin to the effects of miR-22. Importantly, functional investigations also unveiled that the safeguarding benefits provided by miR-22 against oxidative stress injury and apoptosis induced by HG were nullified when Sirt1 was suppressed. In this manner, miR-22 has the potential to serve as a therapeutic target for individuals with diabetes suffering from cardiac insufficiency [71].

6.6. MiR-532

miR-532-5p is situated on the Xp11.23 region of the human chromosome, and the mature form of miR-532-5p comprises 22 nucleotides. MiR-532-5p sequence analysis using ClustalW reveals a conserved sequence across different species, indicating its significant role in the process of evolutionary development [72]. Chandrasekera and colleagues investigate whether diabetes leads to the disruption of miR-532 regulation and whether this dysregulation is linked to increased apoptosis. MiR-532 expression substantially upregulated in the right atrial appendage tissue of individuals with type 2 diabetes who were undergoing coronary artery bypass graft surgery. This upregulation was

correlated with a notable decrease in the expression of its anti-apoptotic target protein, apoptosis repressor with caspase recruitment domain (ARC), and an increase in cardiomyocytes showing a positive signal for the TUNEL assay. Furthermore, a favorable association existed between apoptosis and the levels of miR-532, and elevation of miR-532 occurred before the initiation of pro-apoptotic caspase-3/7 activity. As well, miR-532 silencing in human cardiomyocytes cultured in a high-glucose environment suppressed the reduction of ARC expression and mitigated apoptotic cell death. In summary, diabetes-induced activation of miR-532 significantly contributes to the acceleration of cardiomyocyte apoptosis. Consequently, miR-532 holds promise as a potential therapeutic candidate for counteracting the loss of cardiomyocytes caused by diabetes [73].

6.7. MiR-1

MiR-1 is generated from two distinct precursor molecules, namely miR-1-2 and miR-1-1, which are situated on chromosome 18 and chromosome 20, respectively. Following their translocation to the cytoplasm via Exportin 5, miR-1-1 and miR-1-2 undergo identical maturation processes, resulting in the formation of mature miR-1 [74]. Cheng and colleagues explored the involvement of miR-1 in glucose-triggered apoptosis and elucidated the mechanistic basis for its effects in rat cardiomyocyte H9C2 cells. Their findings revealed a notable upregulation in miR-1 expression alongside a considerable downregulation in LXRα expression within H9C2 cells upon exposure to glucose. Furthermore, silencing of miR-1 led to a substantial reduction in apoptosis, an elevation in mitochondrial membrane potential (ΔΨ), and the inhibition of the cleavage of poly (adenosine diphosphate-ribose) polymerase, caspase-3, and caspase-9. As well, it also induced a notable reduction in the levels of Bcl-2 expression, while concurrently promoting Bax expression. In addition, it was shown that miR-1 exerts regulatory effect over LXRα; transfection with anti-miR-1 markedly enhanced LXRα expression. GW3965 is a synthetic LXR agonist in which could protected HL-1 cells against hypoxia-reoxygenation induced apoptosis. Administration of the LXR agonist GW3965 mitigated apoptosis in cells where anti-miR-1 had been introduced during glucose-induced conditions. In this manner, miR-1 involved in modulating cardiomyocyte apoptosis through LXRα and offer fresh insights into the intricate mechanisms underlying DCM [75,76].

6.8. MiR-483-3p

The Human miR-483 is positioned in the second intron of the IGF2 gene on chromosome 11p15 and is acknowledged to be co-expressed with its host gene, IGF2. The precursor structure of miR-483, characterized by a stem-loop, undergoes maturation resulting in the generation of two distinct mature forms: miR-483-3p and miR-483-5p [77]. Qiao and colleagues explored the role of miR-483-3p in cardiomyocytes exposed to a hyperglycemic environment, conducting investigations in both *in vitro* and *in vivo* settings. Their findings demonstrate an elevation in the expression of miR-483-3p in diabetic mice and in cultured cardiomyocytes designed to mimic a hyperglycemic state. They revealed that the upregulation of miR-483-3p in transgenic mice afflicted with DM intensified cardiomyocyte apoptosis through the transcriptional repression of insulin-like growth factor 1 (IGF1). So, under hyperglycemic conditions, miR-483-3p-IGF1 contributes to the induction of apoptosis in myocardial cells. As well, ectopic expression of miR-483-3p led to a reduction in the protein expression of Bcl2, a pivotal factor in DCM known for its anti-apoptotic function. Hence, it seems that miR-483-3p contributes to the deterioration of myocardial structure and function caused by diabetes in cardiomyocytes via a pathway involving miR-483-3p and Bcl2. Thereby, the increased expression of miR-483-3p exacerbates apoptotic processes in cardiomyocytes within the diabetic context, thus highlighting the potential of miR-483-3p as a therapeutic target [78].

6.9. MiR-29a

The MiR-29 family comprises three individual members, specifically miR-29a, miR-29b, and miR-29c. In humans, miR-29a and miR-29b-1 are encoded on chromosome 7q32.3, whereas miR-29b-2 and miR-29c are encoded on chromosome 1q32.2 [79]. The elevation of miR-29a expression led to enhancements in cardiac structure and function, along with a reduction in myocardial histological irregularities and fibrosis, ultimately mitigating cardiomyocyte apoptosis in rats with DCM. HG conditions induced apoptosis in H9c2 cells, but miR-29a upregulation mitigated the impact of HG on cell function. Importantly, in comparison to the control group, the DCM and HG groups exhibited a significant increase in the protein levels of Bak1, cleaved-caspase3, and Bax, while the expression of Bcl-2 and Mcl-1 was notably reduced. However, the upregulation of miR-29a had the opposite effect, reversing these protein expression changes. Moreover, both bioinformatics-based prediction and Western blot analysis corroborated that miR-29a directly targets Bak1 and induces a reduction of Bak1 expression. In this manner, miR-29a exerted regulatory effect over cardiomyocyte apoptosis induced by both STZ and HG by specifically targeting Bak1, offering a fresh perspective on the pathogenic mechanisms underlying DCM [80].

6.10. MiR-186-5p

The human miR-186 is situated within the chromosomal region 1q31.1. Following the transcription of the human miR-186 gene and the subsequent processing of pri-miR-186, pre-miR-186 is produced. Through Dicer activity, pre-miR-186, characterized by its stem-loop structure, undergoes additional cleavage, leading to the generation of miR-186-3p and miR-186-5p. Based on deep sequencing data, it is evident that miR-186-5p, also known as miR-186, exhibits significantly higher abundance than miR-186-3p [81]. Recent bioinformatics analysis, along with a luciferase activity assay, demonstrated that TLR3 is directly targeted by miR-186-5p. The expression of miR-186-5p exhibited a reduction in cardiomyocytes exposed to HG, and the overexpression of miR-186-5p effectively counteracted HG-induced cardiomyocyte apoptosis while concurrently decreasing the protein level of cleaved caspase-3. As well, the inhibition of TLR3 downregulation attenuated apoptosis induced by HG and led to a decrease in the protein level of cleaved caspase-3 in cardiomyocytes. Notably, upregulation of TLR3 amplified cardiomyocyte apoptosis induced by HG and counteracted the impact of miR-186-5p. In this manner, miR-186-5p could suppress apoptosis in cardiomyocytes triggered by HG by downregulating the expression of TLR3. This indicates that miR-186-5p may represent a novel therapeutic approach for safeguarding against the development of DCM [82].

