

Metabolism and Target Organ Damage

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Extracellular vesicle-mediated communication in diabetic cardiomyopathy: cellular mechanisms, metabolic remodeling, and emerging therapeutic strategies

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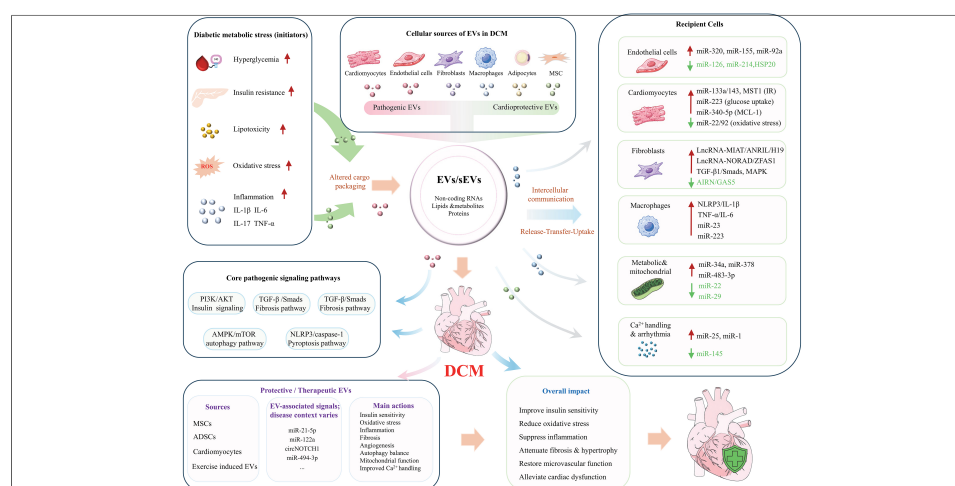
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Abstract

Diabetic cardiomyopathy (DCM) is an increasingly recognized cardiac complication of diabetes and contributes substantially to diabetes-associated cardiovascular morbidity and mortality. Extracellular vesicles (EVs), particularly small EVs (sEVs), have emerged as critical mediators of intercellular communication by transferring diverse bioactive cargoes, including microRNAs (miRNAs), long non-coding RNAs, circular RNAs, and proteins. Although sEVs have frequently been referred to as “exosomes” in previous literature, their precise classification remains challenging because current methodologies cannot reliably distinguish endosome-derived vesicles from other EV populations. Accumulating evidence indicates that EV-associated cargoes, particularly miRNAs, participate in regulating key pathogenic processes in DCM, including cardiomyocyte injury, apoptosis, oxidative stress, inflammation, metabolic remodeling, and fibrosis. Although the field of EVs in DCM remains at an early stage, emerging findings have provided new insights into disease mechanisms and highlighted the potential utility of EVs as biomarkers and therapeutic

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platforms. This review summarizes recent advances in EV biology in DCM, with a focus on their roles in cellular communication networks, metabolic remodeling, and disease progression. We further discuss the translational potential of EV-based approaches, including their applications as diagnostic biomarkers, therapeutic targets, and delivery systems, while addressing current challenges related to EV heterogeneity, cargo specificity, and clinical implementation. A better understanding of EV-mediated signaling networks may facilitate the development of precision strategies for early detection, risk stratification, and targeted intervention in diabetic cardiac disease.

INTRODUCTION

According to the 2025 edition of the International Diabetes Federation (IDF) Diabetes Atlas, an estimated 589 million adults worldwide were living with diabetes in 2024, representing 11.1% of the global adult population. Projections indicate this figure will increase dramatically to 853 million individuals (13% of adults) by 2050. The growing global burden of diabetes has been accompanied by a marked increase in comorbidities, particularly cardiovascular disease; type 2 diabetes increases the risk of myocardial infarction and heart failure (HF) by 72% and 84%, respectively^[1]. Diabetic cardiomyopathy (DCM) is now recognized as a distinct diabetes-related cardiac disorder, defined by the gradual deterioration of myocardial performance in the absence of significant coronary artery disease or hypertension^[2]. The risk of DCM is influenced by several factors, including age, sex, diabetes duration, and quality of glycemic control; notably, men appear to have more than twice the risk of women. Coexisting conditions such as obesity and hypertension further accelerate disease progression^[3,4]. At the molecular level, DCM pathogenesis involves a complex interplay of oxidative stress, neurohormonal activation, inflammation, impaired calcium handling, mitochondrial dysfunction, and dysregulated apoptotic and autophagic signaling^[5]. Although substantial progress has been made in elucidating these mechanisms, the molecular determinants driving DCM initiation and progression remain incompletely understood.

Extracellular vesicles (EVs) are a heterogeneous group of cell-derived, membrane-bound vesicles with diverse sizes, biogenesis pathways, and molecular compositions. They have emerged as important regulators of diabetes-related pathophysiology, with established roles in diabetic complications such as retinopathy, nephropathy, and cardiomyopathy^[6]. They are widely distributed in biological fluids - including blood, urine, breast milk, and cerebrospinal fluid - and carry a diverse array of bioactive molecules that mediate intercellular communication.

Among EV subtypes, small EVs (sEVs) represent a major EV population and are frequently referred to as “exosomes” in the literature. However, current methodologies cannot reliably distinguish bona fide exosomes (of endosomal origin) from other sEV subtypes. Therefore, this review primarily employs the terms “EVs” and “sEVs” in accordance with the minimal information for studies of extracellular vesicles (MISEV2023) guidelines^[7], while reserving the term “exosomes” only for studies that provide convincing evidence of an endosomal origin.

Under hyperglycemic stress, EVs released from cardiomyocytes can carry profibrotic and proapoptotic miRNAs, such as miR-34a and miR-320, thereby exacerbating cardiac dysfunction^[8]. Conversely, EVs derived from mesenchymal stem cells (MSCs) have demonstrated protective effects. They deliver therapeutically beneficial miRNAs, such as miR-126, that mitigate inflammation and restore metabolic balance in the diabetic heart. Importantly, the biological effects of EV-associated miRNAs in DCM should be interpreted according to their cellular origin, endogenous expression patterns, disease context, and experimental manipulation strategies. Changes in miRNA abundance should not be directly equated with therapeutic direction, as restoration or inhibition strategies depend on the specific biological role of each miRNA. Therefore, miRNA-based therapeutic approaches should be distinguished from disease-associated expression changes, particularly for miRNAs with context-dependent functions.

Beyond mediating local intercellular communication, EVs have also been implicated in metabolic and immune remodeling associated with diabetes and cardiovascular disease^[6]. The diverse roles of EVs in cardiovascular diseases - as pathophysiological mediators, diagnostic biomarkers, and therapeutic delivery vehicles - have been comprehensively reviewed elsewhere^[9]. The present review, however, specifically focuses on DCM. Accordingly, we provide an updated synthesis of EV-mediated mechanisms involved in DCM progression, including their effects on cellular communication networks, metabolic remodeling, and cardiac injury. We also evaluate their potential applications as diagnostic biomarkers and therapeutic platforms^[6]. We further assess the translational challenges associated with EV-based approaches, including heterogeneity, cargo specificity, and clinical implementation. Through this, we aim to advance our understanding of DCM pathogenesis and potential therapeutic strategies.

Literature search strategy and evidence classification

This narrative review is based on a comprehensive literature search of the PubMed, Web of Science, and Scopus databases through June 2026 using combinations of the keywords “diabetic cardiomyopathy”, “extracellular vesicles”, “small extracellular vesicles”, “exosomes”, “microRNAs”, and “long non-coding RNAs.” Although substantial mechanistic insights into EV-mediated cardiac remodeling have been obtained from diverse cardiovascular models, including HF, pressure overload, ischemia-reperfusion, and dilated cardiomyopathy models, such findings should not be considered equivalent to direct evidence in DCM. To facilitate interpretation of the available evidence, studies were classified according to an evidence hierarchy based on experimental context. Level 1 represents human clinical evidence derived from patient samples or cohorts; Level 2 includes *in vivo* DCM models with confirmed cardiac dysfunction; Level 3 includes non-diabetic cardiovascular disease models providing indirect mechanistic support that may be relevant to DCM but requires validation in diabetic settings; and Level 4 refers to *in vitro* studies, including high-glucose-treated cardiomyocytes or other relevant cellular models. Throughout this review, mechanistic conclusions regarding DCM are primarily based on evidence from diabetic models with confirmed cardiac phenotypes, whereas findings from non-DCM models are interpreted as supportive or hypothesis-generating evidence rather than established DCM-specific mechanisms. Because available evidence varies among EV cargoes and biological pathways, not all levels are represented in every table.

