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The study of the mechanism of non-coding RNA regulation of programmed cell death in diabetic cardiomyopathy

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Abstract
Diabetic cardiomyopathy (DCM) represents a distinct myocardial disorder elicited by diabetes mellitus, characterized by aberrations in myocardial function and structural integrity. This pathological condition predominantly manifests in individuals with diabetes who do not have concurrent coronary artery disease or hypertension. An escalating body of scientific evidence substantiates the pivotal role of programmed cell death (PCD)—encompassing apoptosis, autophagy, pyroptosis, ferroptosis, and necroptosis—in the pathogenic progression of DCM, thereby emerging as a prospective therapeutic target. Additionally, numerous non-coding RNAs (ncRNAs) have been empirically verified to modulate the biological processes underlying programmed cell death, consequently influencing the evolution of DCM. This review systematically encapsulates prevalent types of PCD manifest in DCM as well as nascent discoveries regarding the regulatory influence of ncRNAs on programmed cell death in the pathogenesis of DCM, with the aim of furnishing novel insights for the furtherance of research in PCD-associated disorders relevant to DCM.

Keywords Non-coding RNA · Programmed cell death · Diabetic cardiomyopathy · Mechanisms of action

Introduction

Diabetic Cardiomyopathy (DCM) serves as a prevalent complication stemming from diabetes mellitus, typified by anomalous ventricular myocardial structure and functionality. The etiology of DCM exists independently of additional pathological factors such as hypertension, coronary heart disease, and valvular disorders. Notably, diabetic individuals are predisposed to a 2–fivefold elevated risk of heart failure in comparison to non-diabetic counterparts [1]. Hyperglycemia exerts detrimental impacts on cardiac function and structure, precipitating myocardial cellular hypertrophy, myocardial fibrosis, and impairments in left ventricular systolic and diastolic functionality, which invariably culminate in heart failure, arrhythmia, and cardiogenic shock [2]. Currently, there is a lack of universal consensus regarding pharmacological interventions for DCM on a global scale. The primary clinical treatment strategies focus on glycemic control and the administration of ACEI inhibitors and β-adrenergic receptor blockers, aimed at decelerating disease progression. However, the prohibitive costs associated with novel targeted pharmacological agents, such as DPP-4 inhibitors and SGLT-2 inhibitors, restrict their clinical application. Furthermore, the pathogenesis of DCM remains complex and is not fully elucidated. Though incompletely understood, extant literature suggests that its pathogenesis may be associated with metabolic dysregulation, oxidative stress, systemic low-grade inflammatory responses, and multiple forms of programmed cell death including apoptosis, autophagy, pyroptosis, and ferroptosis [3]. Therefore, an exhaustive and in-depth examination of DCM's pathogenesis is imperative for the identification of novel and efficacious therapeutic targets and pharmaceutical agents, bearing significant implications for the enhancement of patient prognosis and the amelioration of life quality.

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Programmed cell death (PCD) is an integral biological process that all viable cells inevitably undergo at the terminus of their lifecycle [4]. Classical research primarily categorized cell death into apoptosis and necrosis [5]. Recent burgeoning literature indicates the emergence of a novel form of cell death distinct from apoptosis and necrosis, termed "programmed cell death," encompassing autophagy, pyroptosis, ferroptosis, and necroptosis, each possessing distinct and independent regulatory pathways [6]. Accumulating evidence elucidates the interrelated nature of different PCD pathways at various molecular strata, playing pivotal roles in cardiovascular disorders and specifically in the progression of DCM [7].Strategies to regulate PCD in DCM have thus emerged as one of the focal points in current DCM preventive and therapeutic research. Recent studies indicate that non-coding RNA (ncRNA) plays a regulatory role in PCD within the context of DCM. Consequently, the conceptualization of therapeutic approaches targeting PCD via ncRNAs holds promise as a prospective strategy for DCM treatment. Based on these premises, we summarize the relationships between ncRNAs and four types of PCD (apoptosis, autophagy, pyroptosis, ferroptosis, and necroptosis) observed in DCM, elucidating the role of ncRNAs in modulating PCD for DCM treatment, with the objective of identifying novel therapeutic targets.

Apoptosis in diabetic cardiomyopathy: an in-depth review

Overview of apoptosis

Apoptosis, commonly acknowledged as a seminal and extensively investigated form of Programmed Cell Death (PCD), is characterized by a distinctive set of morphological features including cellular shrinkage, chromatin condensation, membrane blebbing, DNA fragmentation, and the generation of apoptotic bodies [8]. It serves as a critical biological mechanism for the elimination of superfluous, irreversibly damaged, or potentially deleterious cells, thus maintaining cellular homeostasis at an optimal turnover rate [9]. The process of apoptosis is principally instigated through two divergent pathways, specifically, the extrinsic and intrinsic pathways [10].The extrinsic pathway, also known as death receptor-mediated pathway, is initiated upon the binding of death ligands displayed on the cell membrane to their cognate death receptors. The principal receptors implicated in this pathway encompass FAS Cell Surface Death Receptor (FAS), TNF-related Apoptosis-Inducing Ligand Receptor (TRAIL-R), and TNF Receptor Superfamily Member 1A (TNFR1). The consequential ligation of these receptors and their ligands triggers the formation of the Death-Inducing Signaling Complex (DISC), subsequently facilitating the activation of caspase-8 [11]. This cascade culminates in the activation of effector caspases such as caspase-3 and caspase-7, thereby initiating extrinsic apoptotic responses [12].

Contrastingly, the intrinsic pathway—alternatively termed the mitochondrial-mediated pathway—is activated by endogenous stimuli such as hypoxia, DNA damage, ionizing radiation, and chemotherapeutic agents [13]. Under the influence of these stimuli, a dynamic imbalance between pro-apoptotic and anti-apoptotic members of the BCL-2 family is instigated, thereby triggering the intrinsic pathway [14]. BCL-2 family proteins, acting as key regulators in the intrinsic pathway, significantly modulate mitochondrial membrane permeability [15]. For instance, pro-apoptotic proteins (BAX, BAK, and BOK) and anti-apoptotic proteins (BCL-2, BCL-XL, and MCL-1) become activated during the apoptotic process, forming pores on the outer mitochondrial membrane, thereby releasing pro-apoptotic factors and inducing mitochondrial outer membrane permeabilization [16]. This permeabilization event subsequently elevates mitochondrial membrane permeability, facilitating the release of cytochrome c (Cyt-c) from the mitochondrial intermembrane space into the cytosol. Thereupon, Cyt-c forms a complex with pro-caspase-9 and APAF-1, generating the apoptosome complex, which further activates caspase-3 and caspase-7, thus inducing cellular apoptosis (Fig. 1).

Apoptosis in diabetic cardiomyopathy (DCM)

Both in vivo and clinical studies substantiate that cardiac cell apoptosis plays a pivotal role in the deterioration of cardiac function in diabetic patients. Critical target genes in the apoptotic process, such as pro-apoptotic genes caspase-3 and bax, and anti-apoptotic gene bcl-2, exert a crucial influence during the progression of DCM. For instance, one study demonstrated that the expression levels of caspase-3 and bax proteins were elevated in high-glucose (HG)-induced cardiomyocytes and in the hearts of DCM-induced rats, while the expression of the anti-apoptotic gene bcl-2 was diminished. Utilization of a specific caspase-3 inhibitor mitigated cellular apoptosis [2, 17]. Another study revealed that the p38MAPK and JNK signaling pathways serve as intermediaries in DCM-associated cellular apoptosis, and that HG-induced reactive oxygen species (ROS) could activate the MAPK signaling pathway, thereby promoting cardiomyocyte apoptosis [18]. Furthermore, Sirtuin 1 (SIRT1), a member of the Sirtuin family, displayed reduced expression in DCM rats and HG-induced cardiomyocytes. Enhancing its expression alleviated oxidative stress and inhibited cellular apoptosis in DCM [19]. Another study indicated that levels of SGLT1 were markedly elevated in the serum of diabetic patients as compared to non-diabetic subjects. Further research ascertained that the inhibition of SGLT1

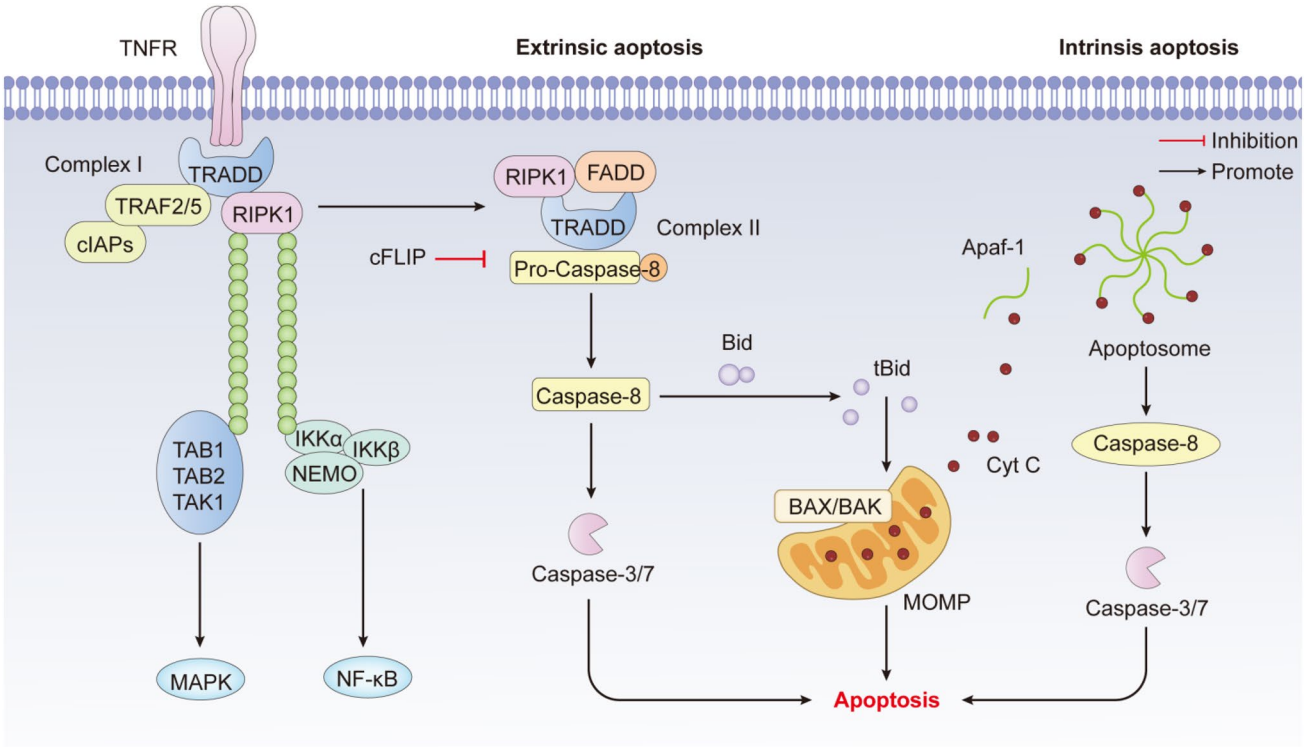

Fig. 1 Molecular mechanism diagram of apoptosis. Cellular apoptosis is induced through various external and internal pathways. Extrinsic apoptosis is triggered by the binding of death ligands (e.g., FasL, TNF-α) to their corresponding death receptors (e.g., Fas, TNF-R). This activates the death-inducing signaling complex (DISC), composed of FADD and TRADD, subsequently leading to the assembly of the DISC and death ligands. Caspase-8 is subsequently brought into close proximity and activated. This initial activation of caspase-8 triggers executioner caspases, specifically caspases-3 and -7, resulting in cellular apoptosis. Additionally, caspase-8 cleaves the protein Bid to produce tBid. The latter inhibits the anti-apoptotic protein Bcl-2 and induces the expression of pro-apoptotic proteins BAX/BAK, thereby promoting apoptosis. The permeabilization of the mitochondrial outer membrane (MOMP) serves as a critical step in apoptosis, leading to the release of intermembrane proteins such as cytochrome c. Cytochrome c forms a complex with Apaf-1, constituting the apoptosome, which in turn activates caspases-3 and -7, culminating in cellular apoptosis

led to a significant down-regulation of apoptotic markers, namely caspase-3 and bax, while upregulating the expression of anti-apoptotic protein bcl-2, thereby suggesting that the attenuation of apoptosis through SGLT1 inhibition could ameliorate cardiac function in DCM [18].

Endoplasmic reticulum (ER) stress and oxidative stress have been posited to play integral roles in the etiopathogenesis of DCM. In essence, persistent hyperglycemic stimulation induces ER stress, which in turn propels the cells toward apoptosis. Mechanistically, ER stress triggers the activation of caspase-12, which subsequently orchestrates the activation of downstream caspases, culminating in cellular apoptosis [21]. Additionally, multiple studies have confirmed that overactivation of the PI3K/AKT/mTOR signaling pathway may inhibit ERS and consequently suppress cellular apoptosis. Activation of the PI3K/Akt pathway promotes the phosphorylation of eNOS and mTOR. The activated eNOS further stimulates the production of nitric oxide (NO), a potent inhibitor of oxidative stress, thereby inhibiting cardiomyocyte apoptosis and exerting a protective effect in DCM [22]. Furthermore, heme oxygenase-1 (HO-1), an important signaling pathway in oxidative stress, mitigates cardiomyocyte apoptosis and ventricular remodeling in diabetic cardiomyopathy mouse models by activating the AKT/HO-1 signaling pathway, thereby exerting a cardioprotective role in DCM mice [23]. In summary, these findings indicate that cellular apoptosis is an empirically substantiated phenomenon in DCM and a significant contributor to the adverse outcomes of this disease. Future work necessitates a comprehensive and impartial analysis to identify key molecules exerting a specific impact on DCM.