6.11. MiR-207

Xing and colleagues sought to explore the functions and underlying mechanisms of miR-207 in type 2 DCM. Their findings revealed an elevated rate of cell apoptosis accompanied by an increase in cleaved-caspase3 expression in the myocardial tissues of mice with Type 2 DCM and in neonatal mouse cardiac myocytes (NMCMs) exposed to PA. Their investigation disclosed a noteworthy increase in the expression of miR-207 in the myocardial tissues of mice with DCM and in NMCMs exposed to PA. Additionally, they observed that miR-207 suppressed the mRNA and protein expression of LAMP2 in NMCMs. Their subsequent investigative revealed that the introduction of miR-207 mimics had a pronounced effect on cellular apoptosis, as evidenced by a substantial augmentation in cleaved-caspase3 expression. Importantly, these observed effects were mitigated when LAMP2 was increased. Thereby, miR-207 exerts its influence on cardiomyocyte apoptosis by directly modulating LAMP2, a factor intricately involved in the pathogenesis of type 2 diabetic cardiomyopathy [83].

6.12. MiR-410-5p

MiR-410, a microRNA originating from the 14q32.2 mega-cluster, is situated within the Dlk-Dio3 domain, a region recognized for its association with processes related to development and growth [84]. The expression of miR-410-5p exhibited an elevation in the myocardial tissue of a rat model with diabetes mellitus. As well, the suppression of miR-410-5p led to heightened Bcl-2 expression while concurrently reducing the levels of cleaved-caspase-3 and Bax. Notably, overexpressing PIM1 yielded analogous effects to the inhibition of miR-410-5p, albeit it should be noted that PIM1's influence on Bcl-2 and Bax was subsequently reversed upon introduction of the miR-410-5p mimic. Additionally, the modulation of myocardial apoptosis by miR-410-5p involved the targeting of PIM1 and its downstream proteins, specifically, the Bcl-2/Bax axis. Thereby, the therapeutic intervention involving anti-miR-410-5p may serve as a viable strategy in the mitigation of cardiac apoptosis [85].

6.13. MiR-200b-3p

The miRNA-200 family, comprised of five individual members (namely, miR-200a, miR-200b, miR-200c, miR-429, and miR-141), holds special significance in the context of human health and the pathogenesis of various diseases. From a chromosomal perspective, the miR-200 family can be categorized into two distinct clusters: the miR-200ba/429 cluster, encompassing miR-200a, miR-200b, and miR-429, positioned on chromosome 1p36, and the miR-200c/141 cluster, housing miR-200c and miR-141, situated on chromosome 12p13 [86]. Xu and co-authors investigated the effects of miR-200b-3p concerning cardiomyocyte apoptosis in the context of DCM, with a specific focus on its regulatory impact within the CD36 and PPAR-γ signaling pathway. In their study, in the case of DCM, miR-200b-3p exhibited downregulated expression, while CD36 displayed an elevated expression level. As well, their findings revealed that the introduction of AgomiR-200b-3p effectively suppressed the CD36 expression, thereby exerting regulatory control over cardiomyocyte apoptosis within the context of DCM. It was also determined that CD36 activation played a pivotal role in the initiation of the PPAR-γ signaling pathway in the context of DCM. Notably, the inhibition of CD36 through either silencing or treatment with GW9662 exhibited a protective effect in rats against the development of DCM. Thereby, miR-200b-3p functions as a regulator of cardiomyocyte apoptosis in DCM by targeting CD36, thereby activating the PPAR-γ signaling pathway. In this manner, miR-200b-3p represents a promising candidate as a therapeutic target for the management of DCM [87].

6.14. MiR-223

The genomic locus for miR-223 is situated at the q12 region of the X chromosome [88]. MiR-223 demonstrated significant upregulation in the cardiomyocyte injury model induced by HG. Moreover, the use of a miR-223 inhibitor further ameliorated myocardial fibrosis and apoptosis, and effectively suppressed NLRP3 inflammasome in HG-induced H9c2 cells. Also, miR-223 silencing effectively dampened the activation of the NLRP3 inflammasome, leading to the alleviation of myocardial fibrosis and apoptosis in a model of DCM in rats. In this manner, the protective effect on DCM was notably achieved by inhibiting miR-223, primarily through its apoptosis-reducing mechanisms. This suggests that miR-223 could be considered as a viable therapeutic target for the management of DCM [89] (F).

7. Apoptosis-related lncRNA/miRNA axis in DCM

Recent findings suggest that ncRNAs assume a prominent role in the pathogenesis of DCM via diverse mechanisms. Of these, the emerging regulatory paradigm involving interplay among lncRNA, miRNA, and mRNA has garnered increased interest. These lncRNAs engage in interactions with miRNAs, subsequently exerting an influence on the expression of pertinent mRNAs. The lncRNA-miRNA-mRNA axis, which is involved in the pathophysiological processes of cardiomyocytes, including apoptosis, plays a significant role in instigating and advancing the development of DCM. In the following section, we underscore the novel advancements related to the lncRNA-miRNA-mRNA axis concerning cardiac apoptosis in the context of DCM progression.

7.1. LncRNA MALAT1/miRNA axis

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) stands out as one of the highly abundant lncRNAs in normal tissues. This particular lncRNA exhibits a high degree of conservation across mammalian species, and *in vitro* experiments have shown its capacity to govern alternative pre-mRNA splicing and gene expression [90]. Cheng and colleagues delved into the fundamental mechanism by which MALAT1 operates in the context of DCM. In their study, they induced a DCM model in mice by administering streptozocin, resulting in evident myocardial tissue cell hypertrophy and apoptosis. Notably, they observed an upregulation of Malat1 expression in the myocardium of the DCM mice. They detected increased expression levels of pro-apoptotic factors, including BAX, cleaved caspase 9, cleaved caspase 3, p21, and p53 along with a concurrent decrease in the expression of the anti-apoptotic factor BCL-2 within the myocardial tissue of DCM. As well, their subsequent *in vitro* analysis revealed a connection between high glucose treatment in cardiomyocytes, heightened Malat1 expression, significant cell apoptosis, and alterations in factors associated with apoptosis. Besides, they confirmed that Malat1 functions as a molecular sponge, sequestering miR-181a-5p, and that p53, a pivotal regulator of apoptosis, is a downstream target of miR-181a-5p. Thereby, their results demonstrate that Malat1 silencing mitigates cardiomyocyte apoptosis induced by HG by releasing miR-181a-5p. This mechanism potentially offers novel insights into diagnostic and therapeutic targets for DCM [91]. Moreover, Wang and colleagues assessed the functional roles of MALAT1 in the development of DCM. In their study, MALAT1 knockdown was observed to mitigate cardiac dysfunction and suppress cardiomyocyte apoptosis in db/db mice, as well as in mouse cardiomyocytes cultured in HG conditions. As well, MALAT1 recruited the histone methyltransferase EZH2 to the promoter region of miR-22, consequently repressing its expression. Notably, EZH2 led to an elevation in ATP-binding cassette transporter A1 (ABCA1) expression, a gene recognized as a target of miR-22. Furthermore, they observed that the inhibition of EZH2 resulted in the enhancement of cardiac function and the suppression of cardiomyocyte apoptosis in db/db mice and mouse cardiomyocytes cultured in HG, especially in the presence of MALAT1. This implies that MALAT1 mediates myocardial damage and apoptosis by orchestrating the recruitment of EZH2 to the promoter region of miR-22. In this manner, their results offer substantiating evidence for their hypothesis, indicating that MALAT1 plays a role in cardiac function and cardiomyocyte apoptosis through the EZH2/miR-22/ABCA1 signaling cascade, holding promise for potential therapeutic insights into DCM [92].