Overview of EVs

EVs have historically been classified according to their biogenesis pathways, physical characteristics, and size distribution. However, because current isolation methods and molecular markers cannot reliably distinguish EV subtypes based solely on biogenesis origin, contemporary EV research increasingly favors operational terminology. EVs may therefore be described using terms such as sEVs and medium/large EVs (m/LEVs) based on experimentally defined characteristics rather than as discrete biological entities. Although exosomes are commonly described as endosome-derived vesicles, definitive identification of bona fide exosomes remains challenging because they cannot be reliably distinguished from other sEV populations using currently available approaches.

EVs carry a diverse repertoire of bioactive molecules, including proteins, lipids, messenger RNAs (mRNAs), microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). This molecular cargo enables EVs to mediate intercellular communication, transferring molecular information from donor to recipient cells. Following interaction with recipient cells, EVs may fuse with the plasma membrane or undergo endocytosis, thereby releasing their cargo into the cytoplasm to regulate gene expression, intracellular signaling, and various cellular processes, including proliferation, differentiation, apoptosis, immune responses, angiogenesis, and tissue repair^[10].

The biological functions of EVs are influenced by multiple factors, including their biogenesis, cargo-sorting mechanisms, membrane composition, and uptake efficiency by recipient cells^[11]. In addition, extrinsic factors, including receptor availability and enzymatic activity in the extracellular milieu, further modulate EV function. Notably, a substantial proportion of circulating miRNAs is encapsulated within EVs, with some miRNA species also associating with high-density lipoproteins, underscoring the central role of EVs in systemic miRNA transport^[12]. Collectively, these characteristics establish EVs as important contributors to intercellular communication and physiological homeostasis. As comprehensively reviewed by Abbas *et al.*, EVs derived from different cellular sources participate in the pathogenesis of diabetes and its complications, including cardiomyopathy, through the transfer of bioactive cargoes involved in inflammation, oxidative stress, and tissue remodeling^[13].

In DCM, EV-mediated intercellular communication orchestrates crosstalk among cardiomyocytes, endothelial cells, and fibroblasts [Figure 1]. Several miRNAs, although not yet experimentally validated as EV cargo in DCM, including miR-1, miR-223, miR-29 and miR-103, have been implicated in diabetes-associated cardiac remodeling and metabolic regulation. By shuttling these signaling molecules between cells, EVs can modulate recipient cell activity and contribute to the initiation and progression of DCM^[9]. Conversely, EVs derived from multiple sources, such as MSCs and macrophages, have shown therapeutic promise in cardiovascular disorders, including DCM^[11]. Accordingly, EVs are regarded as promising candidates for innovative diagnostic biomarkers and therapeutic approaches in DCM management^[14].

Despite growing interest in the role of EVs in disease pathogenesis, fundamental aspects - including biogenesis, cargo loading, target cell specificity, and internalization - remain incompletely understood. Addressing these knowledge gaps will be essential for translating EV biology into clinically applicable diagnostic and therapeutic strategies. Although recent studies have substantially expanded our understanding of EV-mediated signaling, further investigation is required to define their precise contributions to DCM pathogenesis and their translational potential.

INSULIN RESISTANCE AND EV-MEDIATED MODULATION IN DCM

In DCM, cardiac insulin resistance (IR) is characterized by impaired insulin receptor signaling, defective IRS-1/2-phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) activation, and reduced glucose transporter type 4 (GLUT4) translocation to the plasma membrane, ultimately leading to impaired myocardial glucose utilization and metabolic remodeling^[15]. Beyond these canonical mechanisms, accumulating evidence indicates that EV-associated miRNAs contribute to IR-related metabolic disturbances via intercellular communication, modulating GLUT4 trafficking, PI3K/AKT signaling, and inflammatory pathways^[16-20]. In addition to the canonical insulin signaling cascade, metabolic regulators such as AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) integrate cellular energy status, nutrient availability, and adaptive responses in the diabetic heart. Dysregulation of these interconnected pathways contributes to impaired metabolic flexibility and maladaptive myocardial remodeling^[14,21].

Among miRNAs implicated in cardiac IR, miR-133a and miR-143 have been reported to promote IR by suppressing GLUT4 expression and AKT signaling, respectively, whereas miR-223 may enhance insulin sensitivity by facilitating GLUT4 translocation^[22-25]. EV protein cargo also contributes to IR. For example, EV-mediated macrophage stimulating 1 (MST1) released from cardiac microvascular endothelial cells (CMECs) is transferred to cardiomyocytes, where it disrupts the Daxx-GLUT4 interaction by promoting the formation of the MST1-Daxx complex, thereby inhibiting GLUT4 membrane translocation and exacerbating IR^[26].