Involvement of ncRNAs in cellular apoptosis in diabetic cardiomyopathy (DCM)

Modulatory influence of miRNAs on cardiomyocyte apoptosis in DCM

MiRNAs are small RNAs comprising fewer than 25 nucleotides, constituting less than 1% of the human genome.

Predominantly localized in the cytoplasm, miRNAs function by directly binding to the 3' untranslated region (3'UTR) of target mRNA transcripts, thereby inhibiting the expression of specific genes. [24]. An escalating corpus of empirical evidence increasingly underscores the indispensable role of microRNAs (miRNAs) in orchestrating cellular apoptosis, thereby contributing to the etiopathogenesis and subsequent progression of Diabetic Cardiomyopathy (DCM). For example, exposure to elevated concentrations of glucose (HG) conspicuously elicits the upregulation of miR-34a in AC16 cardiomyocytes. Effective mitigation of HG-induced apoptosis in AC16 cells can be achieved through transfection with miR-34a inhibitory molecules. Furthermore, SIRT1 has been identified as a direct downstream target of miR-34a, a molecule with salient involvement in cardiomyocyte apoptosis. Through the downregulation of SIRT1, miR-34a thus exerts a pro-apoptotic effect on cardiomyocytes [25]. In addition, the transfection of AC16 cells with miR-34a mimetics significantly accentuates apoptosis and concurrently attenuates bcl-2 luciferase enzymatic activity. These findings collectively indicate that miR-34a modulates cellular apoptosis in DCM via its influence on multiple target genes [26]. In a parallel vein, miR-410-5p is found to be overexpressed in the myocardial tissue of DCM-afflicted rats as well as in HG-induced cardiomyocytes. Importantly, the application of miR-410-5p inhibitors engenders an upregulation of bcl-2, concomitant with the suppression of bax and caspase-3 expression levels. Such evidence posits that miR-410-5p downregulation might serve as an efficacious strategy for averting cardiomyocyte apoptosis. Subsequent inquiries identified PIM1 as a direct target of miR-410-5p, further implicating miR-410-5p in the promotion of cardiomyocyte apoptosis via the negative modulation of PIM1 [27]. Likewise, miR-483-3p experiences augmented expression in both streptozotocin (STZ)-induced diabetic mice and HG-induced cardiomyocytes. Concomitantly, a decrease is observed in the expression levels of its putative target gene, IGF1. These observations collectively substantiate the notion that miR-483-3p promotes cardiomyocyte apoptosis both in vitro and in vivo through the downregulation of anti-apoptotic proteins such as bcl-2 and IGF1 [28].

In contrast to the above-discussed miRNAs, which promote cardiomyocyte apoptosis in DCM by targeting specific mRNAs, certain miRNAs serve to counteract this apoptotic effect. For instance, a study delineated that miR-29a is underexpressed in both streptozotocin (STZ)-induced DCM in rats and high-glucose (HG)-induced H9C2 cells. Induction of miR-29a expression led to the inhibition of pro-apoptotic genes such as bax, caspase-3, and bak1, while simultaneously enhancing the expression of anti-apoptotic genes like bcl-2 and mcl-1. Further analysis identified the 3' untranslated region (UTR) of bak1 as a direct target of miR-29a, demonstrating that the overexpression of miR-29a mitigates cardiomyocyte apoptosis via the negative regulation of Bak1 [29]. A separate investigation illustrated that overexpression of miR-20a-5p attenuates cardiac dysfunction and HG-induced cardiomyocyte apoptosis in DCM rats. Moreover, the co-transfection with ROCK2 nullified the protective effects of miR-20a-5p overexpression on the heart, substantiating that miR-20a-5p exerts its anti-apoptotic and anti-inflammatory effects via targeting ROCK2 [30]. Similarly, miR-223 exhibits elevated expression levels in DCM and has been empirically substantiated, both in vitro and in vivo, to markedly impact cardiac fibrosis, activation of the NLRP3 inflammasome, and cellular apoptosis in DCM. Cumulative evidence from our research affirmatively suggests that the inhibition of miR-223 confers a significant protective effect against DCM, positing miR-223 as a potential therapeutic target [31]. Lastly, research conducted by Liu et al. ascertained that miR-186-5p is downregulated in HG-induced cardiomyocytes. The overexpression of miR-186-5p reverses HG-induced apoptosis, specifically impacting the expression of the pro-apoptotic protein caspase-3. Additionally, TLR3 has been corroborated as a direct target of miR-186-5p and is negatively regulated by it. In sum, miR-186-5p mitigates HG-induced cardiomyocyte apoptosis via modulating TLR3 expression [32].

LncRNAs and cardiomyocyte apoptosis in diabetic cardiomyopathy (DCM)

LncRNAs are a class of ncRNAs exceeding 200 nucleotides in length but lacking coding potential. Unlike miRNAs, which are solely localized in the cytoplasm, lncRNAs are present in both the cytoplasm and the nucleus. In the nucleus, lncRNAs can interact with transcription factors, thereby disrupting protein-coding genes. In the cytoplasm, they act as miRNA sponges, indirectly modulating cellular death processes. Additionally, lncRNAs directly target key genes and proteins involved in cellular apoptosis [33, 34]. For instance, MALAT1, one of the lncRNAs abundantly expressed in cardiomyocytes, demonstrates upregulated expression in both DCM rat hearts and high-glucose (HG)-induced cardiomyocytes. Silencing of MALAT1 significantly mitigates HG-induced cardiomyocyte apoptosis. Mechanistically, MALAT1 functions as a miRNA sponge for miR-185-5p and activates the RhoA/ROCK signaling pathway, thereby mediating HG-induced cardiomyocyte apoptosis [35]. Moreover, MALAT1 serves as a competing endogenous RNA (ceRNA) and prevents the binding of miR-181a-5p to p53, thus promoting cardiomyocyte apoptosis [36]. Further research by Tang et al. illustrates that another lncRNA, H19, is highly expressed in both DCM rat hearts and HG-induced cardiomyocytes. H19 serves as a molecular sponge for miR-29c and downregulates MAPK13 expression, thereby ameliorating cardiomyocyte apoptosis in

DCM [37]. Similarly, under hyperglycemic conditions, the lncRNA GAS5 is upregulated in both in vivo and in vitro models of DCM. Inhibition of GAS5 expression significantly improves cardiac function and attenuates HG-induced cardiomyocyte apoptosis. Furthermore, through an amalgam of bioinformatics prediction, luciferase reporter assays, and RNA immunoprecipitation assays, miR-26a/b-5p was definitively identified as a target of GAS5. The silencing of GAS5 exerts a protective effect against cardiac fibrosis and HG-induced cardiomyocyte damage by negatively regulating miR-26a/b-5p [38].

LncRNAs exhibit bifunctionality; not only do some serve as molecular sponges for miRNAs but they also actively contribute to cardiomyocyte apoptosis in DCM. For instance, Zhao et al. discovered that both KCNQ1OT1 and PDCD4 are upregulated in HG-treated human cardiomyocytes and STZ-induced DCM mice, while miR-181a-5p was downregulated. The authors further delineated that KCNQ1OT1 functions as a competing endogenous RNA (ceRNA), elevating PDCD4 expression by sponging miR-34a, thereby promoting cardiomyocyte apoptosis in DCM [39]. A study by Wang et al. corroborated that MALAT1 is highly expressed in db/db mice and HG-induced cardiomyocytes. Silencing of MALAT1 manifested an ameliorative impact on both in vivo and in vitro cardiac function while inhibiting cardiomyocyte apoptosis. Additionally, MALAT1 was found to interact with EZH2 in cardiomyocytes, EZH2, in turn, modulates ABCA1 expression through repression of miR-22. MALAT1 promotes cardiomyocyte apoptosis by recruiting EZH2 to downregulate miR-22 expression, highlighting the role of the MALAT1/miR-22/EZH2/ABCA1 signaling cascade in cardiomyocyte damage and apoptosis [40]. According to research by Chen et al., lncRNA MEG3 is overexpressed in HG-treated AC16 cells. Knockout of MEG3 attenuated HG-induced AC16 cell apoptosis. Mechanistically, MEG3 directly interacts with miR-145 in AC16 cells, subsequently upregulating PDCD4 expression, thereby mitigating HG-induced cardiomyocyte apoptosis [41]. Zhou et al. elucidated that MIAT may function as a ceRNA by sponging miR-22-3p to upregulate DAPK2 expression, thereby contributing to cardiomyocyte apoptosis and implicating its role in the pathogenesis of DCM [42].

Apart from functioning as miRNA sponges to indirectly modulate cell death, certain lncRNAs also directly influence proteins associated with apoptosis in the progression of DCM. Multiple studies indicate that the hyperactivation of the PI3K/AKT/mTOR signaling pathway can inhibit endoplasmic reticulum stress (ERS) and cellular apoptosis. Through both in vivo and in vitro investigations, Wang et al. found that lncRNA H19 ameliorates diabetic cardiomyopathy-induced endoplasmic reticulum stress by activating the PI3K/AKT/mTOR signaling pathway, thereby inhibiting ERS-induced cellular apoptosis [22].

Involvement of circRNAs in cardiomyocyte apoptosis and the progression of diabetic cardiomyopathy (DCM)

CircRNAs represent a distinct class of single-stranded ncRNAs. Compared to miRNAs and lncRNAs, the covalently closed-loop structure of circRNAs enhances their stability. They exert regulatory effects by sequestering miRNAs, thereby influencing subsequent transcriptional control. Furthermore, circRNAs serve as sponges for RNA-binding proteins (RBPs) and facilitate the translation of target mRNA transcripts [43, 44]. In recent years, numerous circRNAs have been implicated in the progression of DCM by modulating cellular apoptosis. CircRNA CDR1as has been identified to exhibit elevated expression levels in DCM murine models and in cardiomyocytes induced by high glucose (HG). Knockout of CDR1as has been shown to downregulate the expression of apoptosis-related proteins, such as Bad and Caspase 3. Mechanistically, the silencing of CDR1as promotes ubiquitination of MST1, thereby inhibiting its expression. This culminates in a downstream cascade that decreases the levels of effector molecules LATS2 and p-YAP, ultimately ameliorating cardiac function in DCM mice and mitigating HG-induced cardiomyocyte apoptosis [45]. In a parallel line of inquiry, a significant negative correlation between circHIPK3 and PTEN has been reported in DCM patients. Subsequent in vitro investigations substantiated that overexpression of circHIPK3 attenuates the expression of PTEN in AC16 cells, thereby safeguarding the cells against HG-induced apoptosis (Fig. 2; Table 1) [46].

Autophagy and diabetic cardiomyopathy

Overview of autophagy

Autophagy represents a highly regulated intracellular catabolic process that operates both in the pathophysiological and physiological contexts within cellular systems. Typically, the activation of autophagy is provoked by factors such as nutrient deprivation and oxidative stress. Furthermore, this cellular mechanism is intricately associated with an array of physiological and pathological processes, including but not limited to development, differentiation, neurodegenerative disorders, stress responses, infection, and neoplasia [47].Depending on the mode of lysosomal delivery, autophagy can be categorized into three principal forms: microautophagy, chaperone-mediated autophagy (CMA), and macroautophagy [48]. Microautophagy primarily targets cellular organelles such as mitochondria, the nucleus, and peroxisomes. This mechanism entails the direct fusion of the lysosomal membrane with the substrate slated for degradation, thereby maintaining organelle size, membrane homeostasis, and cellular survival