7.2. LncRNA GAS5/miRNA axis

The lncRNA known as growth arrest-specific 5 (GAS5) emerged as a pivotal component that we first identified in relation to the regulation of cell growth, differentiation, and developmental processes [93]. The expression of GAS5 was observed to be elevated in both AC16 cardiomyocytes treated with HG and in a rat model of diabetic myocardial injury. GAS5 silencing suppress myocardial damage induced by high glucose. As well, the attenuation of GAS5 expression effectively reversed cardiomyocyte injury and apoptosis through its mechanism of targeting miR-138 and subsequently reducing CYP11B2. Importantly, the attenuation of GAS5 expression effectively reversed cardiomyocyte injury and apoptosis through its mechanism of targeting miR-138 and

subsequently down-regulating CYP11B2. These findings offers a novel avenue for elucidating the underlying mechanisms in the development of DCM and identifies potential targets for the treatment of myocardial injury [94]. Furthermore, in another study, Tcf3 was identified as having an association with the Gas5 promoter, thereby facilitating the activation of GAS5 expression. As well, both GAS5 and Tcf3 were observed to stimulate apoptosis in NMC. Additionally, mmu-miR-320-3p exhibited binding affinity towards both GAS5 and Tcf3, and the Gas5/miR-320-3p/Tcf3 pathway was shown to exert a regulatory influence on the apoptosis of NMC. In this manner, modulation of NMC apoptosis in DCM is governed by the lncRNA GAS5, which is activated by Tcf3 [95]. In addition, Zhu and colleagues examined the elusive role of lncRNA GAS5 in the context of DCM. Their findings revealed a substantial increased expression of GAS5, both in *in vitro* and *in vivo* DCM models. Furthermore, they revealed that GAS5 silencing and the upregulation of miR-26a/b-5p not only significantly mitigated myocardial fibrosis in diabetic mice under *in vivo* conditions but also suppressed cardiomyocyte apoptosis induced by HG *in vitro*. In their study, miR-26a/b-5p was determined as a direct target of GAS5. As well, GAS5 silencing effectively mitigated myocardial fibrosis and inhibited HG-induced cardiomyocyte apoptosis by negatively modulating miR-26a/b-5p. In this manner, GAS5 plays a role in the promotion of cardiomyocyte apoptosis and the progression of DCM by modulating miR-26a/b-5p. This suggests that GAS5 could be a promising therapeutic target for DCM [96].

7.3. LncRNA H19/miRNA axis

H19 is characterized as an lncRNA approximately 2.3 kilobase in length, located on human chromosome 11p15.5. It is maternally expressed and subject to mutual imprinting with IGF2. H19 displays robust expression predominantly from the maternal allele in nearly all fetal tissues, while the paternal allele is subject to imprinting. H19 assumes a critical role during embryonic development; nevertheless, following birth, its expression is restricted to the myocardium and skeletal muscle [97]. Li and colleagues endeavored to examine the disease-causing function of H19 in the progression of DCM. In their study, in diabetic rats, there was a significant elevation in the expression of cleaved caspase-3 and an increase in the Bax/Bcl-2 ratio. However, these changes were notably reduced after the administration of pcDNA-H19 treatment. Their investigation revealed an increase in both the protein and mRNA levels of VDAC1 in diabetic rats, and these levels were subsequently decreased following lentivirus pcDNA-H19 administration. Their echocardiographic findings demonstrated that upregulating H19 expression significantly ameliorated the left ventricular dysfunction induced by hyperglycemia. Their ELISA results showed that the H19 enforced expression had a pronounced effect in reducing oxidative stress in myocardial tissue caused by hyperglycemia. Their subsequent experiments revealed that boosting miR-675 expression effectively restrained apoptosis in cardiomyocytes transfected with H19 siRNA, indicating that the reduction of H19 fosters apoptosis by inhibiting miR-675. Furthermore, they demonstrated that the VDAC1 expression was elevated in cardiomyocytes transfected with miR-675 antagomir, leading to a subsequent increase in apoptosis. It was also observed that VDAC1 silencing effectively suppressed apoptosis in cardiomyocytes transfected with miR-675 antagomir, indicating that the reduction of miR-675 prompts apoptosis by elevating VDAC1 expression. They subsequently revealed a correlation between elevated VDAC1 expression and cardiomyocyte apoptosis in response to HG, with H19 overexpression leading to reduced VDAC1 levels and the inhibition of apoptosis in HG-exposed cardiomyocytes. Ultimately, they disclosed that the upregulation of both VDAC1 and H19 had the capacity to enhance apoptosis in cardiomyocytes exposed to HG. In this manner, H19/miR-675 axis plays a role in regulating apoptosis induced by HG through the targeting of VDAC1, suggesting it may represent a new therapeutic approach in DCM treatment [98].

7.4. LncRNA KCNQ1OT1/miRNA axis

KCNQ1 Opposite Strand/Antisense Transcript 1 (KCNQ1OT1), also recognized as KCNQ1 overlapping transcript 1 or LIT1, is a non-spliced lncRNA spanning 91 kilobases in size and situated on chromosome 11p15.5. The KCNQ1OT1 gene is one component of a gene cluster subject to genomic imprinting, which is an epigenetic alteration that results in parent-specific modifications to gene expression [99]. Zhao and colleagues explored the fundamental regulatory mechanisms associated with KCNQ1OT1 in DCM. In their study, in human cardiomyocytes exposed to HG, there was an upregulation in the levels of PDCD4 and KCNQ1OT1, whereas miR-181a-5p exhibited a reduction in expression. Their research illustrated that KCNQ1OT1 had a negative regulatory effect on the expression of miR-181a-5p, while miR-181a-5p, in turn, negatively regulated the expression of PDCD4. Importantly, they confirmed that the downregulation of KCNQ1OT1 curtailed cell apoptosis *in vitro*, while the miR-181a-5p silencing nullified the impacts of KCNQ1OT1 knockdown. They also revealed that the PDCD4 upregulation counteracted the reduction in apoptosis induced by the elevated expression of miR-181a-5p. Altogether, KCNQ1OT1 silencing led to a decrease in the PDCD4 expression by modulating miR-181a-5p and, as a result, mitigated cardiomyocyte apoptosis in the *in vivo* model of DCM. In this manner, in DCM, KCNQ1OT1 and its target gene miR-181a-5p control cardiomyocyte apoptosis by influencing the regulation of PDCD4 [100].