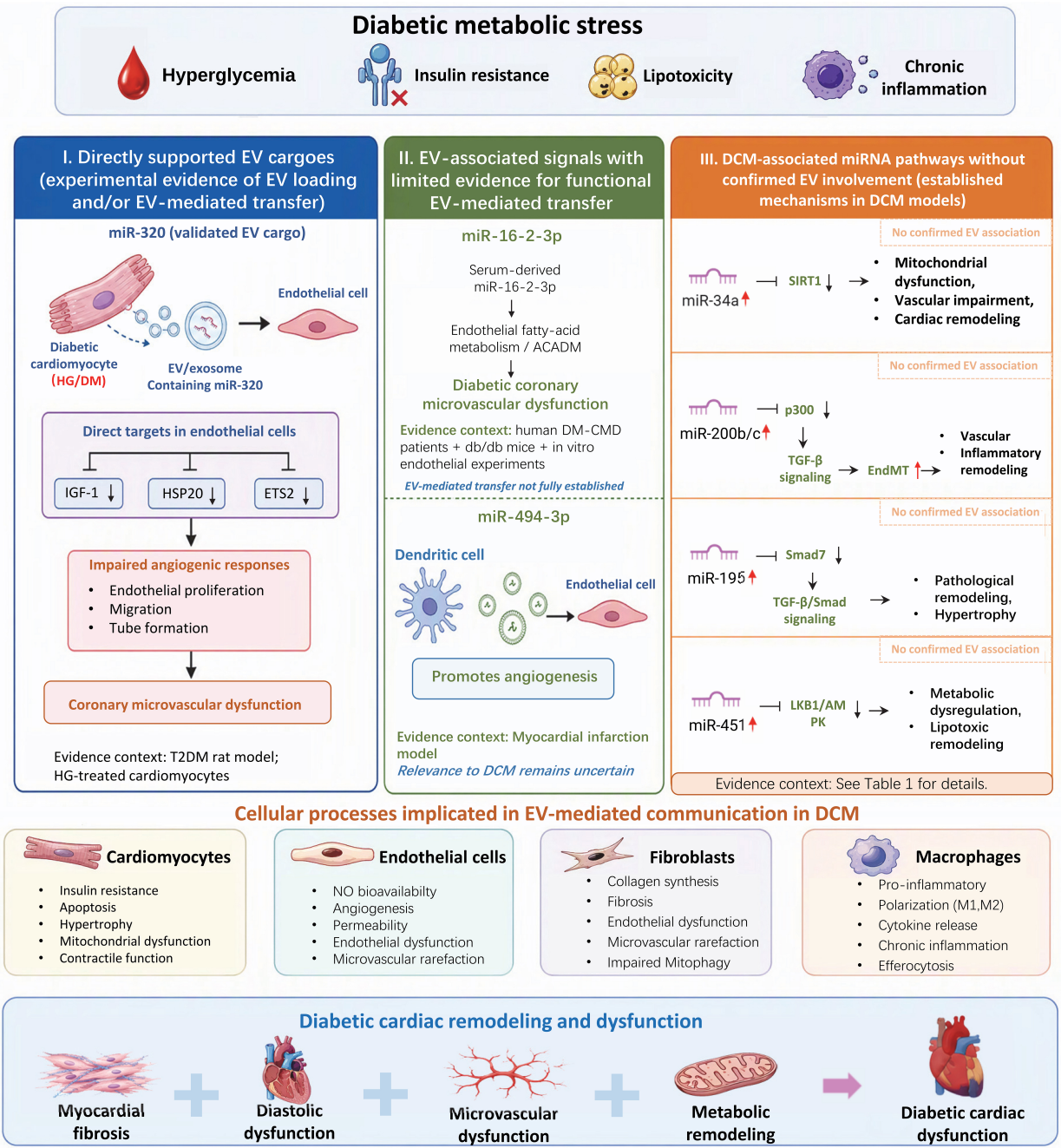


Figure 1. Evidence-based classification of EV-associated and EV-independent miRNA mechanisms in diabetic cardiomyopathy. Diabetic metabolic stress, including hyperglycemia, insulin resistance, lipotoxicity, and chronic inflammation, alters intercellular communication and miRNA-associated signaling in the diabetic heart. I, directly supported EV cargoes: miR-320 is transferred from diabetic cardiomyocytes to endothelial cells through EVs, where it suppresses IGF-1, HSP20, and ETS2 and impairs endothelial proliferation, migration, and tube formation. II, EV-associated signals with context-limited evidence: circulating miR-16-2-3p has been associated with diabetic coronary microvascular dysfunction, whereas dendritic-cell-derived miR-494-3p promotes angiogenesis in a myocardial infarction model; these findings should not be directly extrapolated to DCM. III, DCM-associated miRNA pathways without confirmed EV involvement: miR-34a, miR-200b/c, miR-195, and miR-451 contribute to vascular, fibrotic, hypertrophic, or metabolic abnormalities in diabetic or related cardiac models, but direct EV loading or EV-mediated transfer has not been established. The lower panel summarizes cellular processes potentially affected by EV-mediated communication and their contribution to diabetic cardiac remodeling and dysfunction. This evidence-based classification distinguishes experimentally supported EV cargoes from EV-associated signals and miRNA mechanisms for which direct EV involvement remains unconfirmed. ↑ Indicate upregulated; ↓ indicate downregulated; Solid arrows indicate established direct interactions, whereas dashed arrows denote putative or indirect regulatory relationships that require further experimental validation; T-bars represent inhibition. ACADM: Acyl-CoA dehydrogenase medium chain; AMPK: AMP-activated protein kinase; DCM: diabetic cardiomyopathy; DM: diabetes mellitus; EVs: extracellular vesicles; ETS2: ETS proto-oncogene 2; HG: hyperglycemia; HSP20: heat shock protein 20; IGF-1: insulin-like growth factor 1; LKB1: liver kinase B1; miRNA: microRNA; NO: nitric oxide; PK: pyruvate kinase; SIRT1: sirtuin 1; T2DM: type 2 diabetes mellitus; TGF-β: transforming growth factor beta.

The PI3K/AKT signaling pathway exhibits complex, context-dependent effects in DCM, with its biological consequences largely determined by the duration and magnitude of pathway activation. Under physiological or acute stress conditions, transient PI3K/AKT activation promotes cardiomyocyte survival, glucose utilization, and adaptive hypertrophy, thereby exerting cardioprotective effects. In contrast, chronic metabolic stress associated with diabetes results in persistent alterations in PI3K/AKT signaling, contributing to IR, impaired glucose uptake, pathological cardiac remodeling, and progressive DCM^[15,27]. This context-dependent duality highlights the need for selective modulation of specific signaling nodes rather than nonspecific inhibition or activation of the pathway.

Clinical evidence linking IR to DCM remains largely observational. Population-based studies have demonstrated that IR is associated with an increased risk of incident HF in individuals without overt cardiovascular disease^[28] and is more prevalent among patients with idiopathic dilated cardiomyopathy^[29]. However, direct clinical evidence demonstrating that patient-derived EVs causally contribute to IR-associated myocardial dysfunction in DCM remains limited. Most available clinical studies are cross-sectional and primarily report associations between circulating EV profiles and metabolic phenotypes. The broader role of EV-derived miRNAs in inter-organ crosstalk among insulin-targeted tissues has been comprehensively reviewed elsewhere^[12].

Preclinical studies have provided experimental evidence supporting the therapeutic potential of targeting miRNAs to improve IR and cardiac injury. Overexpression of miR-322 suppresses excessive AKT phosphorylation and attenuates myocardial injury in high-fat diet-fed mice^[19]. Conversely, insulin maintains cardiomyocyte survival partly through inhibition of miR-29a/b/c^[14]. In addition, EVs derived from human umbilical cord mesenchymal stem cells (hUC-MSCs) improve β -cell survival, restore insulin secretion, and enhance systemic insulin sensitivity in experimental diabetes^[30]. Collectively, these findings support EV-mediated regulation of IR as a potential therapeutic strategy for preventing or delaying DCM progression. Nevertheless, robust clinical validation is still required before these approaches can be translated into routine clinical practice.

OXIDATIVE STRESS, MITOCHONDRIAL DYSFUNCTION, AND EV-MEDIATED REGULATION IN DCM

Hyperglycemia and IR drive excessive electron flux from NADH [nicotinamide adenine dinucleotide (reduced)] and reduced flavin adenine dinucleotide (FADH₂) into the mitochondrial electron transport chain (ETC). This overload promotes hyperpolarization of the mitochondrial membrane and electron escape at sites such as complex III, culminating in the overproduction of reactive oxygen species (ROS), including superoxide anions, hydroxyl radicals, and hydrogen peroxide. When ROS production exceeds endogenous antioxidant defenses, oxidative damage to proteins, lipids, and DNA accumulates, ultimately impairing cellular function and promoting myocardial injury.

Under physiological conditions, cardiomyocytes exhibit metabolic flexibility by dynamically switching between glucose and fatty acid oxidation to meet energetic demands. In type 2 diabetes, mitochondrial oxidative stress and impaired oxidative phosphorylation disturb energy homeostasis, shifting myocardial metabolism toward increased reliance on free fatty acid (FFA) oxidation. Excessive fatty acid uptake and oxidation promote the accumulation of toxic lipid intermediates and heightened oxygen consumption, and contribute to mitochondrial uncoupling and inefficiency. Simultaneously, endoplasmic reticulum stress (ERS) and inflammatory signaling exacerbate ROS generation in cardiomyocytes, fueling a vicious cycle of oxidative injury. Sustained oxidative stress aggravates IR and induces myocardial fibrosis, potentially culminating in HF.

Emerging evidence indicates that EVs participate in regulating oxidative stress responses and mitochondrial metabolism in the diabetic heart. Depending on their cellular origin and molecular cargo, EV-associated miRNAs may either promote oxidative injury or enhance protective antioxidant pathways.

Pro-oxidant miRNAs and their pathogenic mechanisms

Chronic metabolic stress in obesity and type 2 diabetes alters the composition and functional properties of circulating EVs, which, upon uptake by cardiomyocytes, impair mitochondrial homeostasis and promote oxidative stress. For instance, adipocyte-derived sEVs from diabetic or high-fat-fed mice increase mitochondrial ROS production, depolarize the mitochondrial membrane, and promote cardiomyocyte injury - partly through transfer of miR-130b-3p, which suppresses peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) expression^[31]. In hyperglycemic conditions, cardiomyocyte-derived EVs enriched with miR-320 are transferred to endothelial cells, where they suppress proliferation, migration, and tube formation, thereby impairing angiogenesis^[32]. Similarly, although miR-340-5p has not been specifically demonstrated to be EV-associated, it has been studied in diabetic heart tissue and cardiomyocytes. This miRNA directly targets the anti-apoptotic protein Mcl-1, causing mitochondrial dysfunction, ROS accumulation, and cardiomyocyte apoptosis in db/db mice. Inhibition of miR-340-5p reduces ROS levels and ameliorates fibrosis and cardiac dysfunction^[33].

Moreover, the miR-181 family exhibits context-dependent effects in the heart. miR-181a/b targets cytosolic proteins such as Phosphatase and Tensin Homolog (PTEN) (thereby influencing PI3K/AKT signaling), whereas miR-181c localizes to mitochondria and targets MT-CO1, resulting in distinct effects on mitochondrial function and infarct size^[34]. These findings highlight that the biological effects of miRNAs cannot be interpreted solely based on expression changes but require consideration of cellular localization, disease context, and experimental models.

Antioxidant miRNAs and miRNA-mediated protective pathways

In DCM, multiple miRNAs have been implicated in modulating oxidative stress and mitochondrial function. The miR-199a/214 cluster is notably upregulated under hypoxic or stress conditions in HF, where it directly suppresses peroxisome proliferator-activated receptor δ (PPAR δ). This repression shifts cardiac metabolism away from mitochondrial fatty acid oxidation toward enhanced glycolysis. *In vivo* silencing of miR-199a/214 in stressed hearts restores mitochondrial β -oxidation of FFA and improves cardiac pump function and structure^[35]. miR-22 is downregulated in diabetic hearts; its overexpression reduces ROS production, decreases lipid peroxidation, as indicated by malondialdehyde (MDA) levels, restores superoxide dismutase (SOD) activity, and attenuates cardiomyocyte apoptosis through upregulation of sirtuin 1 (SIRT1), thereby mitigating high-glucose-induced oxidative injury^[36]. Similarly, miR-92a-2-5p is downregulated in diabetic hearts and high-glucose-stimulated cardiomyocytes; its therapeutic overexpression attenuates ROS accumulation, restores glutathione levels, lowers MDA, and reduces apoptosis by targeting mitogen-activated protein kinase (MAPK)-interacting kinase 2 (MKNK2) and suppressing p38-MAPK pathway phosphorylation^[37]. miR-144 has been implicated in oxidative stress regulation, but its role in DCM remains controversial. Reduced expression has been reported in diabetic cardiac models, whereas other studies suggest it modulates nuclear factor erythroid 2-related factor 2 (NRF2)-related antioxidant responses. Inhibition of miR-144 may hold therapeutic potential, yet whether its upregulation is pathogenic or compensatory is unclear^[38]. Similarly, miR-221 alleviates oxidative stress-induced remodeling via the p27/CDK2/mTOR axis, though this evidence derives primarily from HF models and requires validation in DCM^[39]. Another noteworthy regulator is miR-503, which participates in adaptive antioxidant responses. In a DCM rat model, miR-503 was significantly upregulated, while its direct target Nrf2 and downstream antioxidant enzymes were downregulated. Treatment with the Phase II enzyme inducer CPDT (5,6-dihydrocyclopenta-1,2-dithiole-3-thione) suppressed miR-503 and activated the NRF2/antioxidant response

element (ARE) pathway, thereby mitigating oxidative stress and apoptosis in diabetic hearts^[40]. These findings suggest that increased miR-503 may represent a maladaptive response that suppresses endogenous antioxidant defense rather than a direct protective mechanism.