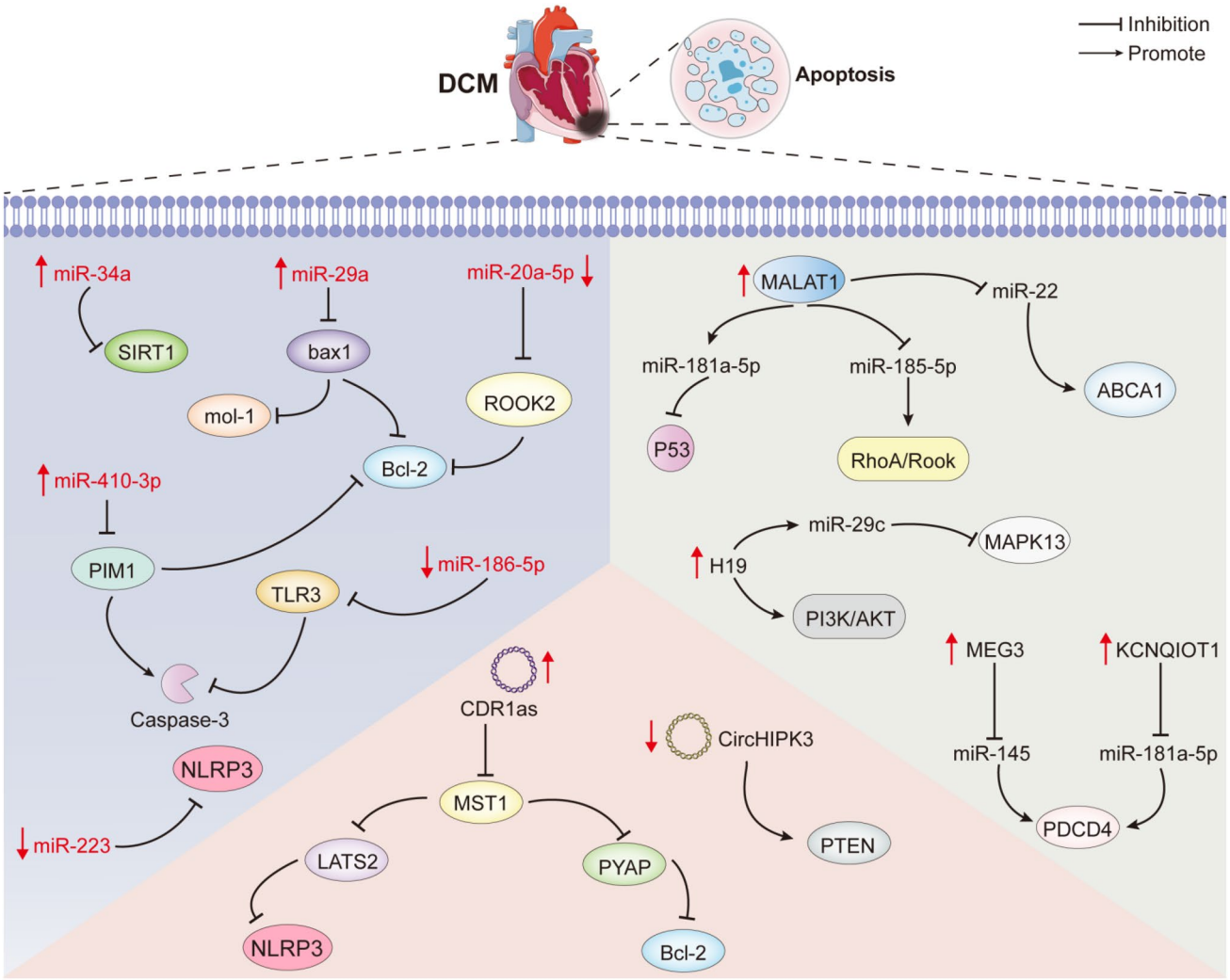

Fig. 2 Mechanism diagram of non-coding RNA regulating apoptosis and intervening DCM. In DCM, cellular apoptosis is associated with dysregulation of ncRNAs. MiRNA modulates the progression of DCM by regulating the expression of apoptotic proteins. LncRNA and circRNA act either as miRNA sponges or as miRNA precursors to modulate the expression of apoptotic proteins. SIRT1:Silent information regulator 3,Bax-1:BCL2-associated X protein 1,Bcl-2:B-cell lymphoma 2,ROCK2:Rho-associated protein kinase 2,PIM1:Polymers of intrinsic microporosity,TLR3:Toll-like receptors 3,NLRP3:NOD-like receptor family pyrin domain containing 3,MALAT1:Metastasis-associated lung adenocarcinoma transcript 1,P53:Cellular tumor antigen p53,ABCA1:ATP binding cassette protein 1,MAPK13:Mitogen-activated protein kinase 13,PI3K/AKT:phosphatidylinositol 3-kinase/ protein kinase B,MEG3:Maternally expressed gene 3,KCNQIOT1:Potassium voltage-gated channel subfamily Q member 1 opposite strand 1,PDCD4:Programmed cell death protein 4,LATS2:Large tumor suppressorkinase2,MST1:Mammalian sterile 20-like kinase 1,PYAP:Phosphorylated yes-associated protein, PTEN:Phosphatase and Tensin Homologue

under conditions of nitrogen limitation [49]. Chaperone-mediated autophagy, conversely, represents a selective type of lysosomal degradation of cytosolic proteins within the cellular milieu [50]. The most extensively researched form of autophagy is macroautophagy, often referred to simply as autophagy for the purposes of this review [51]. The autophagic process encompasses multiple sequential stages, namely initiation and nucleation, elongation, autophagosome formation, autolysosome formation, and ultimately degradation. This highly orchestrated cascade is mediated by a host of autophagy-related genes (ATGs) [52], as well as modulated by autophagy-associated signaling pathways, such as mTOR and AMPK. Although numerous scholarly reviews have elaborated on the molecular events involved in autophagy, we provide here only a cursory summary of the key steps. It is worth noting that moderate autophagy plays a salutary role in eliminating dysfunctional mitochondria that release reactive oxygen species and apoptosis-inducing factors, thereby mitigating cellular damage. Conversely, excessive activation of autophagy may precipitate unwarranted self-digestion and degradation of cellular components, leading to a form of

Table 1 Mechanism of non-coding RNA regulating apoptosis and intervening diabetic cardiomyopathy

ncRNAs	Target	Effects	Mechanism	References
miR-34a	SIRT1	Pro-apoptosis	miR-34a increased cardiomyocyte apoptosis via downregulating SIRT1	[25]
	bcl-2	Pro-apoptosis	luciferase activity of Bcl-2 was decreased by transfecting miR-34a mimic	[26]
miR-410-5p	PIM1	Pro-apoptosis	miR-410-5p amplifying myocardial apoptosis in DCM by antagonistically modulating PIM1	[27]
miR-483-3p	bcl-2 and IGF1	Anti-apoptosis	miR-483-3p augments myocardial apoptosis both in vivo and in vitro through the downregulation of anti-apoptotic entities such as BCL-2 and IGF1	[28]
miR-29a	bak1	Anti-apoptosis	Overexpression of miR-29a can reduce cardiomyocyte apoptosis by negatively regulating the target gene bak1	[29]
miR-20a-5p	ROCK2	Anti-apoptosis	miR-20a-5p dampens inflammatory and apoptotic pathways by targeting ROCK2	[30]
miR-223	NLRP3	Anti-apoptosis	Inhibiting miR-223 can reduce cell apoptosis in DCM	[31]
miR-186-5p	TLR3	Anti-apoptosis	miR-186-5p emerges as a mitigating factor against HG-induced apoptosis by fine-tuning TLR3 expression in myocardial constructs	[32]
MALAT1	miR-185-5p、RhoA/ROCK	Anti-apoptosis	MALAT1 serves as a molecular sponge for miR-185-5p, subsequently potentiating the RhoA/ROCK signaling cascade, a crucial mediator of HG-induced cardiomyocyte apoptosis	[35]
	miR-181a-5p、p53	Pro-apoptosis	MALAT1, adopting the role of a competitive endogenous RNA, obviates the affinity of miR-181a-5p for p53 inadvertently intensifying cardiomyocyte apoptosis	[36]
H19	miR-29c、MAPK13	Anti-apoptosis	H19 can sponge miR-29c and downregulate MAPK13 table and reduce cardiomyocyte apoptosis in DCM	[37]
GAS5	miR-26a/b-5p	Anti-apoptosis	Silencing GAS5 can effectively alleviate myocardial fibrosis and HG-induced myocardial cell damage by negatively regulating miR-26a/b-5p	[38]
KCNQ1OT1	miR-181a-5p	Pro-apoptosis	KCNQ1OT1 acts as ceRNA and increases PDCD4 expression through sponge miR-181a-5p, thereby promoting apoptosis in DCM cardiomyocytes	[39]
MALAT1	miR-22、EZH2、ABCA1	Pro-apoptosis	MALAT1 promotes myocardial injury and cardiomyocyte apoptosis through the miR-22/EZH2/ABCA1 signaling cascade	[40]
MEG3	miR-145、PDCD4	Anti-apoptosis	MEG3 can bind to miR-145 in AC16 cells and upregulate the expression of PDCD4, thereby reducing HG-induced cardiomyocyte apoptosis	[41]
MIAT	miR-22-3p、DAPK2	Pro-apoptosis	MIAT upregulates DAPK2 expression through sponge miR-22-3p, leading to myocardial cell apoptosis	[42]
H19	PI3K/AKT/mTOR	Anti-apoptosis	LncRNA H19 inhibits endoplasmic reticulum stress-induced apoptosis by activating the PI3K/AKT/mTOR signaling pathway	[22]
CDR1as	MST1、LATS2、p-YAP	Anti-apoptosis	CDR1as can promote the ubiquitination level of MST1 and inhibit its expression, thereby improving HG-induced cardiomyocyte apoptosis	[45]
circHIPK3	PTEN	Anti-apoptosis	Overexpression of circHIPK3 can reduce the expression level of PTEN in AC16 cells, thereby protecting them from HG-induced apoptosis	[46]

programmed cell death known as autophagic cell death (Fig. 3).

Autophagy in diabetic cardiomyopathy (DCM)

Autophagy is pivotal for cellular homeostasis and survival, and extant research has established its intimate association with the pathogenesis of Diabetic Cardiomyopathy (DCM). Prior studies have demonstrated an upregulation in the expression of autophagy-related proteins—namely LC3-I, LC3-II, and Beclin-1—in rat models of DCM. These proteins are considered crucial initiators of autophagic activation [53]. Furthermore, the upstream signaling pathways governing autophagy, specifically AMPK/mTOR, have been subjects of exhaustive inquiry. A burgeoning body of evidence elucidates the pivotal role these pathways play in the regulation of autophagy within the context of DCM. AMPK acts as the seminal activator that inhibits mTOR, which in

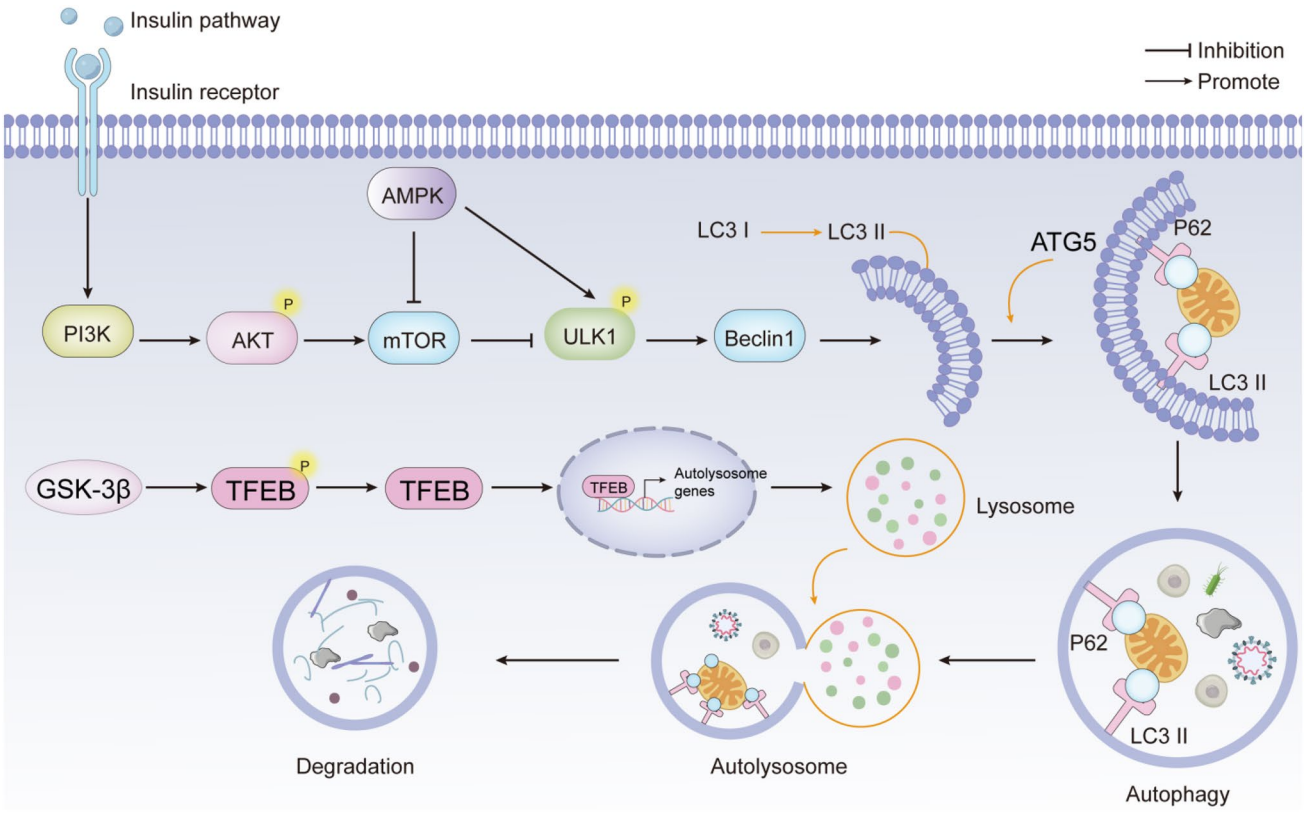

Fig. 3 Molecular mechanism diagram of autophagy. Activation of the insulin receptor stimulates the PI3K/AKT signaling pathway, subsequently promoting the expression of the autophagy regulatory factor mTOR, thereby inducing autophagy. AMPK serves as a key activator that inhibits mTOR, a negative regulator of autophagy. ULK1 functions as an autophagy-initiating kinase; AMPK triggers autophagy by directly inducing ULK1 phosphorylation and can also induce autophagy via Beclin-1. LC3 is indispensable for autophagy; the conversion of LC3-I to LC3-II indicates the induction of autophagy. ATG5 localizes on the outer membrane of autophagosomes and is critical for extension. p62 interacts with LC3-II and undergoes degradation along with its substrate, thereby delivering ubiquitinated proteins to the autophagosome for degradation to facilitate autophagy. TFEB is the principal transcriptional regulator of autophagy and lysosome biogenesis; its activation is vital for lysosomal homeostasis following lysosomal damage. GSK-3β promotes its phosphorylation and participates in the autophagy process

turn serves as a negative regulator of autophagy [54]. In the course of DCM progression, attenuated activation of AMPK and heightened inhibition of mTOR contribute to diminished fatty acid oxidation and glucose uptake. These metabolic derangements culminate in cardiac lipotoxicity and lipomatous degeneration, thus exacerbating the advancement of DCM [55]. ULK1, functioning as an initiating kinase in autophagy, is situated downstream in the AMPK/mTOR signaling axis [56]. AMPK instigates autophagy by directly inducing phosphorylation of ULK1, thereby ameliorating glucose-induced myocardial damage and attenuating the incidence of DCM [57]. Consequently, targeting autophagy via AMPK activation or mTOR inhibition may represent a promising therapeutic intervention for DCM. Additionally, rat models of diabetic cardiac fibrosis have demonstrated a marked upregulation in the expression levels of phosphorylated PI3K and AKT, concomitant with decreased autophagic flux and a significant augmentation in apoptosis-related proteins. These findings suggest that the phosphorylation and excessive activation of the PI3K/AKT pathway may suppress autophagy and induce cellular apoptosis, thereby exacerbating myocardial fibrosis in diabetes [58].