7.5. LncRNA MIAT/miRNA axis

Myocardial infarction-associated transcript (MIAT), alternatively referred to as retina non-coding RNA2 or Gomafu (the mouse homolog of MIAT), was initially identified as an lncRNA in 2006 and is positioned on the human chromosome 12q12.1 [101]. Zhou and colleagues sought to elucidate the pathological function of MIAT in the progression of DCM. In their study, silencing of MIAT expression was observed to decrease cardiomyocyte apoptosis and enhance left ventricular function in rats with diabetes. Their investigation revealed that HG could upregulate MIAT expression and prompt apoptosis in cultured neonatal cardiomyocytes. Their study indicated that HG could enhance the expression of MIAT and trigger apoptosis in cultured neonatal cardiomyocytes. Their luciferase reporter assay and RNA immunoprecipitation assay provided evidence that miR-22-3p interacted with MIAT in a manner reliant on AGO2, and miR-22-3p directly targeted DAPK2. Their results also suggested that the suppression of MIAT reduced DAPK2 expression and effectively hindered apoptosis in cardiomyocytes subjected to HG conditions. Their results further indicated that the silencing of MIAT resulted in a decrease in DAPK2 expression and successfully suppressed apoptosis in cardiomyocytes exposed to HG. In conclusion, MIAT might act as a ceRNA to enhance the expression of DAPK2 by sequestering miR-22-3p, ultimately contributing to cardiomyocyte apoptosis and participating in the pathogenic processes of DCM [102].

7.6. LncRNA AK139328/miRNA axis

Yu and colleagues set out to examine the impact of the lncRNA AK139328 on myocardial ischemia/reperfusion injury (MIRI) in diabetic mice. They observed that lncRNA AK139328 silencing alleviated myocardial ischemia/reperfusion injury in diabetic mice and prevented cardiomyocyte apoptosis in this diabetic context. They observed that the suppression of lncRNA AK139328 alleviated myocardial ischemia/reperfusion injury in diabetic mice and inhibited cardiomyocyte apoptosis in this diabetic context. They also reported that the long non-coding RNA AK139328 directly influenced miR-204-3p. Their subsequent experimental findings demonstrated that the suppression of lncRNA AK139328 resulted in a notable elevation of miR-204-3p expression, leading to the prevention of cardiomyocyte autophagy and

consequently ameliorating myocardial ischemia-reperfusion injury (MIRI) in diabetic mice. In this manner, suppression of AK139328 through miR-204-3p targeting exhibited a mitigating effect on myocardial ischemia-reperfusion injury (MIRI) by modulating the process of apoptosis [103] (Fig. 4).

8. Therapeutic: from herbal medicine to molecular therapy

In the preceding section, a comprehensive elucidation of the molecular mechanisms governing the modulation and control of apoptosis through ncRNAs in DCM has been provided. Leveraging the extensive insights into the ncRNA-mediated molecular regulatory network associated with apoptosis dysfunction in DCM, novel therapeutic strategies for DCM have emerged. Therefore, in the following section therapeutic strategies aimed at modulating apoptotic activity via ncRNAs are discussed.

8.1. Herbal medicine-mediated apoptosis modulation via ncRNAs

Presently, an increasing body of preclinical investigations offers compelling evidence supporting the potential of herbal medicines as a promising therapeutic option for DCM. Catalpol is an iridoid glucoside that is commonly distributed among plant species from various botanical families within the Lamiales order, including Plantaginaceae, Lamiaceae, and Bignoniaceae. Its name was derived from the initial discovery of catalpol within the genus Catalpa in 1962. Catalpol was initially extracted from Rehmannia glutinosa by Kitagawa Hiroshi in 1971, thereby substantiating its influence on hyperglycemia. Rehmannia glutinosa, a herb extensively found in northern and central regions of China, holds a prominent place in traditional Chinese medicine. Its historical significance dates back to its initial documentation in Shen Nong's Herbal Classic, and for over a millennium, it has been employed in clinical practice for the treatment of diabetes. Therefore, catalpol is believed to play a role in the anti-diabetic properties of Rehmannia glutinosa and is increasingly under scrutiny for its potential involvement in the regulation of glycolipid metabolism and the management of diabetic complications, thereby emerging as a promising foundation for the exploration of novel candidates in the development of anti-diabetic drugs [104]. Zou and colleagues examined the cardioprotective mechanism of Catalpol in the context of DCM. They conducted *in vitro* experiments, which conclusively demonstrated that Catalpol effectively reduced the expression of the lncRNA Neat1 induced by HG in mouse cardiomyocytes. Their luciferase reporter analysis demonstrated that Neat1 could downregulate miR-140-5p transcription, thereby positively influencing the expression of HDAC4. Notably, their findings revealed that the miR-140-5p upregulation or the inhibition of HDAC4 effectively reversed the cardiomyocyte apoptosis induced by Neat1. Their subsequent *in vivo* investigations established that Catalpol mitigated myocardial injury in mice with DCM through the regulation of the Neat1/miR-140-5p/HDAC4 axis. Thus, their findings illustrate that Catalpol possesses cardioprotective properties against DCM through the modulation of the Neat1/miR-140-5p/HDAC4 pathway [105]. As well, Honokiol (HKL), a naturally occurring biphenolic compound sourced from the seed cone extract of Magnolia grandiflora, has a well-established history of utilization in traditional Chinese medicine. A multitude of research suggest that the advantageous effects of HKL can be largely ascribed to its antioxidative characteristics. Interestingly, HKL has exhibited robust protective effects against I/R injury in various