Collectively, modulation of oxidative stress-related miRNAs represents a potential strategy for attenuating DCM progression. For example, miR-141 has been reported to regulate mitochondrial phosphate carrier SLC25A3 in diabetic hearts, leading to impaired mitochondrial ATP production and contributing to diabetic cardiac dysfunction^[41], whereas tauroursodeoxycholic acid (TUDCA) treatment suppresses miR-340-5p to preserve mitochondrial homeostasis^[33], ultimately attenuating DCM progression.

ERS, AUTOPHAGY, AND CARDIOMYOCYTE APOPTOSIS IN DCM

ERS

In DCM, ERS acts as an important pathogenic pathway linking glucolipotoxicity, oxidative stress, inflammation, and cardiomyocyte apoptosis. Accumulating evidence indicates that diverse classes of non-coding RNA species (miRNAs, lncRNAs, and circRNAs) modulate DCM progression through regulation of the unfolded protein response (UPR) pathway. For example, lncRNA H19 is downregulated in diabetic hearts; restoring its expression attenuates ERS-induced C/EBP homologous protein (CHOP) upregulation and apoptosis, while concomitantly activating the PI3K/AKT/mTOR axis to promote cardiomyocyte survival^[42]. Levels of miR-30c are diminished in animal models of diabetes; overexpression of this miRNA suppresses PPAR α activity via PGC-1 β targeting, which in turn modulates ERS and autophagy to mitigate DCM^[43]. Members of the miR-30 family, along with miR-214, directly target X-box binding protein 1 (XBP1), a master transcriptional regulator of the UPR, thereby influencing cardiomyocyte adaptation and survival under metabolic stress^[44]. circRNAs have emerged as potential regulators of cardiovascular stress responses. For example, circDLGAP4 was reported to modulate endothelial dysfunction through the miR-143-HECTD1 axis in an ischemic stroke model, suggesting a possible role for circRNA-mediated regulation in cardiovascular remodeling. However, whether similar mechanisms contribute to ERS or DCM remains to be determined^[45]. Several miRNAs, including miR-133a^[46], have been reported to dampen ERS by downregulating the GRP78/CHOP/eIF2 α cascade in various cardiovascular models. Despite these advances, direct evidence from well-characterized DCM models remains limited, and the precise mechanisms involved require further investigation.

Autophagy

Because prolonged ER stress is a well-recognized trigger of autophagy, these two processes constitute an interconnected stress-adaptation network that critically influences cardiomyocyte survival under diabetic conditions. Autophagy represents an essential adaptive response in DCM, yet its functional role is inherently dualistic. At moderate levels, autophagy maintains cellular homeostasis by clearing damaged organelles and protein aggregates, alleviating oxidative burden, and preserving myocardial energy metabolism. Conversely, when autophagic flux becomes excessive or dysregulated, enhanced degradation of essential cellular components may contribute to mitochondrial dysfunction and cardiomyocyte loss, thereby worsening contractile dysfunction and fibrotic remodeling^[47,48]. This delicate equilibrium is governed by key nutrient-sensing pathways, primarily mTOR and AMPK, whose outputs are further fine-tuned by a multilayered ncRNA regulatory network that integrates metabolic and stress cues to shape autophagic responses^[49].

A growing body of evidence has identified multiple non-coding RNAs (ncRNAs) as important modulators of autophagy in DCM. The lncRNA H19, for instance, has been shown to restrain excessive autophagy by attenuating DIRAS3-mediated inhibition of mTOR signaling, thereby preserving cardiac structure and function under hyperglycemic conditions^[49]. In contrast, lncRNA DCRF accelerates disease progression by functioning as a competitive endogenous RNA (ceRNA) for miR-551b-5p, leading to PCDH17 upregulation

and heightened autophagic activity^[50]. Similarly, diminished lncRNA GAS5 expression activates the miR-221-3p/p27/mTOR axis, driving maladaptive autophagy and adverse cardiac remodeling^[51]. The pathogenic role of miR-221 in DCM has been further substantiated by studies demonstrating that angiotensin II exacerbates diabetic cardiac hypertrophy through activation of the JNK/c-Jun/miR-221 axis. This axis directly suppresses p27 and inhibits downstream autophagy^[52]. Conversely, pharmacological intervention with luteolin has been shown to attenuate DCM by suppressing JNK/c-Jun-regulated miR-221 and reversing autophagy inhibition^[53]. Emerging evidence suggests that additional ncRNAs, including circRNAs, may participate in the regulation of autophagy and stress responses, potentially extending autophagic signaling beyond individual cardiomyocytes to the broader diabetic cardiac microenvironment; however, these mechanisms remain incompletely characterized^[54].

Collectively, these observations underscore that autophagy in DCM acts as a highly dynamic, context-dependent process - protective at physiological levels but destructive when unrestrained. The expanding knowledge of ncRNA-mediated regulation offers a potential therapeutic avenue to precisely modulate autophagic flux. Although ncRNA-mediated regulation of autophagy represents a promising therapeutic strategy, defining the optimal timing, magnitude, and disease stage for intervention remains a major challenge. Validation in well-phenotyped preclinical models and prospective clinical studies is therefore essential^[47,48,54].

Cardiomyocyte apoptosis

Persistent ER stress and dysregulated autophagy ultimately converge on apoptotic signaling pathways, making cardiomyocyte apoptosis a major downstream consequence of chronic metabolic injury in DCM. This progressive loss of cardiomyocytes contributes directly to myocardial dysfunction and adverse ventricular remodeling. The metabolic derangements characteristic of diabetes, including impaired substrate utilization, lipotoxicity, ceramide accumulation, and mitochondrial dysfunction, promote excessive ROS generation and activation of caspase-dependent apoptotic pathways, ultimately tipping the balance toward cardiomyocyte death. Experimental studies have shown that apoptotic activity is markedly increased in diabetic myocardium compared with healthy hearts, thereby contributing to contractile dysfunction and adverse ventricular remodeling^[55].

Noncoding RNAs, including lncRNAs and miRNAs, form a complex regulatory network that influences apoptotic susceptibility in DCM [Table 1]. Many upregulated lncRNAs under hyperglycemic stress act as ceRNAs: for example, MALAT1 sponges miR-181a-5p, thereby modulating p53 and the EZH2/miR-22/ABCA1 axis^[72]; MIAT binds miR-22-3p, thereby upregulating DAPK2^[73]; KCNQ1OT1 competes for miR-181a-5p, leading to elevated programmed cell death 4 (PDCD4) levels^[74]; and nuclear paraspeckle assembly transcript 1 (NEAT1) acts as a decoy for miR-140-5p, resulting in increased histone deacetylase 4 (HDAC4) and reduced NRF2^[75]. In contrast, downregulation of lncRNA H19 in DCM diminishes its processing into miR-675, thereby lifting repression of voltage-dependent anion channel 1 (VDAC1) and promoting mitochondrial permeability transition, inflammatory signaling, and apoptosis^[76]. Increased miR-34a expression has been associated with reduced SIRT1 signaling and enhanced apoptotic and fibrotic responses in diabetic cardiac models^[60,77]. Accordingly, inhibition of miR-34a has shown protective effects in experimental settings^[60,77]. However, the biological interpretation of miR-34a requires caution, as its functional consequences may vary according to disease stage, cellular origin, and experimental intervention strategy. Notably, the long noncoding RNA HOX transcript antisense RNA (HOTAIR) can function as a molecular sponge for miR-34a, thereby relieving miR-34a-mediated translational repression of SIRT1 and attenuating oxidative stress-induced cell death^[60]. Similarly, miR-22 upregulates SIRT1 to counteract injury^[36], and miR-29a targets Bak1 to blunt apoptotic signaling in high-glucose or Streptozotocin (STZ)-induced models^[78].