Non-coding RNAs and autophagy in diabetic cardiomyopathy (DCM)

Role of miRNAs in autophagy within the context of DCM

MicroRNAs (miRNAs) exert regulatory control over autophagy in DCM by directly targeting autophagy-related genes. For instance, miR-494 is upregulated in the myocardium and cardiomyocytes of DCM rats induced by high-glucose (HG) conditions. Functionally, its overexpression amplifies HG-induced cellular apoptosis and autophagy. Mechanistically, miR-494 orchestrates these cellular processes by modulating the PI3K/AKT/mTOR signaling

pathway, thereby mitigating myocardial cell damage following HG induction [59]. LAMP2, a transmembrane protein intricately associated with autophagy, is abundantly expressed in cardiac and skeletal muscle tissues, miR-207 can directly target LAMP2, inhibiting cardiomyocyte autophagy and thereby promoting apoptosis [60]. According to research by Ni et al., miR-34a expression is elevated in the myocardial tissue of diabetic mice and HG-induced cardiomyocytes, inhibiting its expression is beneficial for augmenting mitochondrial autophagy, eliminating damaged or aberrant mitochondria, and thereby maintaining cellular homeostasis [61]. Moreover, Nandi et al. employed transcriptomic sequencing to explore the role of miR-133a and the mTOR pathway in DCM. The inhibition of mTOR, a known autophagy suppressor, occurs through the downregulation of miR-133a, resulting in the upregulation of autophagy in diabetic heart failure patients. This finding suggests that miR-133a may offer a viable therapeutic strategy by modulating the mTOR signaling cascade to attenuate DCM progression [62]. Foxo3 is a crucial pro-autophagic factor in cardiomyocytes and has been identified as a potential therapeutic target for DCM associated with autophagy dysregulation. According to a study by Ucar et al., the overexpression of miR-212 leads to the downregulation of Foxo3, subsequently impairing basal autophagy at normal levels and inducing severe heart failure in mice [63].

Recent investigations have demonstrated that miR-21 is upregulated in the cardiac tissue of diabetic mice and HG-induced cardiomyocytes. Post-transfection with a miR-21 inhibitor, a pronounced increase in the protein levels of SPRY1 and a significant decrease in the levels of phosphorylated ERK and mTOR were observed. These data collectively indicate that miR-21 modulates autophagy via the SPRY1/ERK/mTOR signaling pathway [64]. Additionally, a study by Chen et al. revealed that the overexpression of miR-30c in db/db mice led to a decline in BECN1 levels and the LC3-II:I ratio, suggesting the suppression of autophagic flux, thereby potentially preserving cardiac function in diabetic db/db mice [65].

Involvement of long non-coding RNAs (lncRNAs) in autophagy in diabetic cardiomyopathy (DCM)

Emerging evidence delineates the contributory role of various lncRNAs in the orchestration of cellular autophagy, thereby implicating their significance in the pathophysiology of DCM. For instance, GAS5 is underexpressed in both streptozotocin (STZ)-induced diabetic rats and high-glucose (HG)-treated cardiomyocytes. The overexpression of GAS5 facilitates myocardial autophagy and subsequently ameliorates cardiac function in DCM by sponging miR-221-3p to upregulate P27 expression [66]. A study by Feng et al. revealed an upregulation of lncRNA DCRF in the myocardium of diabetic rats and HG-treated cardiomyocytes. Mechanistically, the knockdown of DCRF attenuates myocardial cell autophagy, alleviates myocardial fibrosis, and enhances cardiac function. This is mediated through the augmented inhibitory action of miR-551b-5p on PCDH17, thereby retarding the progression of myocardial autophagy and DCM [67]. Recently, multiple studies have substantiated the pivotal role of lncRNA H19 in modulating autophagy in the development of DCM. A study by Zhuo et al. reported the significant activation of autophagy-related proteins and autophagosomes, such as LC3-II, BECN1, and ATG7, in a streptozotocin-induced diabetic rat model; despite the reduced expression of H19 in the myocardium, its overexpression attenuates autophagy and ameliorates left ventricular dysfunction associated with hyperglycemia, and this regulatory effect is attributed to the interaction of H19 with PRC2, which epigenetically inhibits the transcription of DIRAS3, thereby mitigating autophagy in myocardial cells (Fig. 4; Table 2) [68].

Pyroptosis and diabetic cardiomyopathy (DCM)

Overview of pyroptosis

In 2001, Cookson and Brennan identified a novel form of regulated cell death in macrophages infected with Salmonella typhimurium that was caspase-1-dependent, as opposed to caspase-3-dependent, this led them to coin the term "pyroptosis" to describe this unique modality of cell death [69]. Pyroptosis is characterized as a caspase-1-dependent form of programmed cell death with pro-inflammatory consequences. Morphologically, it bears similarities to both necrosis and apoptosis but is distinctly different in its hallmark features, which include the formation of transmembrane pores, cellular membrane swelling, rupture, and the release of pro-inflammatory contents [70]. In 2011, Kayagaki et al. discovered that pyroptotic cell death in macrophages infected with Escherichia coli was dependent on caspase-11 rather than caspase-1. They proposed this as an atypical inflammasome-driven pyroptotic pathway [71]. Subsequent studies conducted independently by Shi et al. and Kayagaki et al. in 2015 identified gasdermin D (GSDMD) as a critical downstream target of both caspase-1 and caspase-11 [70, 72]. Furthermore, as insights into the molecular mechanisms of pyroptosis have deepened, caspase-3, caspase-8, and GSDME have also been delineated as participating elements in the pyroptotic process [73].

According to the classification posited by Kayagaki et al., pyroptotic pathways can be dichotomized into the caspase-1-mediated canonical inflammasome pathway and the caspase-4/5/11-mediated non-canonical inflammasome

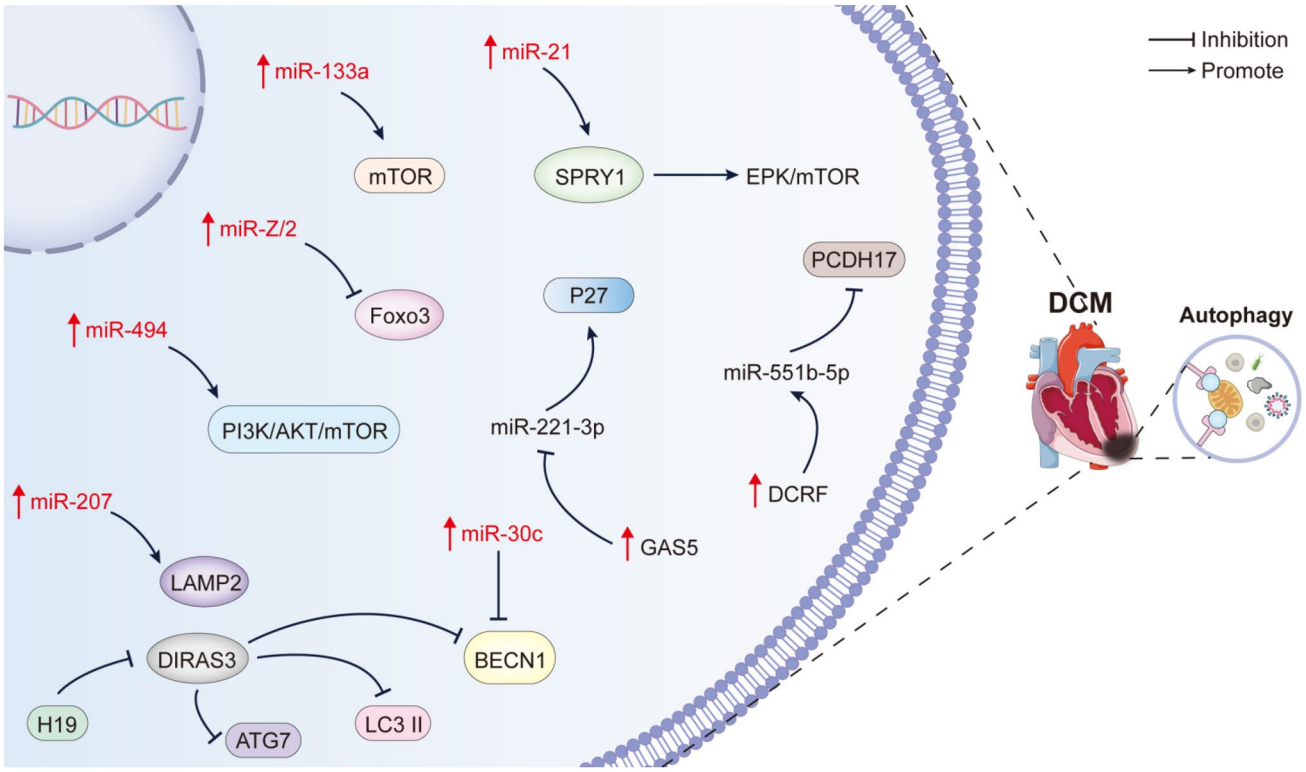

Fig. 4 Mechanism diagram of non-coding RNA regulating autophagy and intervening DCM. In the context of dilated cardiomyopathy (DCM), autophagy is related to the dysregulation of non-coding RNA (ncRNA). MicroRNA (miRNA) modulates the progression of DCM by regulating the expression of autophagy-related proteins. Long non-coding RNA (lncRNA) acts either as a miRNA sponge or as a miRNA precursor to modulate the expression of autophagy-associated proteins. PI3K/AKT/mTOR:phosphatidylinositol 3-kinase/ protein kinase B/ mammalian target of rapamycin,SPRY1:Sprouty 1,Foxo3:Forkhead box 3,P27:Cellular tumor antigen p27,LAMP2:lysosomal-associated membrane protein 2,DIRAS3:GTP-binding protein Di-Ras3,ATG7:Autophagy protein 7,GAS5:Growth arrest specific transcript 5,DCRF:DCM-related factor, PCDH17: Protocadherin 17

Table 2 Mechanism of non-coding RNA regulating autophagy in diabetic cardiomyopathy

ncRNAs	target	Effects	Mechanism	References
miR-494	PI3K/AKT/mTOR	Pro-autophagy	Overexpression of miR-494 promotes HG-induced cell autophagy	[59]
miR-207	LAMP2	Anti-autophagy	MiR-207 can directly target LAMP2 to inhibit autophagy of myocardial cells and promote apoptosis of myocardial cells	[60]
miR-34a		Pro-autophagy	Inhibiting the expression of miR-34a is beneficial for increasing mitochondrial autophagy and eliminating damaged or abnormal mitochondria	[61]
miR-133a	mTOR	Pro-autophagy	Inhibition of miR-133a expression will reduce the level of mTOR expression, thus upregulating autophagy in patients with diabetes and heart failure	[62]
miR-212	Foxo3	Anti-autophagy	Overexpression of miR-212 can lead to downregulation of Foxo3 and damage normal levels of basal autophagy	[63]
miR-21	SPRY1/ERK/mTOR	Pro-autophagy	MiR-21 regulates autophagy through the SPRY1/ERK/mTOR pathway	[64]
miR-30c	BECN1	Anti-autophagy	Overexpression of miR-30c leads to a decrease in BECN1 levels and LC3-II: I ratio, thereby inhibiting autophagy	[65]
GAS5	miR-221-3p、P27	Pro-autophagy	GAS5 overexpression promotes P27 expression through sponge miR-221-3p, thereby promoting autophagy in myocardial cells	[66]
DCRF	miR-551b-5p、PCDH17	Anti-autophagy	Inhibition of autophagy and DCM progression in myocardial cells	[67]
H19	PRC2、DIRAS3	Anti-autophagy	H19 can bind to PRC2 and epigenetic inhibit the transcription of DIRAS3, thereby inhibiting autophagy in myocardial cells	[68]

pathway [71]. The initiation of the canonical inflammasome pathway is critically contingent upon the activation of classic inflammasomes, which are intimately associated with intracellular receptor proteins like NLRP1/3, NLRC4, and AIM2, with NLRP3 inflammasome research being the most extensively studied [70]. The NLRP3 inflammasome complex comprises the apoptosis-associated speck-like protein containing a CARD (ASC), NLRP3, and pro-caspase-1. It is principally activated through a two-step signaling process [74]. The first step predominantly involves recognition by pattern recognition receptors (PRRs) of pathogen-associated molecular patterns (PAMPs) present on the surface of toxins, viruses, and bacteria, or damage-associated molecular patterns (DAMPs) produced following tissue or cellular insult. Concomitantly, under PRR stimulation, the inflammasome complex autocatalytically cleaves pro-caspase-1 into its active form, caspase-1, which subsequently enzymatically processes pro-IL-1β and pro-IL-18 into their mature secreted forms, thereby instigating an inflammatory response [75]. The second step predominantly involves the activation of pro-caspase-1 into caspase-1 within the inflammasome. The activated caspase-1 cleaves GSDMD into its N-terminal (GSDMD-NT) and C-terminal (GSDMD-CT) fragments. The formation of membrane pores at the N-terminus ultimately precipitates the release of cytokines, efflux of potassium ions, cellular swelling, and lysis [76]. Moreover, mature IL-1β and IL-18 are generated from pro-IL-1β and pro-IL-18 through caspase-1 cleavage and are extracellularly discharged through GSDMD pores. This culminates in the recruitment of immune cells and the establishment of an inflammatory microenvironment, consequently instigating pyroptotic cell death [77].