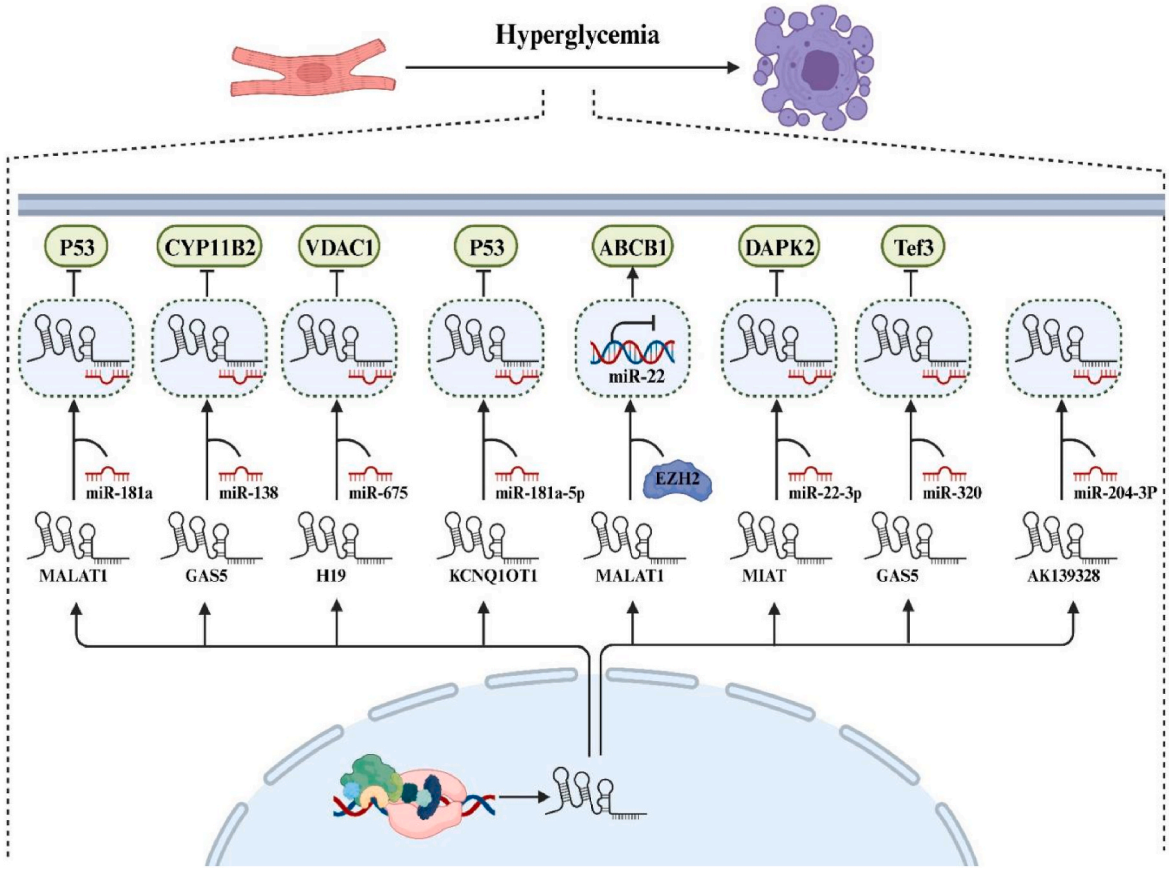

Fig. 4. A schematic representation of lncRNAs-miRNAs axis in cardiomyocyte apoptosis in DCM. This figure illustrating the intricate interplay of the lncRNAs and miRNAs axis in regulating cardiomyocyte apoptosis, pivotal in the pathogenesis of DCM. This depiction highlights the complex molecular interactions and regulatory mechanisms implicated in the progression of cardiac complications in diabetes.

organs, including the heart, brain, kidneys, and ovaries [106]. Furthermore, Zhang et al. observed that HKL significantly enhanced post-ischemic cardiac function, reduced infarct size, mitigated myocardial apoptosis, and attenuated the generation of ROS. They also revealed that HKL prominently stimulated the SIRT1 signaling pathway, facilitated the translocation of Nrf2 into the cell nucleus, augmented antioxidative signaling, and reduced apoptotic signaling. However, these effects were substantially nullified when SIRT1 siRNA was employed. Additionally, their *in vitro* investigations revealed that the cytoprotective effects of HKL were attenuated in the presence of Nrf2 siRNA, while SIRT1 expression and activity remained unaffected. Collectively, HKL mitigates MI/R injury in individuals with T1D through the improvement of oxidative damage and apoptosis within the myocardium, achieved by modulating the SIRT1-Nrf2 signaling pathway [107]. In this manner, Herbal medicines like Catalpol and Honokiol demonstrate potential in modulating apoptosis through ncRNAs, offering promising therapeutic options for DCM (Fig. 5).

8.2. Exosome-mediated apoptosis modulation via ncRNAs in DCM

Exosomes, small extracellular vesicles, are ubiquitously released by various cell types, fulfilling pivotal roles in intercellular communication during both states of well-being and pathophysiological conditions [108]. These roles primarily encompass the transmission of cellular payloads, including biologically active proteins, metabolites, and nucleic acids, to target cells [109]. They have garnered substantial attention for potential clinical utilization as therapeutic modalities. In this regard, Liu and colleagues sought to investigate the impact of exosomes on cardiomyocytes subjected to oxidative stress. They extracted exosomes from ADSCs and subsequently subjected them to scrutiny through the assessment of protein marker profiles, examination via transmission electron microscopy, and quantitative analysis via nanoparticle tracking. They employed exosomes derived from ADSCs to conduct ex vivo experiments examining the cardioprotective potential on cardiomyocytes following their exposure to oxidative stress. In their study, the exosomes derived from ADSCs displayed a diameter measuring 150 nm and demonstrated the presence of marker proteins, namely CD29 and CD9. Their findings revealed that ADSC-derived exosomes did not influence the proliferation of untreated cardiomyocytes; nevertheless, these exosomes derived from ADSCs mitigated apoptosis in myocardial cells exposed to oxidative stress. Thereby, exosomes derived from ADSCs could shield cardiomyocytes from the adverse effects of oxidative stress [110]. As well, the idea that endogenous proteins, as well as coding and ncRNA molecules enclosed within exosomes, are transported between cells and that the contents of exosomes retain functionality in target cells carries significant implications for the management of DCM. In this context, Sun and colleagues investigated the impact of exosomes originating from bone marrow stromal cells (BMSC-exo) on cardiomyocyte apoptosis and the injury associated with myocardial ischemia-reperfusion (MIRI). In their study, BMSC-exo promoted H9C2 cell proliferation and rescued these cells from apoptosis in the hypoxia/reoxygenation (H/R) model, underscoring the protective potential of BMSC-exo against cardiomyocyte injury induced by H/R. They employed transgenic H9C2 cells to demonstrate that miR-486-5p contained within BMSC-exo effectively inhibited H/R-induced apoptosis in H9C2 cells, with BMSC-exo downregulating PTEN expression in H9C2 cells through miR-486-5p, subsequently activating the PI3K/AKT pathway in an *in vitro* context. They ultimately established that BMSC-exo successfully ameliorated myocardial injury induced by ischemia/reperfusion *in vivo* by activating the PI3K/AKT pathway through the action of miR-486-5p. They revealed that miR-486-5p contained within BMSC-exo assumes a central role in the regulatory mechanism, wherein it acts by downregulating PTEN expression, stimulating the PI3K/AKT signaling pathway, and subsequently restraining apoptosis in damaged cardiomyocytes. Therefore, exosomes derived from BMSCs confer protection against myocardial ischemic injury [111]. Importantly, Wen and colleagues sought to investigate the mechanisms by which miR-144, a microRNA encapsulated within exosomes derived from MSCs, imparts a cardioprotective influence on cardiomyocyte apoptosis within a hypoxic environment, while also identifying the associated underlying mechanisms. In their study, exosomes were efficiently taken up by H9C2 cells following a 12-h co-incubation period, and the safeguarding of H9C2 cells from apoptosis mediated by exosomes coincided with the elevation of *p*-AKT levels. They noted that the transfection of cells with a miR-144 inhibitor attenuated the protective effect of exosomes against apoptosis. Their