Table 1. miRNAs implicated in DCM: direct EV evidence and EV-independent mechanistic studies

miRNA	Expression	EV evidence/Cellular context	Target/Mechanism	Biological Effect/Disease relevance	Experimental/Evidence context	Ref.
Directly supported EV-associated miRNAs						
miR-320	↑	Cardiomyocyte-derived EVs (Validated)	IGF-1	Impairs angiogenic responses and contributes to fibrotic remodeling	T2DM rat model (Level 2); HG-treated cardiomyocytes (Level 4)	[32]
miR-130b-3p	↑	Adipocyte-derived sEVs (validated inter-organ transfer)	PGC-1 α	Promotes mitochondrial dysfunction, oxidative stress, and cardiomyocyte apoptosis	Diabetic mouse model (Level 2)	[31]
miR-21	↑ in CPC-derived exosomes under oxidative stress	Validated in cardiac progenitor cell (CPC)-derived	PDCD4	Inhibits cardiomyocyte apoptosis via miR-21/PDCD4 axis	Oxidative stress/cardiac injury model (Level 3)	[56]
miR-21-5p	Not specified	MSC-derived exosomal cargo	Paracrine survival-related signaling	Enhances cardiac tissue contractility; cardioprotective potential, but DCM relevance requires further validation	Human cardiac tissue model (Level 3)	[57]
EV-associated signals (context-specific)						
miR-16-2-3p	Not specified	Circulating exosomal miRNA associated with diabetic coronary microvascular dysfunction	Fatty acid degradation pathways in endothelial cells	Associated with endothelial metabolic dysfunction and coronary microvascular impairment	Diabetic vascular dysfunction model (Level 2)	[58]
miR-494-3p	↑	Dendritic-cell-derived exosomal miRNA	Angiogenic signaling pathways	Promotes angiogenesis after myocardial infarction; relevance to DCM remains uncertain	Myocardial infarction model (Level 3)	[59]
EV-independent miRNA mechanisms (no confirmed EV association)						
miR-34a	↑	No confirmed EV association	SIRT1	Impairs angiogenic responses and contributes to fibrotic remodeling	STZ-induced T1DM mouse (Level 2)	[60]
miR-340-5p	↑	No confirmed EV association	MCL-1	Promotes mitochondrial dysfunction and cardiomyocyte apoptosis	db/db mouse model (Level 2)	[33]
miR-195	↑	No confirmed EV association	Smad7, TGF- β /Smad	Promotes pathological cardiac remodeling, including hypertrophic responses	STZ-induced mouse (Level 2); HG-treated cardiomyocytes (Level 4)	[61,62]
miR-143	↑	No confirmed EV association	ORP8 (inhibits AKT signaling)	Impairs insulin signaling and contributes to cardiomyocyte IR <i>in vitro</i>	HG-treated cardiomyocytes (Level 4)	[24]

miR-133a	↑ in IR context	No confirmed EV association	GLUT4 (via KLF15)	Reported to impair glucose uptake in insulin-resistant cardiomyocyte models; broader cardiac effects remain context dependent	Cardiac myocytes (Level 4)	[23]
miR-451	↑	No confirmed EV association	LKB1/AMPK	Disrupts AMPK-related metabolic adaptation and aggravates lipotoxic remodeling	HFD-fed mouse (Level 2)	[63]
miR-200b/c	↑	No confirmed EV association	p300/TGF-β (induces EndMT)	Induces EndMT, vascular inflammatory remodeling	Diabetic mouse model (Level 2)	[64,65]
miR-483-3p	↑	No confirmed EV association	IGF-1 pathway	Disrupts calcium homeostasis and promotes cardiomyocyte apoptosis	STZ-induced mouse (Level 2); HG-treated cardiomyocytes (Level 4)	[66]
miR-25	↑ in failing heart models	No confirmed EV association	SERCA2a	Impairs Ca ²⁺ reuptake, reduces cardiac contractility. Its specific role in DCM and EV-mediated transfer remains unclear	Failing heart model (Level 3)	[67]
miR-141	↑ in T1DM heart	No confirmed EV association	SLC25A3 (mitochondrial phosphate carrier)	Inhibit mitochondrial ATP production, restores mitochondrial ATP production when inhibit miR-141	T1DM heart (Level 2)	[41]
miR-223	Altered expression reported in DCM models	No confirmed EV association	GLUT4 (promotes translocation)	Reported to regulate glucose metabolism and inflammatory responses; protective effects remain dependent on cellular context	Cardiomyocyte study (Level 4)	[25]
miR-29	↓	No confirmed EV association	Collagen, ECM components	Suppresses collagen expression and attenuates cardiac fibrosis	STZ-induced diabetic mouse (Level 2)	[19]
miR-92a-2-5p	Reduced in HG-treated cardiomyocytes	No confirmed EV association	MKNK2/p38-MAPK	Therapeutic restoration of miR-92a-2-5p alleviates oxidative stress in DCM cardiomyocytes	HG-treated cardiomyocytes (Level 4)	[37]
miR-22	↓ (in diabetic heart models)	No confirmed EV association	SIRT1	Regulates mitochondrial metabolism and stress responses; effects may vary according to disease context	Diabetic heart (Level 2)	[36]

miR-199a/214	↑ Induced under hypoxic stress as an adaptive response	No confirmed EV association	PPAR-δ	Suppresses PPARδ-dependent fatty acid oxidation; inhibition restores mitochondrial metabolic flexibility	Stressed heart model (Level 3)	[35]
miR-126	Not specified	No confirmed EV association	VEGF-related angiogenic signaling	miR-126/VEGF signaling associated with angiogenesis	Myocardial infarction rat model (Level 3)	[68]
miR-30c	↓	No confirmed EV association	PGC-1β/PPARα	Modulates ER stress and autophagy-related pathways to alleviate cardiac dysfunction	Diabetic animal model (Level 2)	[43]
miR-9	↓	No confirmed EV association	Regulates PRC2-associated fibrotic signaling downstream of ZFAS1	Loss of miR-9 promotes fibroblast activation and cardiac fibrosis	Diabetic model (Level 2)	[69]
miR-150	↓ in HG-treated cardiomyocytes	No confirmed EV association	p300	Suppresses hypertrophic signaling <i>in vitro</i>	HG-treated cardiomyocytes (Level 4)	[70]
miR-499-5p	↓	No confirmed EV association	TUG1 (lncRNA, upstream regulator)	Reported to attenuate hypertrophic remodeling and diastolic dysfunction	DCM model (Level 2)	[71]
miR-181a/b	Context-dependent (↑ in some models; ↓ in others)	No confirmed EV association	PTEN (indirectly activates AKT/mTOR)	Exacerbates or attenuates oxidative damage depending on model	Ischemia-reperfusion model (Level 3)	[34]
miR-144	Context-dependent	No confirmed EV association	NRF2-associated oxidative stress regulation	Regulates oxidative stress responses through NRF2-associated pathways; protective effects remain model dependent	STZ-induced diabetic mouse (Level 2)	[38]
miR-503	↑ correlated with Nrf2	No confirmed EV association	Downstream of NRF2/ARE (inhibited by NRF2 activation)	Promotes oxidative stress and apoptosis through inhibition of antioxidant responses	DCM rat model (Level 2)	[40]

Functional classification: The categorization of miRNAs as pathogenic, protective, or context-dependent reflects their predominant reported effects in DCM-related studies and should not be interpreted as an absolute functional designation. The biological effects of individual miRNAs may vary depending on cellular origin, disease stage, experimental model, and intervention strategy. miRNAs with divergent or context-dependent effects are indicated accordingly. Evidence classification: “Directly supported EV-associated miRNAs” refers to miRNAs with experimental evidence demonstrating EV loading and/or EV-mediated transfer. “EV-associated signals” refers to circulating or cell-derived EV associations without definitive proof that the miRNA acts as a functional EV cargo. MiRNAs listed under “EV-independent mechanisms” have established biological roles in DCM or related cardiac metabolic models, but direct EV involvement has not been confirmed. ↑ Indicate upregulated; ↓ indicate downregulated. AKT: Protein kinase B; AMPK: AMP-activated protein kinase; ARE: antioxidant response element; CPC: cardiac progenitor cell; DCM: diabetic cardiomyopathy; ECM: extracellular matrix; EndMT: endothelial-to-mesenchymal transition; ER: endoplasmic reticulum; EVs: extracellular vesicles; GLUT4: glucose transporter 4; HF: heart failure; HG: high glucose; HFD: high-fat diet; IGF-1: insulin-like growth factor 1; IR: insulin resistance; LKB1: liver kinase B1; lncRNA: long non-coding RNA; MAPK: mitogen-activated protein kinase; MCL-1: myeloid cell leukemia 1; miRNA: microRNA; MSCs: mesenchymal stem cells; MST1: macrophage stimulating 1; mTOR: mechanistic target of rapamycin; NFAT: nuclear factor of activated T cells; NRF2: nuclear factor erythroid 2-related factor 2; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGC-1β: peroxisome proliferator-activated receptor gamma coactivator 1-beta; PPARα: peroxisome proliferator-activated receptor alpha; PPARδ: peroxisome proliferator-activated receptor delta; PDCD4: programmed cell death 4; PRC2: polycomb repressive complex 2; PTEN: phosphatase and tensin homolog; ROS: reactive oxygen species; sEV: small extracellular vesicle; SERCA2a: sarco/endoplasmic reticulum Ca²⁺-ATPase 2a; SIRT1: sirtuin 1; SLC25A3: solute carrier family 25 member 3; STZ: streptozotocin; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; TGF-β: transforming growth factor beta; TUG1: taurine upregulated 1; VEGF: vascular endothelial growth factor; ZFAS1: ZNF1 antisense RNA 1.