Distinct from the caspase-1-mediated canonical inflammasome pathway, the non-canonical inflammasome pathway is principally orchestrated by caspase-11 in mice and caspase-4/5 in humans. These caspases can be directly activated by lipopolysaccharides (LPS), components of Gram-negative bacteria, thereby fulfilling functions analogous to those of caspase-1 [78]. It is well established that caspase-11 is indispensable for LPS-induced pyroptosis in murine cells [79], while caspase-4/5 serve a functionally comparable role in human cells. Intriguingly, within the ambit of the non-canonical inflammasome pathway, pyroptosis induced by activated caspase-4/5/11 does not directly catalyze the maturation of pro-IL-1β and pro-IL-18. Instead, it operationalizes this process indirectly through the activation of the NLRP3/ASC/caspase-1 axis, thereby facilitating the maturation and secretion of IL-1β and IL-18 [80]. In summary, both the caspase-1-mediated canonical inflammasome pathway and the caspase-4/5/11-mediated non-canonical inflammasome pathway converge functionally in the orchestration of pyroptotic cell death, sharing several key regulatory elements (Fig. 5).

Pyroptosis in diabetic cardiomyopathy (DCM)

Inflammatory responses represent a pivotal pathological process in the progression of Diabetic Cardiomyopathy (DCM), with pyroptosis serving as a form of programmed cell death closely associated with inflammation and implicated in the development of DCM [81]. Initial observations employing electron microscopy have revealed the presence of swollen collagen fibers and mitochondrial characteristics in dying cardiomyocytes of diabetic rats and mice, which are morphologically congruent with pyroptotic events [82]. Recent investigations have accentuated the seminal role of NLRP3 inflammasomes in mediating cardiomyocyte pyroptosis in the context of DCM [83]. During the development of DCM, elevated glucose levels contribute to an increase in reactive oxygen species (ROS), which subsequently activate NF-κB and trigger the activation of NLRP3, culminating in the release of IL-1β and IL-18, thus promoting pyroptotic progression in DCM [84]. Emerging evidence substantiates that, in comparison to cardiac tissues from non-diabetic individuals, those from diabetic patients exhibit an upregulation of NLRP3 inflammasome activation and cardiomyocyte pyroptosis. Further investigations have elucidated that elevated glucose levels (35 mM glucose) significantly induce the expression of NLRP3, caspase-1, and IL-1β in human ventricular cardiomyocytes, accompanied by a marked occurrence of pyroptosis. These findings corroborate the unique role of NLRP3 inflammasome-mediated pyroptosis in the pathogenesis of DCM [85]. Additionally, according to a study by Luo et al., NLRP3 inflammasomes and caspase-1-mediated pyroptosis are expressed in the myocardium of diabetic rats, the inhibition of NLRP3 expression ameliorated cardiac inflammation, pyroptosis, and myocardial function [86].

Moreover, diverse cell types, including cardiac fibroblasts (CFs), cardiomyocytes, and endothelial cells, undergo pyroptosis upon stimulation by high glucose levels, inevitably exacerbating the onset and progression of DCM [7]. For instance, during DCM, NLRP3 inflammasomes exacerbate cardiac fibrosis and promote the activation of CFs induced by elevated glucose [87]. In the context of DCM progression, CFs are activated and transdifferentiate into myofibroblasts under hyperglycemic (HG) conditions; concurrently, inflammasomes within CFs are activated, facilitating the production of IL-1β and IL-18 [88, 89]. Similarly, a hyperglycemic environment promotes the hyperactivation of NLRP3 in cardiomyocytes. The activated NLRP3 assembles with ASC and pro-caspase-1 to form inflammasomes, inducing the activation of GSDMD-N, pore formation on the cell membrane, and the subsequent maturation and secretion of IL-18 and IL-1β, ultimately leading to cardiomyocyte pyroptosis and the accelerated progression of DCM

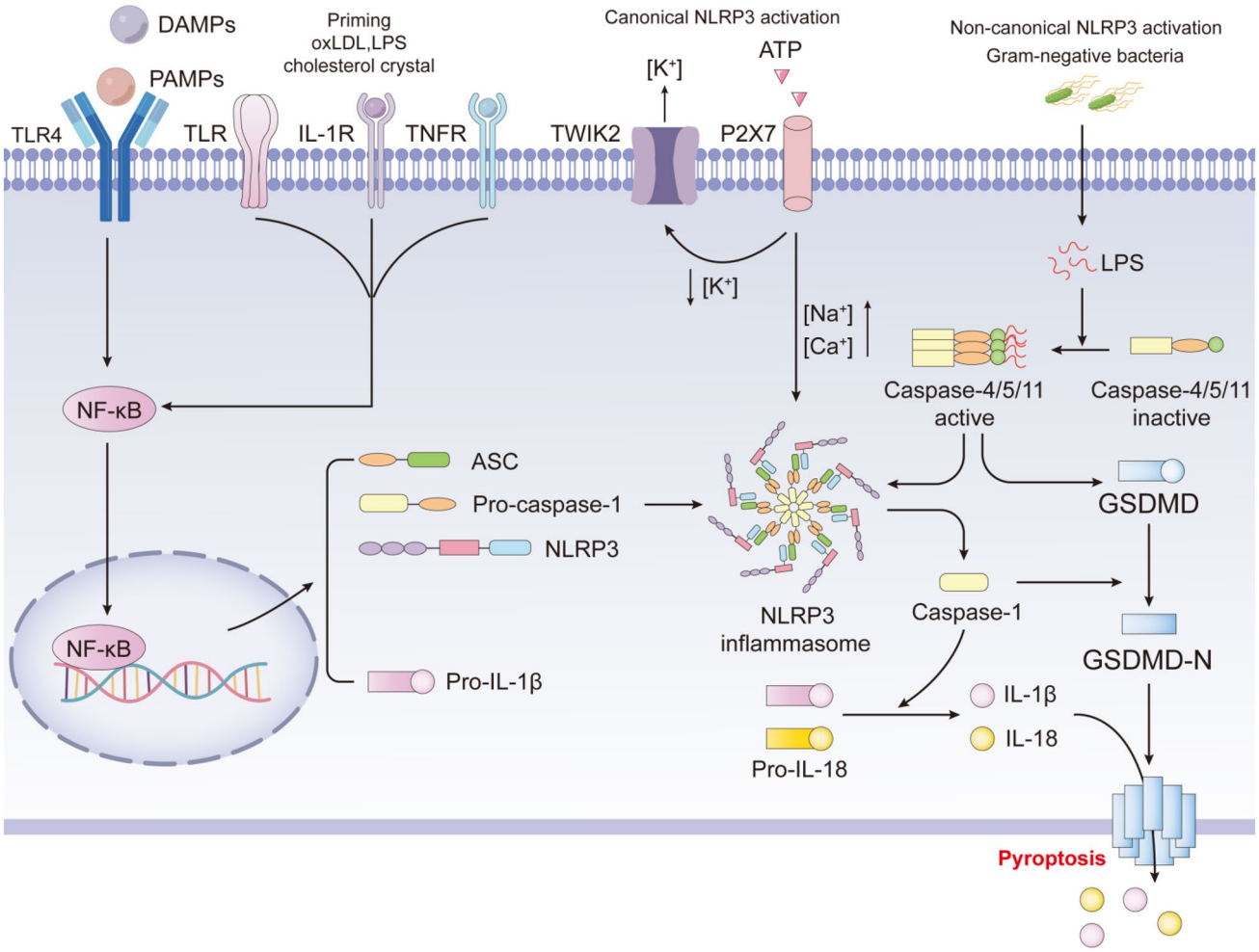

Fig. 5 Molecular mechanism diagram of Pyroptosis. In the canonical pathway, danger-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), as well as LPS stimulation, activate the TLR4/NF-κB classical signaling pathway. Subsequently, NLRP3 recruits the adaptor ASC, which in turn recruits procaspase-1, leading to the maturation and release of bioactive IL-1β and IL-18, culminating in pyroptosis. In the non-canonical pathway, LPS directly activates procaspase-4/5/11. Upon binding of procaspase-4/5/11 to LPS, it cleaves GSDMD into GSDMD-NT. The activation of caspase-4/5/11 can stimulate the Pannexin-1 channel, thereby releasing cellular ATP and prompting the opening of the cytoplasmic channel P2X7, ultimately leading to potassium ion efflux and triggering NLRP3-mediated pyroptosis

[90]. Furthermore, it is worth noting that endothelial cell pyroptosis is implicated in the developmental course of DCM. Elevated glucose levels induce the formation and activation of NLRP3 inflammasome complexes in mouse coronary artery endothelial cells; silencing of NLRP3 expression resulted in a near disappearance of caspase-1 activity [91], indicating that high-glucose-induced NLRP3 inflammasomes contribute to endothelial cell dysfunction. In summary, the NLRP3 inflammasome and its associated induction of pyroptosis manifest a unique role in DCM, offering potential therapeutic targets for its treatment through the inhibition of pyroptotic signaling pathways. However, research related to DCM is still in its nascent stage, and numerous questions await further exploration.

Non-coding RNAs (ncRNAs) and pyroptosis in diabetic cardiomyopathy (DCM)

MicroRNAs (miRNAs) and pyroptosis in DCM

Copious empirical evidence underscores the pivotal role of microRNAs (miRNAs) in modulating pyroptosis through a multifaceted repertoire of mechanisms. For example, in cardiomyocytes subjected to high-glucose (HG) treatment, miR-214-3p demonstrates a significant downregulation. Augmenting the expression of this miRNA has been shown to attenuate the levels of critical pyroptosis-associated markers such as NLRP3, caspase-1, and IL-1β, thereby substantially mitigating HG-induced cardiomyocyte pyroptosis [92].

In the same vein, Foxo3a and ARC, integral transcription factors in regulating cellular apoptosis, manifest notable downregulation in HG-induced cardiomyocytes. Intriguingly, miR-30d efficaciously represses Foxo3a and ARC expression both in vivo and in vitro. This downregulation culminates in an elevated expression of caspase-1 and pro-inflammatory cytokines IL-1β and IL-18, which subsequently impede HG-induced cardiomyocyte pyroptosis [93]. In a seminal study led by Prince Jeyabal et al., ELAVL1 is identified as a prospective molecular target of miR-9. Inhibition of miR-9 results in a consequential elevation of ELAVL1 protein expression, alongside an upregulation of caspase-1 and IL-1β, thereby inhibiting the pyroptosis of HG-treated cardiomyocytes [85]. Moreover, the miR-18a-3p/GSDMD signaling axis is modulated by berberine, an inherently anti-DCM (Diabetic Cardiomyopathy) compound extracted from traditional herbal medicine. Berberine has been shown to inhibit pyroptosis in HG-treated H9C2 cells via this signaling axis, thereby retarding the progression of DCM [94]. Analogous to the aforementioned studies, lenalidomide is reported to stimulate the expression of miR-135b in cardiac fibroblasts under HG conditions, this miRNA directly interacts with caspase-1, and its overexpression inhibits the levels of IL-1β and GSDMD, thereby constraining cardiac fibroblast pyroptosis and diminishing collagen deposition [95].

In a compelling departure, certain miRNAs serve to promote the development of DCM by facilitating cardiomyocyte pyroptosis. A study by Peng et al. unveils miR-21-3p as an activator of pyroptosis, its overexpression leading to an augmented accumulation of NLRP3 and caspase-1 in both STZ-induced diabetic cardiac fibrotic tissue and HG-treated cardiac fibroblasts, thus accelerating HG-induced cardiac fibroblast pyroptosis [96]. Further corroborating this paradigm, a study by Zhao et al. discloses an upregulation of miR-223-3p in HG-treated cardiomyocytes, concomitant with an elevated SPI1 expression. Transfection with a miR-223-3p inhibitor induces a subsequent SPI1 downregulation and attenuates the expression levels of NLRP3, GSDMD-N, caspase-1, and IL-1β. These findings substantiate that miR-223-3p exacerbates DCM progression by inducing cardiomyocyte pyroptosis through upregulating SPI1 [97].

lncRNAs and cellular pyroptosis in diabetic cardiomyopathy (DCM)

Emerging data over the past few years increasingly substantiate the pivotal role of long non-coding RNAs (lncRNAs) as crucial regulators in cellular pyroptosis. For instance, according to a study by Xiong et al., the expression levels of pyroptosis-associated proteins, such as NLRP3, caspase-1, IL-1β, and IL-18, are markedly upregulated in high-glucose (HG) treated cardiomyocytes. However, following the transfection of HOTAIR plasmid, the lncRNA interacts with FUS to activate SIRT3 expression, resulting in the downregulation of NLRP3, caspase-1, IL-1β, and IL-18, subsequently attenuating cellular pyroptosis in DCM [98].

A multitude of studies have corroborated that various lncRNAs, including MIAT, MALAT1, GAS5, and kcnq1ot1, partake in the pathophysiological progression of DCM by modulating cellular pyroptosis. Prior investigations revealed that lncRNA MIAT is implicated in diverse pathological mechanisms such as microvascular dysfunction, myocardial ischemia–reperfusion injury, and diabetes. Recent findings demonstrate elevated MIAT expression both in the serum of diabetic patients and in HG-induced cardiomyocytes, as well as in the serum of diabetic mice. Both in vivo and in vitro silencing of MIAT ameliorate cellular pyroptosis in DCM. Mechanistically, MIAT acts as a competitive endogenous lncRNA, and it inhibits miR-214-3p, which in turn regulates the expression of its downstream target CASP1. The regulation of pyroptosis in diabetic cardiomyopathy by lncMIAT may thus be orchestrated through targeting the MIAT/miR-214-3p/CASP1 axis [92]. Similarly, MALAT1 expression surges in HG-treated cardiomyocytes. Upon MALAT1 knockdown, levels of pyroptosis-related proteins such as ASC, GSDMD-N, caspase-1, and NLRP3 are diminished, accompanied by an increase in GSDMD and miR-141-3p expression, suggesting that MALAT1 might participate in DCM pathogenesis by targeting miR-141-3p and regulating the expression of pyroptosis-related proteins [99]. Furthermore, GAS5 is found to be underexpressed in the cardiac tissues of DCM mice and in HG-induced HL-1 cells. Overexpression of GAS5 suppresses NLRP3, caspase-1, Procaspase-1, IL-1β, and IL-18, thereby improving cardiac function. Subsequent studies reveal that GAS5 functions as a competing endogenous RNA that 'sponges' miR-34b-3p to facilitate AHR expression, thereby inhibiting NLRP3 inflammasome-mediated pyroptosis and ameliorating DCM [100]. Kcnq1ot1, a widely investigated lncRNA, exhibits augmented expression in diabetic patients, in HG-induced AC16 cardiomyocytes, and in cardiac tissues of diabetic mice. Silencing Kcnq1ot1 suppresses caspase-1 through miR-214-3p in cardiomyocytes, thereby inhibiting cellular pyroptosis [101].