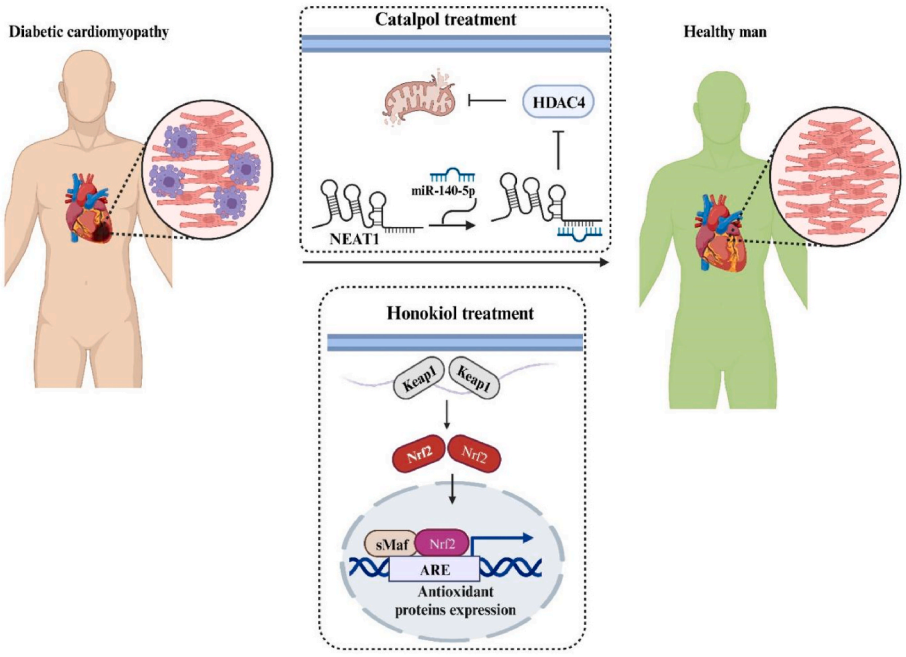

Fig. 5. A schematic representation of therapeutic effects of herbal medicine on DCM. This figure depicting the pivotal role of herbal compounds, Honokiol and catalpol, in averting apoptosis in DCM by targeting distinct pathways—Honokiol via Nrf2 signaling modulation and catalpol through non-coding RNA regulation.

subsequent functional investigations revealed that subjecting cells cultured under hypoxic conditions to miR-144 mimics led to a reduction in PTEN expression, an augmentation of *p*-AKT expression, and a prevention of H9C2 cell apoptosis, while the application of a miR-144 inhibitor resulted in an elevation of PTEN expression, a reduction in *p*-AKT expression, and an intensification of H9C2 cell apoptosis under hypoxic conditions. They also confirmed, using a luciferase reporter assay, that PTEN was indeed a target of miR-144. They finally demonstrated that cells subjected to SF1670, a specific inhibitor of PTEN, exhibited elevated levels of *p*-AKT expression and reduced apoptosis in H9C2 cells. Their results illustrate that exosomes originating from MSCs mitigate apoptotic cell injury under hypoxic conditions by transporting miR-144 to the recipient cells, which subsequently acts on the PTEN/AKT pathway. In this manner, exosomes derived from MSCs offer a potential and promising platform for delivering miRNA-based therapies aimed at improving ischemic conditions [112]. Additionally, Chen and colleagues conducted a study with the objective of examining the impact of exosomes derived from BMSCs loaded with miR-125b on rats subjected to ischemia-reperfusion injury (I/R). They initially forecasted and subsequently validated the target associationbetween miR-125b and SIRT7, employing both StarBase3.0 and a dual-luciferase reporter gene assay. In their study, the levels of miR-125b were found to be decreased in both myocardial tissues and cells subjected to ischemia-reperfusion (I/R), while the introduction of BMSC-Exo-125b substantially elevated miR-125b expression in I/R myocardial cells. They revealed that the administration of BMSC-Exo-125b markedly enhanced cell viability, reduced the apoptotic rate, decreased the expression of caspase-3 and Bax, elevated Bcl-2 levels, and mitigated the concentrations of IL-6, IL-1β, and TNF-α in I/R myocardial cells. Notably, it was established that BMSC-Exo-125b effectively reduced the expression of SIRT7 in myocardial cells. They ultimately disclosed that the administration of BMSC-Exo-125b ameliorated the pathological impairments and attenuated the expression of SIRT7 within the myocardial tissues of I/R rats. Thereby, exosomes derived from BMSCs containing miR-125b exhibited myocardial protection against I/R injury through the specific targeting of SIRT7 [113]. In this manner, exosomes, particularly those derived from ADSC, and BMSCs, play a critical role in reducing cardiomyocyte apoptosis under HG conditions through the delivery of specific miRNAs, which modulate key apoptosis-related signaling pathways like PI3K/AKT and target genes like PTEN and SIRT7. These findings highlight the therapeutic potential of exosome-mediated miRNA delivery in managing DCM (Fig. 6).

8.3. *Locked nucleic acid (LNA)-miRNAs complex-mediated apoptosis modulation in DCM*

Locked Nucleic Acids (LNAs) represent a recent addition to the repertoire of RNA analogs, characterized by enhanced binding affinity, sequence specificity, thermal stability, and resistance to nuclease degradation, attributed to their distinctive structural properties [114]. Ghosh and colleagues sought to elucidate the pathological significance of miR-320, a pro-apoptotic microRNA predominantly found in cardiomyocytes, in the pathogenesis of non-ischemic diabetic heart disease (NiDHD). They observed a substantial increase in the expression of miR-320, which correlated with a decrease in its target protein, insulin-like growth factor-1 (IGF-1), in the right atrial appendage tissue from advanced stages of cardiomyopathy in type 2 diabetic db/db mice, as well as in human ventricular cardiomyocytes (AC-16 cells) cultured in a HG environment. As well, in their study, *in vitro* silencing of miR-320 in AC-16 cells exposed to HG, accomplished through the application of Locked Nucleic Acid (LNA) anti-miR-320, significantly mitigated HG-induced apoptosis by reinstating the expression of Bcl-2 and IGF-1. They finally revealed that *in vivo* silencing of miR-320 in 24-week-old db/db mice afflicted with type 2 diabetes resulted in diminished cardiomyocyte apoptosis, reduced interstitial fibrosis, and the restoration of vascular density. Their investigation furnishes substantiation that miR-320 represents a tardily responsive microRNA exacerbating apoptosis and cardiac dysfunction in the context of DCM, and therapeutic suppression of miR-320 proves advantageous in partially ameliorating the compromised cardiac functionality [115]. Importantly, long-term studies are needed to assess the safety and efficacy of LNA anti-miR-320, including potential off-target effects and the optimal delivery methods for clinical application.