Beyond intracellular ncRNA regulation, EV-mediated intercellular transfer of ncRNAs provides an additional mechanism by which apoptosis is propagated or restrained within the diabetic myocardium. For instance, miR-21, which is enriched in circulating exosomes, has been identified as a novel biomarker for the diagnosis of subclinical DCM^[79]. Furthermore, cardiac progenitor cell-derived exosomal miR-21 has been shown to protect cardiomyocytes from apoptosis by targeting PDCD4, as shown in models of oxidative stress and cardiac injury^[56]. These findings support a potential cardioprotective role of miR-21-containing EVs in specific experimental contexts; however, miR-21 may exert distinct effects depending on EV origin and disease setting. In contrast, cardiomyocyte-derived EVs with elevated levels of miR-320 contribute to functional deterioration by impairing endothelial repair and angiogenic capacity^[32]. Consistent with this observation, inhibition of miR-320 reduces apoptosis and improves cardiac function in experimental diabetes, suggesting that miR-320 contributes to DCM progression^[80]. miR-25 has also been shown to protect cardiomyocytes against oxidative damage by directly targeting the mitochondrial calcium uniporter (MCU), thereby reducing mitochondrial Ca^{2+} overload and inactivating the mitochondrial apoptosis pathway^[81].

In addition to ncRNAs, several additional miRNAs have emerged as significant modulators of cardiomyocyte fate in DCM, often operating at the interface of apoptosis and other stress responses. miR-483-3p is upregulated in STZ-induced diabetic mice and high-glucose-treated cardiomyocytes, where it promotes apoptosis under glucose stress^[66]. Members of the miR-30 family, notably miR-30c, modulate the p53-p21 axis to influence hypertrophic and apoptotic responses in high-glucose conditions^[82], whereas miR-30d has been shown to regulate pyroptosis through direct targeting of FOXO3a, thereby linking inflammasome-driven cell death to diabetic cardiac injury^[83]. Therapeutic inhibition of miR-195 in STZ mice attenuates cardiac hypertrophy and reduces apoptosis, revealing a deleterious role for miR-195 in DCM^[61]. The cardiac-enriched miR-378 modulates the IGF-1/IGF receptor (IGF-1R) signaling axis, linking metabolic remodeling with cardiomyocyte survival^[84]. Finally, miR-1 controls apoptosis in part through modulation of liver X receptor α (LXR α) and mitochondrial ROS pathways in glucose-stressed cardiomyocytes, illustrating how miRNAs can integrate nuclear receptor signaling with mitochondria-dependent cell death^[85]. Collectively, these findings highlight that both intracellular and EV-associated ncRNAs converge on key apoptotic signaling pathways - including p53, SIRT1, IGF-1/IGF-1R, BAK1, FOXO3, and CD36/PPAR γ - to regulate cardiomyocyte survival in DCM. Given the context-dependent functions of several miRNAs, future therapeutic strategies will require careful consideration of RNA species, cellular origin, disease stage, and delivery approach. These shared molecular nodes may represent promising therapeutic targets for limiting myocardial injury and delaying DCM progression.

REGULATION OF CALCIUM SIGNALING AND RELATED PATHWAYS

Disrupted Ca^{2+} homeostasis constitutes a hallmark of DCM, and accumulating evidence implicates EVs in this dysregulation through the delivery of regulatory ncRNAs and proteins. Under hyperglycemic conditions, cardiomyocytes exhibit impaired sarcoplasmic reticulum (SR) Ca^{2+} reuptake owing to reduced sarco/endoplasmic reticulum Ca^{2+} -ATPase 2a (SERCA2a) activity, impaired $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX) function, and abnormal ryanodine receptor 2 (RyR2) gating, ultimately resulting in cytosolic Ca^{2+} overload and contractile dysfunction^[5]. Emerging data further indicate that ncRNAs regulate multiple components of the cardiac Ca^{2+} handling machinery, including SERCA2a, RyR2, and mitochondrial Ca^{2+} signaling pathways. Beyond SR Ca^{2+} cycling, dysregulated mitochondrial Ca^{2+} uptake through the MCU complex has emerged as an important contributor to oxidative stress, mitochondrial dysfunction, and metabolic remodeling in DCM. This mitochondrial Ca^{2+} axis may represent an additional regulatory interface through which EV-associated ncRNAs influence cardiomyocyte stress responses and survival. For instance, MSC-derived EVs enriched in miR-21-5p enhance Ca^{2+} cycling and contractility by upregulating SERCA2a and Ca^{2+} -ATPase expression in cardiomyocytes, thereby attenuating high-glucose-induced functional impairment^[57]. miR-25 directly suppresses SERCA2a, leading to defective Ca^{2+} reuptake and diminished cardiac contractility; conversely,

miR-25 inhibition restores SERCA2a levels and improves cardiac performance in failing hearts^[67]. The SERCA-phospholamban (PLN)-dwarf open reading frame (DWORF) regulatory axis has emerged as a key pathway linking impaired calcium handling to diabetic cardiac injury. In DCM, diminished SERCA2a function delays diastolic calcium reuptake, which in turn activates pro-hypertrophic calcineurin-nuclear factor of activated T cells (NFAT) signaling and promotes excessive mitochondrial Ca^{2+} accumulation, ultimately contributing to contractile dysfunction^[86]. Beyond SR calcium cycling, mitochondrial calcium (mito Ca^{2+}) homeostasis has emerged as a key link between metabolic stress and DCM. Diabetic stimuli - hyperglycemia, lipid overload, and oxidative stress - impair mito Ca^{2+} handling through dysregulated MCU, mitochondrial permeability transition pore (mPTP), and mitochondrial $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCLX), leading to energy failure and cell death. Targeting these mito Ca^{2+} pathways may therefore offer therapeutic potential in DCM^[87]. miR-1 targets Junctin, an integral component of the RyR2 Ca^{2+} release complex, promoting diastolic dysfunction, pathological hypertrophy and arrhythmogenesis^[88]. By contrast, miR-145 mitigates Ca^{2+} overload and curbs oxidative stress-induced apoptosis in experimental diabetic cardiomyocyte models^[89]. This protective role is further supported by evidence that miR-145 suppresses inflammatory responses and oxidative stress in hyperglycemic cardiomyocytes, and inhibits pyroptosis via the miR-145/gasdermin A (GSDMA) axis in DCM^[90]. Macrophage-derived miR-155-enriched EVs have been shown to restrain cardiac fibroblast proliferation while simultaneously promoting pro-inflammatory responses^[91]. Whether these EVs directly modulate Ca^{2+} handling remains unclear. Nevertheless, given the established link between fibroblast activation and cardiac remodeling, such EV-mediated effects may indirectly contribute to Ca^{2+} dysregulation in the diabetic heart.

Notably, Ca^{2+} signaling not only serves as a downstream effector of EV-mediated regulation but also feeds back to modulate EV biogenesis itself. Sustained hyperglycemia induces Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) activation in endothelial cells via an O-GlcNAcylation-dependent loop, leading to continuous release of miR-15/16-enriched sEVs that impair cardiac function, suggesting a potential Ca^{2+} -EV regulatory axis in diabetic cardiac injury^[92]. Proteins involved in vesicle fusion, such as Munc13-4 and synaptotagmin, are required for the release of multivesicular bodies, indicating a bidirectional interplay between intracellular Ca^{2+} oscillations and EV secretion^[93]. Collectively, these observations reveal a dynamic feedback circuit in which EVs modulate Ca^{2+} handling through their molecular cargoes, whereas Ca^{2+} signaling regulates EV release and composition, cooperatively governing cardiomyocyte apoptosis, autophagy, and metabolic remodeling in DCM. Targeting the EV- Ca^{2+} signaling axis therefore represents a promising strategy for restoring excitation-contraction coupling and preserving cardiac function in diabetic hearts.

EV-MEDIATED REGULATION OF MYOCARDIAL HYPERTROPHY AND REMODELING IN DCM

Myocardial hypertrophy represents a prominent morphological and functional manifestation of DCM, characterized by cardiomyocyte enlargement, extracellular matrix remodeling, and increased stiffness of the ventricles. Chronic hyperglycemia drives early ultrastructural alterations in cardiomyocytes, including sarcomeric disorganization, mitochondrial fragmentation, lipid accumulation, and excessive collagen deposition. These maladaptive changes impair both diastolic relaxation and systolic performance, potentially progressing to HF.