CircRNAs and cellular pyroptosis in diabetic cardiomyopathy (DCM)

Recent investigations have illuminated the instrumental role circRNAs play in the progression of DCM, predominantly acting as molecular sponges for miRNAs via the competing endogenous RNA (ceRNA) mechanism to modulate downstream gene expression and target cellular pyroptosis. According to a study by Fu et al., circ_0071269 was observed to be significantly upregulated in high-glucose

(HG)-treated H9c2 cells, the overexpression of circ_0071269 facilitates pyroptosis in DCM cells by sponging and upregulating miR-145, which in turn augments the expression of GSDMA [102]. Employing bioinformatic prediction methodologies, Yang and colleagues identified circRNA CACR, subsequent experiments corroborated its elevated expression in both HG-treated cardiomyocytes and the serum of diabetic patients. Mechanistically, the silencing of CACR significantly mitigates HG-induced cellular pyroptosis. CACR operates as a competing endogenous RNA and its silencing is proposed to sponge miR-214-3p, thereby inhibiting the expression of caspase and attenuating cellular pyroptosis in DCM [103].

In addition to its role as a miRNA sponge, circRNAs have also been found to exert direct influence on gene expression, thus contributing to the pathological progression of DCM. For example, in a study conducted by Yuan et al., pyroptosis-related proteins such as GSDMD, ASC, NLRP3, and caspase-1 were substantially activated in both in vivo models of Type 2 Diabetes Mellitus (T2DM) and in vitro cardiomyocytes treated with AGEs (Advanced Glycation End-products). The overexpression of circRNA DICAR significantly inhibited the activation of these pyroptosis-related proteins. Moreover, further clinical trials have indicated that DICAR expression levels in diabetic patients were considerably lower than those in healthy controls. This concurs with the downregulation of DICAR in the cardiac tissues of diabetic mice, suggesting that DICAR overexpression could potentially serve as a novel therapeutic target for the inhibition of cardiomyocyte pyroptosis and the subsequent amelioration of diabetic cardiomyopathy (Fig. 6; Table 3) [104].

Ferroptosis and diabetic cardiomyopathy (DCM)

Overview of ferroptosis

Ferroptosis, a distinct iron-dependent regulated form of cellular death, was initially identified and characterized by Dixon et al. in 2012 [105]. Morphologically divergent from other modalities of cell death, ferroptosis is principally characterized by intact cellular nuclei, reduced mitochondrial size and cristae, along with mitochondrial membrane rupture [106]. The hallmark biochemical features of this form of cell death are the accumulation of free iron and reactive oxygen species (ROS), and it is intricately linked with iron metabolism, lipid peroxidation, and compromised antioxidative defense systems [107]. Below, we elucidate the specific mechanisms underpinning ferroptosis.

Iron is an indispensable trace element pivotal for maintaining cellular energy metabolism. In biological systems, it predominantly exists in its Fe^{2+} and Fe^{3+} states, participating in a plethora of metabolic pathways [108]. Under physiological conditions, the Transferrin Receptor 1 (TFR1) recognizes Fe^{3+} by binding to free transferrin (TF) on the cell membrane, which is then reduced to Fe^{2+} under the action of ferrireductases [109]. Subsequently, Divalent Metal Transporter 1 (DMT1) shuttles Fe^{2+} into the cytoplasmic Labile Iron Pool (LIP) for participation in various metabolic processes. Excessive iron is stored in the form of Fe^{3+} within ferritin or exported out of the cell via Ferroportin (FPN) [110, 111]. The Fe^{2+} within the LIP not only induces ferroptosis through the synthesis of key lipid peroxidation enzymes like Lipoxygenases (LOXs) but also participates in Fenton reactions with hydrogen peroxide, generating hydroxyl radicals that target cellular components and thereby cause ferroptosis [112]. Ferritin, as a primary iron storage protein complex, undergoes autophagic degradation in the cytoplasm or lysosomes, a process referred to as ferritinophagy. This, in turn, leads to elevated cellular iron levels, resulting in unstable iron overload, subsequent lipid peroxidation, and accumulation of ROS, thereby precipitating ferroptosis [113]. Furthermore, the Nuclear Receptor Coactivator 4 (NCOA4) serves as a crucial receptor in the ferritinophagy process and plays an indispensable role in maintaining iron homeostasis. The silencing of NCOA4 expression can inhibit ferritinophagy, thus averting iron overload, lipid peroxidation, and ferroptosis [114, 115].

Lipid peroxidation is a cardinal step in the cascade of events constituting ferroptosis, operating as a free-radical mediated reaction. The primary substrates involved in this process are polyunsaturated fatty acids (PUFA). Phospholipids with PUFA as substrates undergo transformation into lipid hydroperoxides under the enzymatic influence of Acyl-CoA Synthetase Long-Chain Family Member 4 (ACSL4) and Lysophosphatidylcholine Acyltransferase 3 (LPCAT3). Moreover, Fe^{2+} contributes to the Fenton reaction with lipid hydroperoxides, engendering toxic lipid radicals [116, 117]. These toxic lipid radicals are capable of inflicting cellular damage, thereby precipitating ferroptosis. Additionally, Nuclear Factor Erythroid 2-Related Factor 2 (NRF2), a quintessential regulatory element in cellular antioxidative stress responses, translocates to the nucleus to instigate the transcription of genes containing antioxidant response elements (ARE). The NRF2 pathway mitigates PUFA oxidation, attenuating lipid peroxidation, and ultimately inhibiting ferroptosis [118]. Furthermore, enzymatic reactions mediated by Arachidonate Lipoxygenase (ALOXs) or Cytochrome P450 Oxidoreductase (POR) have also been shown to accelerate lipid peroxidation, thereby inducing ferroptosis [119].

The deactivation of intracellular oxidative defense mechanisms leads to the insufficient clearance of lipid peroxides, resulting in their extensive accumulation within the cell and the subsequent onset of ferroptosis. The Cystine/Glutamate Antiporter System (System Xc-) serves as

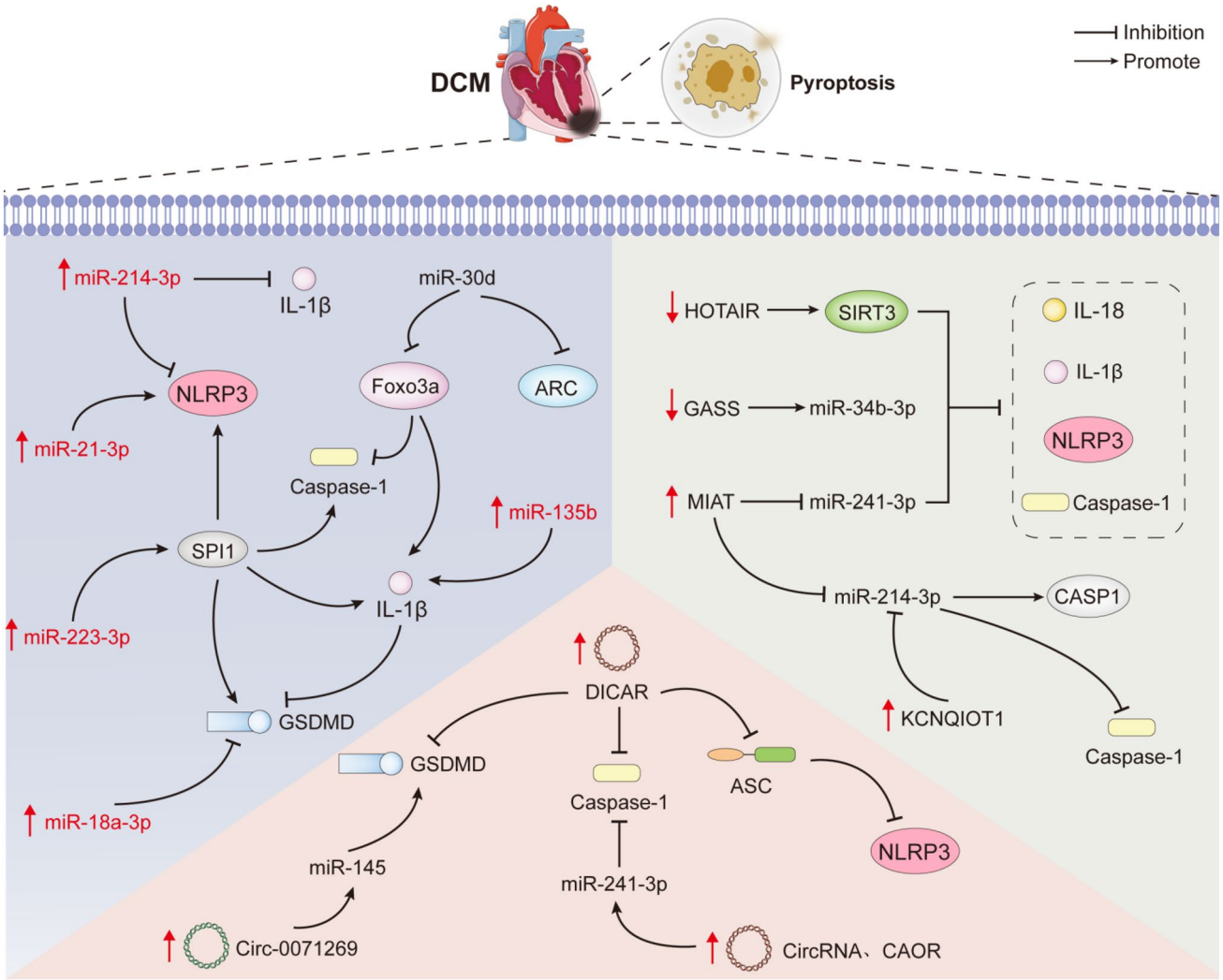

Fig. 6 Mechanism diagram of non-coding RNA regulating pyroptosis and intervening DCM. In the context of DCM, microRNA (miRNA) modulates the progression by regulating the expression of pyroptotic proteins. Long non-coding RNA (lncRNA) and circular RNA (circRNA) either act as miRNA sponges or function as miRNA precursors to regulate the expression of proteins involved in pyroptosis. NLRP3:NLR family pyrin domain containing 3,Foxo3a:Forkhead box 3a,ARC:Activity regulated cytoskeleton,SPI1:Salmonella pathogenicity island 1,GSDMD:Gasdermin D,IL-1 β:interleukin-1β,IL-18:interleukin-18,GAS5:Growth arrest specific transcript 5,KCNQIOT1:Potassium voltage-gated channel subfamily Q member 1 opposite strand 1,MIAT:Myocardial infarction associated transcript, HOTAIR:Hox transcript antisense intergenic RNA

a salient antioxidative system within the cell. Composed of two subunits, SLC7A11 and SLC3A2, which are ubiquitously distributed across the cell membrane, cystine and glutamate are reciprocally exchanged intracellularly and extracellularly via System Xc- [112]. Thus, by inhibiting the activity of System Xc-, the uptake of cystine can be obstructed, consequently impairing the synthesis of Glutathione (GSH) and reducing the activity of Glutathione Peroxidase 4 (GPX4). This, in turn, compromises cellular antioxidative capabilities [120]. Additionally, p53 downregulates SLC7A11 expression, thereby attenuating the uptake of cystine by the System Xc- across the organism. This results in the deactivation of cystine-dependent Glutathione Peroxidase, culminating in lipid peroxidation and ferroptosis (Fig. 7) [121].