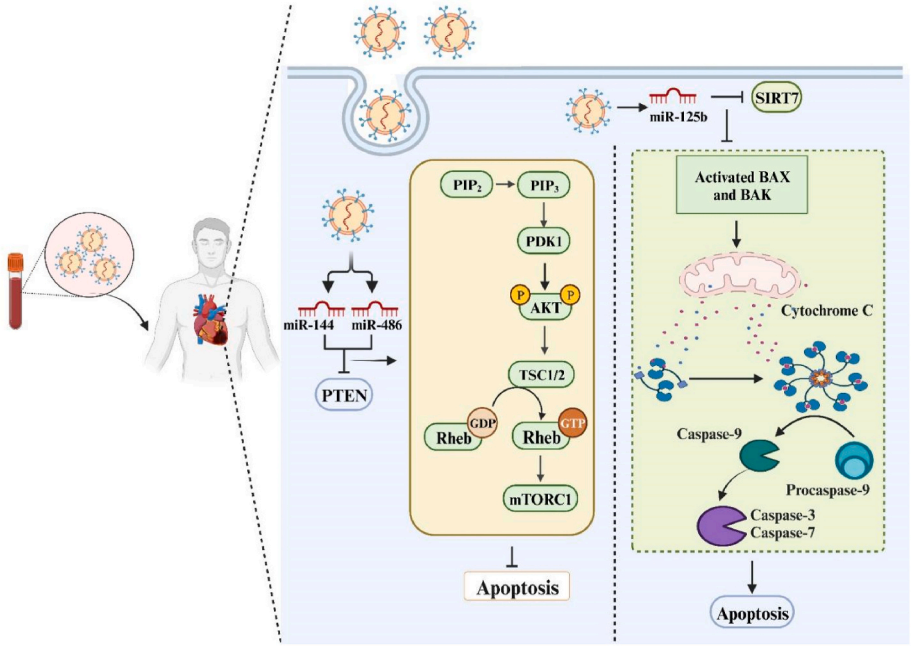

Fig. 6. Exosomal miRNA-mediated Regulation of Apoptosis in DCM. Exosomal miR-486-5p and miR-144 target PTEN, leading to the activation of the PI3K/AKT signaling pathway, which subsequently inhibits apoptosis in cardiomyocytes. Additionally, exosomal miR-125b targets and represses SIRT7, preventing cardiomyocyte apoptosis and providing further protection. These pathways highlight the crucial roles of exosomal miRNAs in regulating cell survival and suggest potential therapeutic strategies for preventing DCM development.

8.4. NcRNA-mediated apoptosis modulation in DCM via viral vector

Viral vectors are commonly employed instruments in the toolkit of molecular biologists for the delivery of genetic material into cellular structures [116]. Adenoviral vectors are created by substituting viral genes with exogenous transgenes, facilitating their delivery to a broad spectrum of cells, including both proliferating and quiescent ones, while also enabling robust transgene expression. As well, Adeno-associated viruses (AAVs) stand out as frequently utilized vectors for precision gene delivery, and their extensive examination has led to the authorization of numerous gene therapies designed to address human ailments [117]. The AAV vector possesses distinctive characteristics that offer clinical advantages, such as a wide range of cell targeting, limited immunogenic response, straightforward manufacturing, non-pathogenicity, infrequent integration into the host chromosome, and the capacity for sustained transgene expression in long-term [118]. Yin et al. explored the effectiveness of a miR-30c-centric therapeutic approach for both the management and prevention of DCM. Initially, they observed an upregulation of PGC-1β in the cardiac tissue of db/db mice, which was implicated in the perturbation of cardiac metabolism. Then, they established that miR-30c exerted regulatory control over PGC-1β, both in *in vivo* and *in vitro* experimental settings. Subsequent functional investigations revealed that the introduction of exogenous miR-30c through the rAAV system in db/db mice effectively enhanced glucose and lipid utilization, reduced excessive ROS generation, mitigated myocardial lipid accumulation, and consequently ameliorated cardiomyocyte apoptosis and cardiac dysfunction via the PGC-1β/PPARα signaling pathway. These findings substantiated the cardioprotective function of miR-30c in the context of cardiac metabolism in diabetes, presenting a novel and promising strategy for addressing DCM [119]. Furthermore, Wu et al., using gain-of-function and loss-of-function methodologies, unveiled the pro-apoptotic roles of Meg3 in cardiomyocytes of rodent origin. They noted that under hypoxic conditions, Meg3 is directly elevated by p53 and plays a role in the regulation of apoptosis by directly interacting with the RNA-binding protein FUS (fused in sarcoma). As well, in their study, adult mice with MI who received intramyocardial injections of an adeno-associated virus serotype 9 (AAV9) system containing Meg3 shRNA demonstrated a notable enhancement in cardiac function. They also noted an elevation of MEG3 in clinical samples of heart failure and observed its rather conservative pro-apoptotic role in human cardiomyocytes derived from human embryonic stem cells. Together, their findings suggest that the Meg3–FUS complex induced by p53 plays a significant role in cardiomyocyte apoptosis following MI. The targeted suppression of this complex in cardiomyocytes using the AAV9 system holds promise as a method worthy of preclinical investigation for MI treatment [120]. Moreover, Chen et al. sought to investigate the possible involvement of the lncRNA MEG3 and to delve into the mechanisms underlying its actions in human AC16 cardiomyocytes exposed to HG conditions. Their findings indicated an elevated expression of MEG3 in AC16 cells exposed to HG conditions, and MEG3 silencing effectively mitigated the apoptosis induced by HG in AC16 cells. Their mechanistic investigation revealed that MEG3 directly interacts with miR-145 within AC16 cells, resulting in the upregulation of PDCD4 expression. Their rescue experiments illustrated that the impact of MEG3 in AC16 cells subjected to HG conditions was, to some extent, contingent on its inhibitory effect on miR-145. Thereby, elevation of miR-145 levels conferred protection to human cardiomyocytes against apoptosis induced by HG, implying that miR-145 represents a promising novel therapeutic approach for safeguarding against the development of DCM [121]. Importantly, Wu et al. sought to investigate the functional significance of HMGA1 in streptozotocin-induced diabetic cardiomyopathy and elucidate the associated mechanisms. In their study, they observed an elevation in HMGA1 expression within the hearts of diabetic mice and in cardiomyocytes exposed to HG. They observed that HMGA1 upregulation expedited cardiomyocyte apoptosis induced by HG, whereas HMGA1 silencing alleviated apoptosis in cardiomyocytes exposed to HG. Their findings revealed that upregulating HMGA1 levels in mouse hearts through the AAV9 delivery system exacerbated the inflammatory response, elevated apoptosis, and hastened the onset of cardiac dysfunction in a streptozotocin-induced diabetic mouse model. Their mechanistic investigation determined that HMGA1 impeded autophagy through the regulation of the P27/CDK2/mTOR signaling pathway, primarily inhibiting autophagy formation rather than its degradation. Furthermore, their study demonstrated that the overexpression of P27 in the hearts of mice mitigated the enhanced cardiac remodeling, encompassing apoptosis and dysfunction, induced by elevated levels of HMGA1 in diabetic mice. Their luciferase reporter assay validated that HMGA1's influence on P27 was mediated through miR-222, and the introduction of a miR-222 antagomir effectively counteracted the pro-apoptotic effects of HMGA1 *in vitro*. Taken together, HMGA1 is involved in the progression of cardiac apoptosis and dysfunction in the context of DCM through a regulatory pathway dependent on miR-222, modulating P27/CDK2/mTOR-mediated autophagy. Thus, novel therapeutic approaches directed at miR-222 and HMGA1 hold promise for the potential treatment of DCM [122]. In addition, *Zheng* and colleagues explored whether the suppression of miR-195 could mitigate DCM in a mouse model with type 1 diabetes induced by streptozotocin (STZ). In their study, the expression of miR-195 exhibited an elevation, while the levels of its target proteins, specifically B cell leukemia/lymphoma 2 and sirtuin 1, were reduced in the hearts of mice with type 1 diabetes induced by STZ and those with type 2 diabetes in the db/db model. As well, systemic administration of an adenoviral vector carrying an anti-miR-195 construct resulted in miR-195 suppression within the cardiac tissue, leading to reduced caspase-3 activity, decreased oxidative stress, alleviated myocardial hypertrophy, improved myocardial function, and a simultaneous upregulation of B cell leukemia/lymphoma 2 and sirtuin 1 in mice induced with STZ-induced diabetes. As well, increased expression of miR-195 is effective in inducing apoptosis in cardiomyocytes and reducing angiogenesis in cardiac endothelial cells in *in vitro* experiments. Notably, suppression of miR-195 effectively inhibited apoptosis in cardiac endothelial cells when exposed to NEFA, a significant characteristic associated with diabetes. Therefore, therapeutic inhibition of miR-195 mitigated myocardial hypertrophy and apoptosis, suggesting a potential novel treatment approach for mitigating DCM [123]. These finding demonstrated that ncRNA-mediated therapies, delivered via viral vectors such as adenoviral and AAVs, show significant promise in modulating apoptosis and improving cardiac function in DCM (Table 1).