Although many hypertrophy-associated noncoding RNAs have been identified through intracellular studies, emerging evidence suggests that EV-mediated transfer provides an additional layer of intercellular regulation within the diabetic heart. Recent evidence underscores that dysregulation of noncoding RNAs, particularly miRNAs and lncRNAs, plays a central role in hypertrophic signaling in DCM [Table 2]. Several miRNAs known to maintain cardiac structure and contractile function under physiological conditions are markedly altered in the diabetic myocardium. For instance, miR-195 promotes cardiomyocyte hypertrophy by

suppressing Smad7 and activating the transforming growth factor beta (TGF- β)/Smad signaling pathway, whereas its inhibition confers protection against glucose- or palmitate-induced apoptosis^[61,62]. Systemically, miR-195 inhibition reduces apoptosis and improves DCM^[67]. In contrast, cardiac-enriched miRNAs such as miR-133a and miR-1 exert antihypertrophic effects by repressing serum and glucocorticoid-regulated kinase 1 (SGK1), IGF-1R, myocyte enhancer factor 2A (MEF2a), and GATA binding protein 4 (GATA4); their downregulation under hyperglycemia permits pathological growth^[104-106]. Likewise, miR-30c and miR-181a modulate the p53-p21 axis, while miR-373 affects hypertrophic remodeling through the p38-MEF2C pathway^[107-109]. miR-150 and miR-499-5p have been reported to exert protective/adaptive effects that counterbalance these pro-hypertrophic signals^[70,71], whereas miR-208a, miR-200c, and miR-451 enhance remodeling by targeting myostatin, dual specificity protein phosphatase 1 (DUSP1), or liver kinase B1 (LKB1)/AMPK signaling, respectively^[63,110,111].

Emerging studies have revealed that EVs act as crucial mediators of intercellular communication in the diabetic heart, amplifying or suppressing hypertrophic signaling through miRNA transfer. Heat-shock protein 20 (HSP20) interacts with tumor susceptibility gene 101 (TSG101) to augment EV secretion from cardiomyocytes under diabetic conditions. In diabetic mouse models, enhanced cardiomyocyte-derived exosome production associated with HSP20 signaling correlated with improved angiogenesis, reduced oxidative stress, attenuated myocardial remodeling, and improved cardiac function. However, HSP20 should be considered primarily as a regulator of EV biogenesis and EV-associated cardioprotective signaling rather than a validated EV cargo molecule^[112]. Under high-glucose conditions, miR-195 is upregulated in neonatal cardiomyocytes, where it directly targets and downregulates Smad7 and further activates the TGF- β /Smad cascade, thereby promoting cardiomyocyte hypertrophy^[62]. Conversely, miR-133a, a cardioprotective intracellular miRNA, is reduced in diabetic myocardium, although whether EV-mediated delivery contributes to restoration of this pathway remains unclear^[105]. Moreover, EVs released from CMECs under hyperglycemic stress deliver MST1 protein to cardiomyocytes. This protein inhibits autophagy-related molecules such as ATG5 and LC3-II and enhances caspase-3-dependent apoptosis, thereby contributing to adverse remodeling^[26].

The role of lncRNAs as both disease markers and therapeutic targets in diabetes has been recently reviewed^[113]. In the context of DCM, several such lncRNAs have been linked to hypertrophic signaling. Silencing of TUG1 upregulates miR-499-5p and suppresses hypertrophic gene expression^[71], while overexpression of HOTAIR alleviates hypertrophy by sponging miR-19 and restoring PTEN signaling^[102]. More recently, macrophage-derived MALAT1 is significantly upregulated under high-glucose conditions and functions as a sponge for miR-204-5p, leading to elevated ATG7 levels and modulation of autophagic responses in H9C2 cardiomyocytes and STZ-induced diabetic rat hearts, thereby contributing to cardiac remodeling and hypertrophy^[54]. In parallel, circulating lncRNAs such as LIPCAR and SENCAR are further associated with diastolic dysfunction and ventricular remodeling in diabetic patients, underscoring their potential as biomarkers for subclinical myocardial injury^[103].

By contrast, stem cell-derived EVs exert multifaceted protective effects against diabetic cardiac injury. MSC-derived EVs carry anti-inflammatory and metabolic regulatory cargoes - including miR-122a and members of the miR-30 family - that restore metabolic homeostasis, enhance autophagy, and reduce pathological remodeling^[114,115]. Vascular cell adhesion molecule-1 positive (VCAM-1⁺) umbilical cord MSC-derived EVs suppress ferroptosis through rat sarcoma virus (RAS)/rapidly accelerated fibrosarcoma (RAF)/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK)/c-Fos proto-oncogene (c-FOS) pathway inhibition^[116]; and circulating EV-associated miRNAs (e.g., miR-126a-5p, miR-30d-5p) correlate with clinical parameters of diastolic dysfunction and remodeling, serving as promising biomarkers^[117]. Moreover, bioengineering approaches - such as cargo loading, surface modification, and

Table 2. lncRNAs implicated in DCM: EV-associated and non-EV evidence

Category	lncRNA	Expression	EV association/source	Recipient cell	Molecular mechanism and functional effect	Experimental/Evidence context	Ref.
Pathogenic lncRNAs	DCRF	↑	No confirmed EV association	Cardiomyocytes	Functions as a ceRNA by sponging miR-551b-5p and regulating PCDH17, promoting cardiomyocyte autophagy, fibrosis, and cardiac dysfunction	STZ-induced rat DCM model (Level 2); HG-treated cardiomyocytes (Level 4)	[50]
	MALAT1	↑	No confirmed EV association	Cardiomyocytes	Regulates multiple pathogenic pathways through miRNA interactions (miR-181a-5p, miR-141) and activation of p53, NLRP3, EZH2/miR-22/ABCA1, and TGF-β1/Smad signaling, promoting apoptosis, inflammation, and fibrosis	STZ mouse (Level 2)	[72,94]
	MIAT	↑	No confirmed EV association	Cardiomyocytes	Acts as a ceRNA for miR-22-3p and miR-214-3p, regulating DAPK2- and IL-17-associated pathways and promoting apoptosis and cardiac fibrosis	STZ mouse (Level 2)	[73,95]
	KCNQ1OT1	↑	No confirmed EV association	Cardiomyocytes	Sponges miR-181a-5p and regulates PDCD4-associated apoptotic signaling, contributing to cardiomyocyte injury	DCM model (Level 2)	[74]
	NEAT1	↑	No confirmed EV association	Cardiomyocytes	Regulates miR-140-5p/HDAC4/Nrf2 signaling and promotes oxidative stress-associated apoptosis	HG cardiomyocytes (Level 4)	[75]
	NORAD	↑	No confirmed EV association	Cardiac fibroblasts	Functions as a ceRNA for miR-125a-3p and regulates Fyn-related signaling, promoting fibroblast activation, fibrosis, and inflammation	DCM model (Level 2)	[96]
	ZFAS1	↑	No confirmed EV association	Cardiac fibroblasts	Regulates miR-9 availability and PRC2-associated epigenetic remodeling, promoting fibroblast activation and fibrosis	Diabetes model (Level 2)	[69]
	ANRIL	↑	No confirmed EV association	Cardiomyocytes	Silencing reduces myocardial oxidative stress, inflammation, apoptosis, and collagen deposition, thereby improving cardiac function and pathological remodeling	STZ-induced rat diabetic model; (Level 2)	[97]
	H19	↑ Fibrotic context	No confirmed EV association	Cardiac fibroblasts	Functions as a ceRNA for miR-455 and regulates CTGF expression, promoting extracellular matrix deposition and cardiac fibrosis	Diabetic mouse myocardium (Level 2)	[98]
	H19	↓ (ERS/apoptosis context)	No confirmed EV association	Cardiomyocytes	Activates PI3K/AKT/mTOR signaling and suppresses ER stress-related pathways (PERK, IRE1α, ATF6, CHOP), reducing oxidative stress and apoptosis	STZ-induced T1DM mouse DCM model; (Level 2); HG-stimulated HL-1 cells (Level 4)	[42]
Protective/compensatory lncRNAs	SNHG1	Context-dependent	No confirmed EV association	Cardiomyocytes	Regulates miR-15a-5p/HMGA1 signaling and suppresses hypertrophic remodeling in experimental cardiac hypertrophy models	TAC/PE-induced cardiac hypertrophy model (Level 3)	[99]
	GAS5	↓	No confirmed EV association	Cardiomyocytes and cardiac fibroblasts	Functions as a ceRNA: regulates miR-221-3p/p27 axis to promote cardiomyocyte autophagy, modulating miR-21/PTEN/MMP-2 signaling to attenuate cardiac fibroblast activation and fibrosis	STZ-induced diabetic rat DCM model (Level 2); HG-treated H9C2 cardiomyocytes/Cardiac fibroblasts (Level 4)	[51,100]
	Airn	↓	No confirmed EV association	Cardiac fibroblasts	Regulates the m6A-IMP2-p53 axis and suppresses fibroblast activation, exerting anti-fibrotic effects	STZ-induced diabetic mouse DCM model (Level 2); HG-treated cardiac fibroblasts (Level 4)	[101]
	HOTAIR	↓	No confirmed EV association	Cardiomyocytes/fibroblasts	Modulates miR-34a/miR-19-associated pathways and regulates SIRT1/PTEN signaling, reducing oxidative stress, inflammation, hypertrophy, and fibrosis	STZ-induced diabetic mouse DCM model (Level 2); HG-treated cardiac fibroblasts (Level 4) TAC-induced cardiac hypertrophy mouse model (Level 3)	[60,102]