Role of ferroptosis in diabetic cardiomyopathy (DCM)

Ferroptosis, recognized as a novel form of regulated programmed cell death, plays an indispensable role in the pathogenesis and progression of Diabetic Cardiomyopathy (DCM). Studies have ascertained that systemic iron overload not only precipitates the onset of Type 2 Diabetes Mellitus (T2DM) and exacerbates the risk of insulin resistance, but also amplifies cardiovascular complications via the Fenton

Table 3 Mechanism of non-coding RNA regulating pyroptosis in diabetic cardiomyopathy

ncRNAs	Target	Effects	Mechanism	References
miR-214-3p	NLRP3、caspase-1、IL-1β	Anti-pyroptosis	Promoting miR-214-3p expression can significantly reduce high-glucose-induced myocardial cell pyroptosis	[92]
miR-30d	Foxo3a、ARC	Anti-pyroptosis	MiR-30d can inhibit the expression of Foxo3a and ARC in vitro and in vivo, thereby inhibiting HG-induced myocardial cell pyroptosis	[93]
miR-9	ELAVL1	Anti-pyroptosis	Inhibiting miR-9 leads to the expression of ELAVL1 protein, as well as caspase-1 and IL-1 β Elevated expression, thereby inhibiting HG-induced myocardial cell pyroptosis	[85]
miR-18a-3p	GSDMD	Anti-pyroptosis	Inhibiting pyroptosis of H9C2 cells treated with high glucose and inhibiting DCM progression	[94]
miR-135b	IL-1β、GSDMD	Anti-pyroptosis	Inhibiting cardiac fibroblast pyroptosis and reducing collagen deposition	[95]
miR-21-3p	NLRP3、caspase-1	Pro-pyroptosis	Overexpression of miR-21-3p accelerates HG-induced cardiac fibroblasts pyroptosis	[96]
miR-223-3p	SPI1	Pro-pyroptosis	MiR-223-3p induces myocardial cell apoptosis and accelerates DCM development by upregulating SPI1 expression	[97]
HOTAIR	FUS、SIRT3	Anti-pyroptosis	HOTAIR can bind to FUS and activate SIRT3 expression, thereby downregulating NLRP3, caspase-1, and IL-1 β And IL-18 protein expression, thereby inhibiting cell apoptosis in DCM	[98]
MIAT	miR-214-3p、CASP1	Anti-pyroptosis	MIAT may regulate the scorch death of diabetes cardiomyopathy by targeting MIAT/miR-214-3p/CASP1 axis	[92]
MALAT1	miR-141-3p、ASC、GSDMD-N、caspase-1、NLRP3	Anti-pyroptosis	MALAT1 may participate in the development of DCM by targeting miR-141-3p to regulate the expression of pyroptosis-related proteins	[99]
GAS5	miR-34b-3p、AHR	Anti-pyroptosis	Inhibition of NLRP3 inflammasome activation mediated cell apoptosis and improvement of DCM	[100]
Kcnq1ot1	miR-214-3p、caspase-1	Anti-pyroptosis	Kcnq1ot1 can inhibit caspase-1 through miR-214-3p in myocardial cells, thereby inhibiting cell apoptosis	[101]
circ_0071269	miR-145、GSDMD	Pro-pyroptosis	Overexpression of circ_0071269 promotes miR-145 and GSDMD expression through sponge, thereby promoting cell apoptosis in DCM	[102]
CACR	miR-214-3p、caspase-1	Anti-pyroptosis	CACR silencing inhibits caspase-1 expression through sponge miR-214-3p, thereby inhibiting cell apoptosis in DCM	[103]
DICAR		Anti-pyroptosis	Overexpression of DICAR may prevent cardiomyocyte pyroptosis caused by diabetes and inhibit the development of diabetes cardiomyopathy	[104]

reaction [122]. Additional research indicates that elevated glucose levels in diabetic patients lead to an augmentation of Advanced Glycation End-products (AGEs). These terminal metabolites facilitate intracellular lipid accumulation and the ensuing lipotoxicity [123]. Subsequent studies delineate that both AGEs and intracellular lipid accumulation culminate in the excessive production of reactive oxygen and nitrogen species, thereby catalyzing the onset and progression of DCM [124]. Moreover, investigations in myocardial tissue from murine models of T2DM-induced DCM and rats with Heart Failure with Preserved Ejection Fraction (HFpEF) reveal an inhibited Xc-/GSH/GPX4 axis, accompanied by an overexpression of Transferrin Receptor 1 (TFR1) and Ferritin Heavy Chain (FTN-H) [125]. Furthermore, the expression levels of Nuclear Factor Erythroid 2-Related Factor 2 (NRF2), SLC7A11, and Glutathione (GSH) were observed to be significantly downregulated in myocardial tissue treated with AGEs and in murine models of DCM. The diminished expression of these ferroptosis-associated proteins compromises cellular functionality and intensifies lipid peroxidation, thereby engendering ferroptosis and serving as a pivotal pathogenic factor in the development of DCM [126].

Interplay between ncRNA and ferroptosis in diabetic cardiomyopathy (DCM)

Recent investigations underscore the pivotal role of long non-coding RNA (lncRNA)-mediated regulation of ferroptosis in the progression of DCM. Ni et al. delineated that in the left ventricular myocardial tissue of db/db mice and high-glucose (HG)-treated cardiomyocytes, lncRNA ZFAS1 was markedly upregulated, concomitant with an increase in ferroptosis. The inhibition of ZFAS1 was found

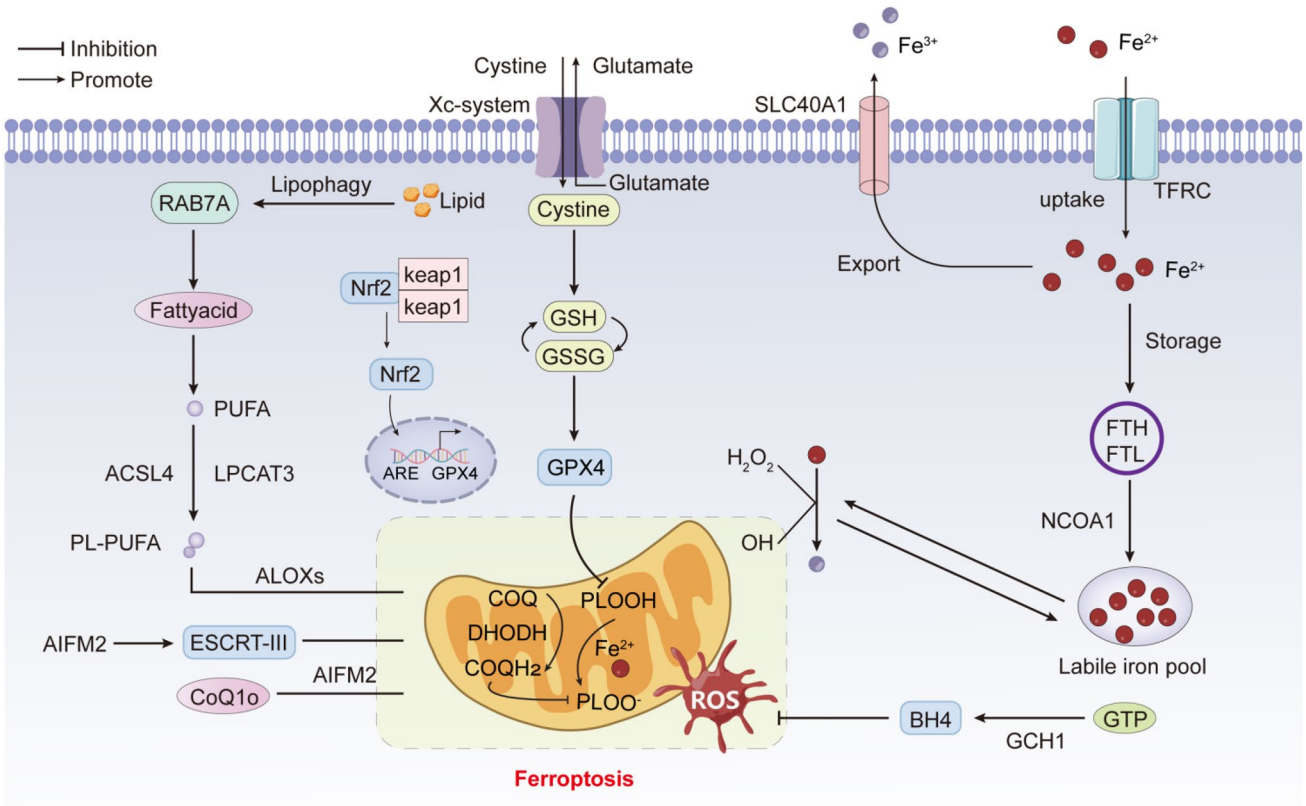

Fig. 7 Molecular mechanism diagram of ferroptosis. Free PUFA can be converted into PUFA-phospholipids (PUFA-PL) via ACSL4 and LPCAT3 enzymes. When PUFA-PLs undergo oxidation to lipid peroxides under the influence of arachidonate lipoxygenases (ALOXs), this triggers ferroptosis within the cell. AIFM2, a Coenzyme Q10 (CoQ10) oxidoreductase, functions in a parallel pathway with GPX4 to mitigate lipid peroxidation. GPX4 converts glutathione (GSH) to its oxidized form (GSSG), and the GSH/GSSG system acts as an antioxidant mechanism that inhibits ferroptosis by reducing reactive oxygen species (ROS). Intracellular iron in the form of Fe2 + is transported by transferrin and stored in an unstable iron pool as ferritin (FTH and FTL). C-reactive protein captures and oxidizes it to Fe3 +, which binds with transferrin (TF) and transferrin receptor (TFR) in the circulatory system. NCOA1 mediates autophagic degradation of ferritin in the lysosome, promoting the release of Fe2 +. Excess Fe2 + undergoes Fenton reaction with hydrogen peroxide, leading to lipid peroxidation and subsequent ferroptosis. Additionally, in the GCH1 protective pathway, GCH1 serves as the rate-limiting enzyme for the biosynthesis of tetrahydrobiopterin (BH4), and also regulates pantothenate levels

to restore the expression levels of Ferritin Heavy Chain 1 (FTH1) and Glutathione Peroxidase 4 (GPX4), as well as to attenuate the expression of 4-Hydroxynonenal (4-HNE). Subsequent studies revealed that ZFAS1 inhibition potentially ameliorates cardiomyocyte ferroptosis by sponging miR-150-5p to activate Cyclin D2 (CCND2), thereby mitigating ferroptotic cardiomyocyte death and attenuating DCM progression [127].Currently, research pertaining to lncRNA-mediated regulation of ferroptosis in DCM is rather limited and predominantly confined to cellular and molecular experiments; thus, there is a conspicuous dearth of clinical studies. Future endeavors should integrate both clinical and molecular investigations to broaden the scope of DCM-related research. Moreover, microRNA (miRNA) and circular RNA (circRNA) have been established as critical regulatory factors in ferroptosis [128, 129]. However, extant evidence concerning the role of miRNA and circRNA in modulating ferroptosis during the progression of DCM remains scant. Subsequent lines of inquiry should prioritize the elucidation of the mechanistic roles of miRNA and circRNA in the targeted regulation of ferroptosis within the context of DCM.

Necroptosis and diabetic cardiomyopathy (DCM)

Overview of necroptosis

Necroptosis was initially identified by Degterev and colleagues in 2005 as a unique form of cell death governed by a signaling cascade that could be inhibited by necrostatin-1 (Nec-1) [130]. In 2018, the Nomenclature Committee on Cell Death formally designated this caspase-independent mode of cell death as "necroptosis" [131]. This phenomenon amalgamates characteristics of both necrosis and apoptosis,

primarily manifesting as cellular volume augmentation, organelle swelling, membrane integrity disruption, and ultimate activation of cellular disintegration [132]. Necroptosis can be induced by a multitude of factors, including Tumor Necrosis Factor α (TNF-α), Fas ligand (FASL), TNF-Related Apoptosis-Inducing Ligand (TRAIL), Interferon-γ (IFN-γ), lipopolysaccharides (LPS), double-stranded RNA (dsRNA), and viral infections. Among these, the pathway mediated by TNF-α/TNF Receptor 1 (TNFR1) has been most extensively scrutinized [133]. Preliminary investigations reveal that TNF-α, upon binding to its membrane receptor TNFR1, instigates a conformational change in the TNFR1 trimer. Subsequently, TNFR1 recruits a multitude of proteins, including RIPK1/3, TRADD (TNFR-Associated Death Domain), cIAP1 (Cellular Inhibitor of Apoptosis Protein 1), cIAP2, and TRAF2/5 (TNFR-Associated Factors 2/5), to form a supramolecular structure termed "Complex I" [134]. Within Complex I, RIPK1 plays a dual role in modulating cellular survival and death. On one hand, its ubiquitination by cIAP1/2 enhances Complex I stability, thus activating the nuclear factor kappa B (NF-κB) pathway and promoting cellular survival. On the other hand, its deubiquitination by cylindromatosis (CYLD) leads to inhibition of the NF-κB pathway, thereby activating the cell death signaling cascade and enhancing the cell's susceptibility to necroptosis [135, 136]. Moreover, deubiquitinated RIPK1, under the influence of CYLD, dissociates from Complex I, leading to the formation of Complex IIb, which includes FADD, pro-caspase-8, RIPK3, and RIPK1. This promotes the activation of caspase-8 and initiates cellular apoptosis [137, 138]. However, when the activity of caspase-8 is suppressed by caspase inhibitors such as zVAD or FLICE inhibitory protein (FLIP), Complex IIb transmutes into a necrosome, thereby inducing necroptosis (Fig. 8) [139].

Necroptosis in diabetic cardiomyopathy (DCM)

In contrast to other modalities of cell death, the role of necroptosis in DCM is in its nascent stage, and research explicitly linking necroptosis to DCM is relatively scant. Receptor-interacting protein kinase 3 (RIPK3) has been postulated to act as a pivotal regulator of necroptosis in diabetes, in a RIPK1-dependent manner. Preliminary investigations have elucidated that hyperglycemia markedly augments the expression of RIPK3 and mixed lineage kinase domain-like pseudokinase (MLKL) necroptotic signaling in both cardiac myocytes and the heart. Furthermore, the inhibition of RIPK3 can forestall MLKL phosphorylation and necroptosis in cardiac myocytes under hyperglycemic conditions [140, 141]. A recent study has disclosed that under high glucose (HG) stimulation, the activity and expression of aldehyde dehydrogenase 2 (ALDH2) are diminished, concomitant with an escalation in the expression of key necroptotic mediators such as RIPK3, RIPK1, and MLKL. Additionally, the upregulation of ALDH2 and downregulation of reactive oxygen species (ROS) expression can effectively quell necroptosis, thereby mediating cardioprotective effects under hyperglycemic conditions [142]. Sirtuin 3 (SIRT3), a deacetylase ubiquitously present in the heart, has been demonstrated to exacerbate mitochondrial damage induced by hyperglycemia, facilitate ROS accumulation, and promote the expression of necroptotic factors RIPK1 and RIPK3. It further activates the NLRP3 inflammasome, consequently aggravating the pathological manifestation of DCM in murine models [143]. In a novel revelation, Calcium/calmodulin-dependent protein kinase II (CaMKII), recognized as a new substrate for RIPK3, has been found to mediate myocardial necroptosis induced by ischemia and oxidative stress. Recent investigations indicate that its phosphorylation and oxidation are markedly enhanced in DCM mice and cardiac myocytes stimulated by advanced glycation end-products (AGEs). Silencing RIPK3 expression was shown to mitigate CaMKII activation and ameliorate necroptosis in DCM mice [144, 145].