9. Conclusion

DCM represents a form of cardiac dysfunction that emerges independently of hypertensive heart disease, coronary artery disease, and valvular heart disease. Typically, DCM is marked by the presence of left ventricular hypertrophy and diastolic dysfunction. A growing body of evidence has shown that apoptosis constitutes a significant component of DCM. However, the precise molecular mechanisms through which elevated glucose levels trigger cardiomyocyte apoptosis remain incompletely elucidated. Numerous categories of ncRNAs exist, and among the primary classes of functional ncRNAs that do not undergo translation into proteins are miRNAs and lncRNAs. Studies have documented the involvement of ncRNAs in the progression of DCM through their regulatory roles in both transcription and post-transcriptional processes. NcRNAs have recently gained prominence as significant modulators of cardiomyocyte apoptosis, thereby underscoring their potential involvement in cardiomyocyte injury, which contributes to the onset and advancement of DCM. In this regard, recent investigation has explored the involvement of miRNAs in the regulation of the p53-p21 pathway in HG-induced cardiomyocyte hypertrophy and apoptosis. The experimental results revealed increased myocardial expression of p21 and p53 genes and significantly diminished expression of miR-181a

Table 1
Therapeutic agents used for modulating gene expression to reduce apoptosis in cardiomyocytes under HG conditions.

Therapeutic agent	Category	Mechanism of action	Ref.
G-CSF	Cytokine	By reducing miR-34a inhibit cardiomyocyte apoptosis	[124]
Dh404	Synthetic compound	By activating Nrf2 reduce cardiomyocytes apoptosis	[61]
GW3965	Synthetic chemical compound	By activating LXRα reduce cardiomyocytes apoptosis	[75]
GW9662	Synthetic chemical compound	By inhibiting CD36 reduce cardiomyocytes apoptosis	[87]
Catalpol	Herbal	By decreasing lncRNA Neat1, increase miR-140-5p, and decrease HDAC4, reversed the cardiomyocyte apoptosis	[105]
Honokiol	Herbal	By modulating SIRT1-Nrf2 signaling pathway mitigated myocardial apoptosis	[107]
BMSC-*exo*-miR-486-5p	Exosomal miRNA	miR-486-5p by targeting PTEN, activate PI3K/AKT pathway, inhibit cardiomyocyte apoptosis	[111]
MSCs-*exo*-miR-144	Exosomal miRNA	miR-144 by targeting PTEN, activate PI3K/AKT pathway, inhibit cardiomyocyte apoptosis	[125]
BMSC-*exo*-miR-125b	Exosomal miRNA	miR-125b by targeting SIRT7 inhibit cardiomyocyte apoptosis	[126]
LNA-*anti*-miR-320	Synthetic miRNA	By silencing miR-320, mitigated HG-induced apoptosis in cardiomyocytes	[115]
rAAV9-miR-30c	Viral vector-mediated miRNA	miR-30c by targeting PGC-1β ameliorated cardiomyocyte apoptosis	[127]
AAV9- Meg3 shRNA	Viral vector-mediated miRNA	By inhibiting Meg3 Reduce cardiomyocyte apoptosis and improve cardiac function	[120]
si-MEG3	Synthetic miRNA	By inhibiting Meg3, and upregulating miR-145 suppressed the HG-induced apoptosis in cardiomyocyte	[128]
AAV9-shHMGA1	Viral vector-mediated miRNA	By silencing HMGA1 increases miR-222 and alleviated apoptosis in cardiomyocytes exposed to HG	[129]
Ad-*anti*-miR-195	Viral vector-mediated miRNA	By silencing miR-195 prevented apoptosis in cardiac endothelial cells	[130]

and miR-30c in diabetic patients, DCM rats, and cardiomyocytes treated with HG. As well, the luciferase assay verified that miR-30c and miR-181a directly target p53. Notably, the upregulation of miR-30c or miR-181a resulted in reduced levels of p53, p21, ANP, cardiomyocyte cell size, and apoptosis in cardiomyocytes exposed to HG. Subsequently, simultaneous upregulation of these microRNAs led to a more pronounced reduction in cardiomyocyte hypertrophy and apoptosis, indicating a synergistic impact of these microRNAs. Therefore, perturbation in the expression of miR-30c and miR-181a is implicated in the overactivity of the p53-p21 pathway, ultimately resulting in cardiomyocyte apoptosis and the subsequent progression of DCM [71]. Importantly, in the final section, we demonstrated that ncRNAs can effectively modulate apoptotic processes in DCM, offering a promising therapeutic strategy against this condition.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

No research data was included in this study.

Competing interests

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Declaration of generative AI and AI-assisted technologies in the writing process

The authors did not use generative AI or AI-assisted technologies in the development of this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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