Non-coding RNA (ncRNA) and necroptosis in diabetic cardiomyopathy (DCM)

Although the overarching theme of this article pertains to the role of ncRNA-mediated programmed cell death (PCD) in DCM, it is imperative to note that existing research on ncRNA-mediated necroptosis remains relatively scarce, thereby indirectly impeding the advancement of studies in the domain of necroptosis. Despite the limited body of work on ncRNA-mediated necroptosis in the context of DCM, select ncRNAs implicated in necroptosis in diseases associated with diabetes or cardiac dysfunction warrant considerable attention as potential therapeutic targets for DCM. For instance, Gao et al. observed that the expression of circRNA CNEACR is diminished post-myocardial ischemia–reperfusion (I/R), leading to myocardial necroptosis, whereas its overexpression ameliorates cardiac injury and enhances myocardial cell survival by upregulating Foxa2 and inhibiting RIPK3 transcription through a direct interaction with HDAC7 [146]. Similarly, Zhang et al. demonstrated that the expression of miR-325-3p is downregulated in myocardial infarction (MI) mice, and its overexpression attenuates the expression of necroptotic proteins such as RIPK1 and RIPK3, as well as phosphorylated MLKL, thereby mitigating the extent of infarction and tissue damage [147]. Corroborating these findings, Qin and colleagues verified through in vivo and in vitro assays that both miR-223-5p and -3p are expressed in myocardial tissues and target DR6, TNFR1, and the NLRP3 inflammasome, collectively dampening myocardial I/R-induced necroptosis [148]. While these ncRNAs have not yet been proven to function in DCM specifically,

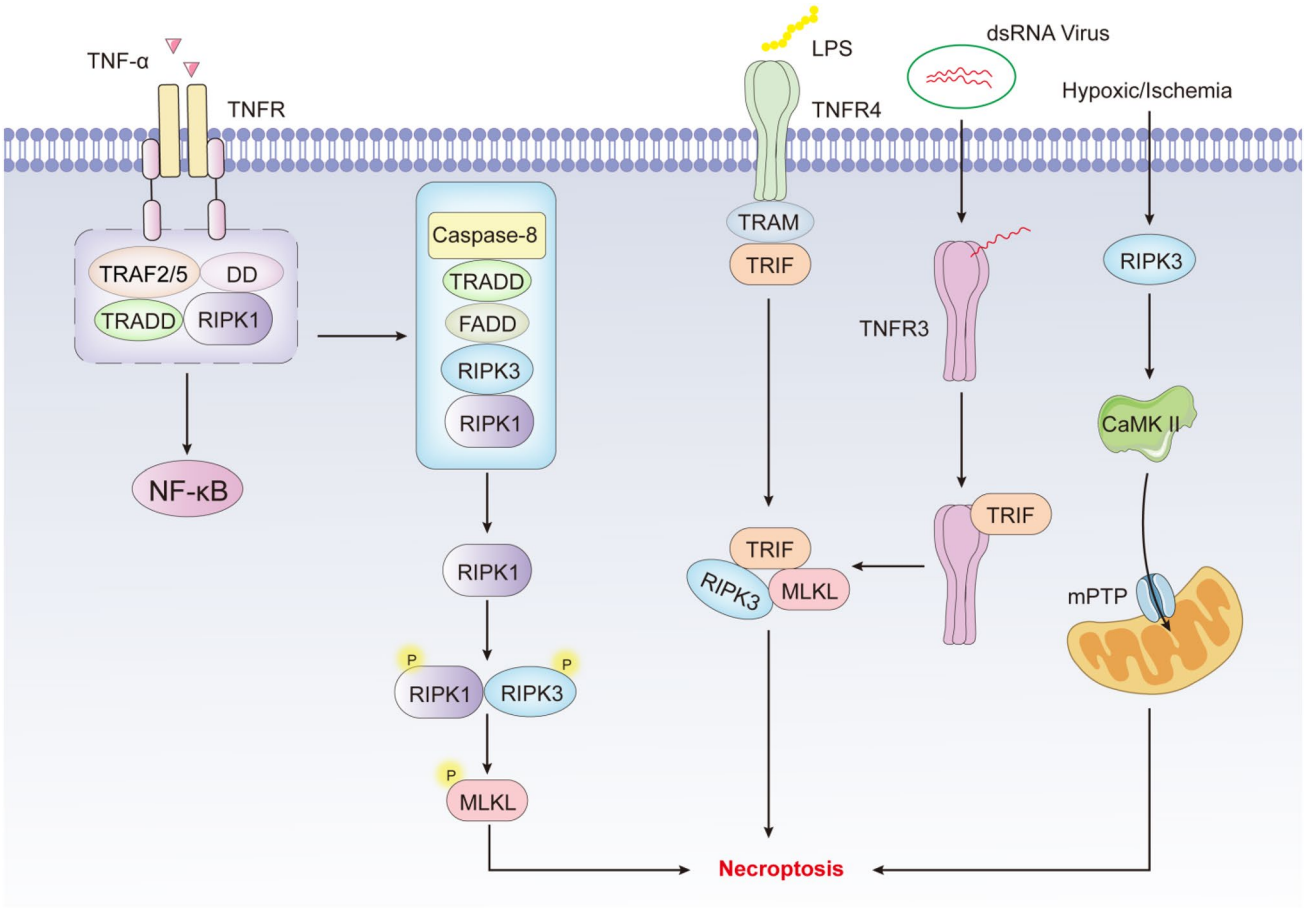

Fig. 8 Molecular mechanism diagram of necroptosis. Upon binding with its receptor TNFR, TNF-α recruits a cohort of proteins, including TRADD, RIPK1, and TRAF2/5, to form Complex I. Ubiquitination of RIPK1 in the upstream pathway activates NF-κB signaling. Complex I can subsequently evolve into Complex II, consisting of caspase-8, TRADD, RIPK1, and RIPK3. RIPK1 undergoes autophosphorylation, enabling its RHIM domain to bind with RIPK3 and form filamentous heterodimeric scaffolds known as necrosomes. Necrosomes recruit additional RIPK3, mediating its homodimerization, autophosphorylation, and activation, eventually leading to the phosphorylation of MLKL, which culminates in membrane rupture and necroptotic death. Distinct from the above mechanism, TLR3 can recognize viral double-stranded RNA and directly induce necroptotic death through a complex composed of TRIF, RIPK3, FADD, and caspase-8. On the other hand, TLR4 recognizes LPS through a complex that includes TRIF, RIP1, and RIP3. Phosphorylation of RIP1 and RIP3, along with the receptor interactions between TRIF and RIP3, leads to the phosphorylation of MLKL, triggering necroptotic death

their study presents an intriguing avenue for future research into ncRNA-mediated PCD in DCM.

Discussion

The incidence of diabetes has been on an upward trajectory in recent years, and DCM, as one of the significant cardiovascular complications of diabetes, presents a considerable threat to human health. Characterized by structural and functional anomalies in myocardial tissues induced by long-term diabetes or hyperglycemia, DCM eventually culminates in heart failure. Given the intricate pathophysiological mechanisms underlying DCM and the absence of effective therapeutics explicitly targeting this disorder, a deeper exploration into the cellular and molecular mechanisms, as well as potential biomarkers in DCM, is urgently needed. Increasing attention has been paid to various forms of PCD as they have been closely implicated in the pathogenesis and progression of various diseases, including DCM. Myocardial PCD is considered a critical pathological factor in the onset and development of DCM, and targeting the regulation of myocardial PCD could serve as an essential therapeutic strategy. Moreover, accumulating evidence indicates that dysregulated ncRNAs play a pivotal role in DCM progression by modulating PCD. Therefore, elucidating the intricate interplay between ncRNA and PCD, along with their regulatory mechanisms in DCM, will contribute to a more comprehensive understanding of DCM's etiology and pathogenesis, thereby offering new avenues for diagnosis and treatment.

Emerging from the comprehensive review presented herein, it becomes unequivocally evident that distinct modalities of cell death are intrinsically involved in the progression of Diabetic Cardiomyopathy (DCM). Furthermore, the inhibition of virtually any form of PCD, excluding autophagy, has been shown to substantially alleviate impairments in myocardial structure and function, thereby highlighting these distinct forms of cell death as potential therapeutic targets for DCM. However, it is pivotal to recognize that PCD is a dynamically evolving process, exerting divergent impacts at different stages of disease progression. For instance, autophagy is traditionally considered vital in maintaining cardiac structure and function. Yet, both the inhibition and hyperactivation of cardiac autophagy yield significant repercussions on DCM. Numerous studies underscore the dual role of autophagy across various DCM subtypes; for example, autophagic markers are elevated in the hearts of type 2 diabetic patients, but diminished in primary myocardial cells cultured in high glucose and in type-1 diabetic myocardium [56]. This underscores the intricate regulation of cardiac autophagy within a diabetic milieu as a conundrum warranting expansive future research, including the development of novel autophagy modulators for DCM treatment. Additionally, it is important to delineate that different cell death modalities do not operate in isolation, rather, they engage in mutual crosstalk. For instance, miR-207 has been shown to inhibit autophagy while augmenting apoptosis in neonatal mouse cardiomyocytes [60], indicating a concerted involvement of both autophagy and apoptosis in DCM pathogenesis. Furthering this discourse, one study demonstrated that metformin could activate the AMPK signaling pathway, thereby promoting autophagy via inhibition of the mTOR signaling pathway and, in turn, suppressing NLRP3 inflammasome-induced pyroptosis in DCM [149]. Another investigation substantiated a connection between autophagy and necroptosis, where RIPK1 and RIPK3, along with their phosphorylated forms, are upregulated in HGF-treated cardiac fibroblasts and diabetic rat myocardial tissue. Inhibition of either RIPK1 or RIPK3 restored autophagic flux in HGF-treated cardiac fibroblasts, indicating that shared molecular mechanisms between necroptosis and autophagy could serve as promising therapeutic targets for DCM [150]. In summary, our findings elucidate that various types of cell death might co-exist and potentially occur concurrently during the onset and progression of DCM. Interfering with any single modality of cell death could potentially induce compensatory changes in other forms of cell death, thereby exacerbating the complexity of DCM's pathogenic mechanisms and complicating its treatment landscape. Therefore, a nuanced understanding of the intricate crosstalk between diverse PCD modalities and their predominant roles in the pathogenesis of DCM is indispensable. This knowledge will be instrumental in the future development of combined therapeutic strategies targeting multiple types of PCD.

In addition to the overarching themes discussed, this review consolidates the evidence concerning the interplay between non-coding RNA (ncRNA) and Programmed Cell Death (PCD) in Diabetic Cardiomyopathy (DCM). The data underpin the immense therapeutic potential of ncRNAs as regulators of PCD modalities, thereby positing them as promising targets for DCM intervention. Nonetheless, our investigation harbors certain limitations that must be candidly acknowledged. For instance, the complexity of miRNA–target gene interactions is multifaceted; a single miRNA can regulate multiple target genes, and conversely, a single target gene can be modulated by multiple miRNAs. As a case in point, LAMP2 not only possesses binding sites for miR-207 but also for other miRNAs like miR-221, which can inhibit autophagy by directly targeting LAMP2 and thus modulate TGF-β1-induced activation of hepatic stellate cells [151]. Additionally, miRNAs may also govern PCD through the regulation of other target genes, thereby exerting a significant influence on the course of DCM. Moreover, lncRNA and circRNA do not act via singular signaling pathways in their regulatory roles on PCD within the DCM context; rather, they function as competing endogenous RNAs (ceRNAs), sequestering miRNAs to modulate the expression of target genes. Such intricate dynamics, involving the orchestrated mediation of lncRNAs and miRNAs, circRNAs and miRNAs, in the progression of PCD in DCM, propose the modulation of ncRNA-mediated PCD as a novel strategic approach for DCM therapy. Of note, existing studies have demonstrated that the transfection or injection of ncRNA analogs, agonists, and antagonists could effectively decelerate DCM progression [64, 92, 104]. However, the expression levels and roles of ncRNAs can vary across different samples, and the bulk of current research is confined to molecular biology and disease model experimentation. The translational leap from bench science to clinical implementation remains a long traverse. Furthermore, while a plethora of studies focus on ncRNA-mediated regulation of autophagy, apoptosis, pyroptosis, and ferroptosis in DCM, there is a relative paucity of research pertaining to ncRNA-regulated necroptosis in DCM. As such, future investigations will prioritize elucidating the role of ncRNA-mediated necroptosis in DCM pathogenesis. In spite of these challenges, there exists cogent justification for optimism. With an increasingly sophisticated understanding of ncRNA-mediated PCD in DCM and the delineation of the underpinning mechanisms, we remain sanguine that new avenues for intervention will be uncovered in the prevention and treatment of DCM.

Author contributions ZBR contributed to the conception and design of this manuscript. ZL has critically revised the entire manuscript. WH, ZJW, and CC are responsible for manuscript structure and English grammar. All authors participated in manuscript revision, read and approved the submitted version. All authors revised and approved the final manuscript. "The author(s) read and approved the final manuscript."

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Declarations

Competing interests The authors declare no competing interests.

Conflict of interests The authors declare that they have no conflicts of interest.

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