Biomarker-associated lncRNAs	LIPCAR	No significant difference reported	Circulating biomarker; EV association not confirmed	-	Circulating lncRNA associated with cardiac remodeling; inversely correlated with E/A ratio and associated with diastolic dysfunction parameters	T2DM patients (Level 1)	[103]
	SENCR	↓	Circulating biomarker; EV association not confirmed	Smooth muscle cells/endothelial cells	Associated with vascular phenotype regulation and cardiac remodeling indices, including LV mass/LV end-diastolic volume ratio	T2DM patients (Level 1)	[103]

EV association classification: EV association was classified according to available experimental evidence. “Validated EV-associated” indicates that the lncRNA has been directly detected or enriched in EV preparations and/or experimentally demonstrated to participate in EV-mediated communication. “No confirmed EV association” indicates that the lncRNA has been investigated in cellular or tissue models, but EV-mediated transport has not been experimentally established. “Circulating biomarker; EV association not confirmed” indicates detection in circulating samples without evidence of EV localization. Because direct validation of EV-associated lncRNAs remains limited in DCM, intracellular studies and related cardiovascular models are included to provide mechanistic context. Context-dependent regulation: Some lncRNAs (e.g., H19 and SNHG1) exhibit context-dependent effects that vary according to cellular origin, disease stage, and experimental conditions. Evidence levels were categorized as follows: Level 1, human clinical evidence; Level 2, *in vivo* DCM models with confirmed cardiac dysfunction; Level 3, non-diabetic cardiovascular models providing mechanistic relevance; and Level 4, *in vitro* cellular studies. Evidence levels indicate experimental context and translational relevance rather than the strength of causal evidence. ↑ Indicate upregulated; ↓ indicate downregulated. AKT: Protein kinase B; ABCA1: ATP-binding cassette subfamily A member 1; Airn: antisense of Igf2r RNA; ANRIL: antisense non-coding RNA in the INK4 locus; ATF6: activating transcription factor 6; ceRNA: competing endogenous RNA; CHOP: C/EBP homologous protein; CTGF: connective tissue growth factor; DAPK2: death-associated protein kinase 2; DCM: diabetic cardiomyopathy; ECM: extracellular matrix; ER: endoplasmic reticulum; ERS: endoplasmic reticulum stress; EV: extracellular vesicle; GAS5: growth arrest-specific 5; HDAC4: histone deacetylase 4; HG: high glucose; HMGA1: high mobility group AT-hook 1; HOTAIR: HOX transcript antisense intergenic RNA; IRE1α: inositol-requiring enzyme 1 alpha; KCNQ1OT1: KCNQ1 opposite strand/antisense transcript 1; LIPCAR: long intergenic non-coding RNA predicting cardiac remodeling; lncRNA: long non-coding RNA; m6A: N6-methyladenosine; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; MIAT: myocardial infarction-associated transcript; MMP-2: matrix metalloproteinase 2; mTOR: mechanistic target of rapamycin; NEAT1: nuclear paraspeckle assembly transcript 1; NLRP3: NLR family pyrin domain containing 3; NORAD: non-coding RNA activated by DNA damage; Nrf2: nuclear factor erythroid 2-related factor 2; PCDH17: protocadherin 17; PDCD4: programmed cell death 4; PERK: protein kinase R-like endoplasmic reticulum kinase; PI3K: phosphoinositide 3-kinase; PRC2: polycomb repressive complex 2; PTEN: phosphatase and tensin homolog; SENCN: smooth muscle and endothelial cell-enriched migration/differentiation-associated long non-coding RNA; SIRT1: sirtuin 1; SNHG1: small nucleolar RNA host gene 1; STZ: streptozotocin; T1DM: type 1 diabetes mellitus; TAC: transverse aortic constriction; T2DM: type 2 diabetes mellitus; TGF-β1: transforming growth factor beta 1.

hybrid nanocarrier systems - are now being leveraged to improve EV targeting and stability, positioning EVs not only as biomarkers but also as next-generation therapeutic platforms^[115,118].

Collectively, these findings support the concept that EVs function as dynamic carriers of noncoding RNAs that coordinate crosstalk among cardiomyocytes, endothelial cells, and fibroblasts during diabetic stress. By transferring pathogenic or protective cargoes, EVs may amplify or counteract hypertrophic remodeling; however, the contribution of specific miRNAs requires validation according to cellular origin, disease stage, and experimental context. Targeting pathogenic EV cargoes, such as inhibiting miR-195 or miR-451, or restoring protective mechanisms involving miR-133a, represents a potential strategy for modulating hypertrophic signaling and myocardial remodeling in DCM^[63]. However, the direct involvement of these miRNAs as EV cargoes in DCM remains insufficiently established.

EV-MEDIATED REGULATION OF MYOCARDIAL FIBROSIS IN DCM

Myocardial fibrosis is a hallmark of advanced DCM and a major determinant of ventricular stiffness and diastolic dysfunction. Persistent hyperglycemia promotes the accumulation of AGEs, enhances collagen cross-linking, and triggers chronic inflammatory responses characterized by increased production of interleukin (IL)-17, IL-6, tumor necrosis factor-alpha (TNF-α), and IL-1β. These inflammatory mediators activate profibrotic pathways, including TGF-β/Smad and MAPK signaling, ultimately driving excessive extracellular matrix (ECM) deposition and adverse myocardial remodeling^[95,119,120]. Because myocardial fibrosis represents a key pathological substrate contributing to ventricular stiffening and HFpEF development in diabetes, therapeutic strategies aimed at limiting fibrotic remodeling may potentially help prevent DCM progression.

Various ncRNAs, particularly lncRNAs and circRNAs, regulate multiple profibrotic signaling pathways by functioning as ceRNAs or directly modulating inflammatory mediators [Table 2]. For example, MIAT acts as a sponge for miR-214-3p, resulting in elevated IL-17 levels that drive fibrotic progression. Silencing of AK081284 or ANRIL reduces production of inflammatory cytokines and oxidative stress, thus ameliorating fibrosis^[95,97,119]. The NORAD-miR-125a-3p-FYN ceRNA network and ZFAS1/miR-9 axes further promote fibroblast activation and ECM synthesis^[69,96]. Conversely, Airn exerts anti-fibrotic effects by stabilizing p53 via the m6A-IMP2-p53 pathway^[101]. Additionally, H19 enhances fibrosis by sequestering miR-455 and upregulating connective tissue growth factor (CTGF)^[98], whereas GAS5 and MALAT1 modulate miR-21 and miR-141, respectively, to influence the PTEN/matrix metalloproteinase 2 (MMP-2) and NLR family, pyrin domain containing 3 (NLRP3)/TGF- β 1 pathways^[94,100].

Recent studies have further linked EV-mediated signaling to inflammatory cell death during DCM progression. For example, adipose-derived stem cell (ADSC)-derived EVs suppress cardiomyocyte pyroptosis through inhibition of the CHIT1/NLRP3/caspase-1 pathway, thereby attenuating inflammation and subsequent myocardial fibrosis in experimental diabetes^[121]. These findings provide mechanistic evidence supporting a potential role for EVs in regulating inflammasome activation, although their relevance to human DCM requires further validation.

miRNAs represent another important regulatory layer involved in fibrotic remodeling in DCM. The miR-29 family suppresses collagen synthesis, while inhibition of miR-34a, overexpression of miR-133a, and maintenance of miR-15a/b levels each attenuate myocardial fibrosis^[122-125]. Ranolazine reduces myocardial pyroptosis by upregulating miR-135b^[126]. CircRNAs, exemplified by circHIPK3, act as competing endogenous RNAs to sponge miR-29b-3p, thereby modulating fibrotic gene expression^[127]. In endothelial cells, silencing miR-195-5p inhibits endothelial-to-mesenchymal transition (EndMT) by targeting Smad7 and disrupting the TGF- β 1/Smad/Snail pathway^[128].

Beyond intracellular ncRNA regulation, EV-mediated intercellular communication provides an additional mechanism by which fibrotic signals are propagated throughout the diabetic myocardium. Cardiomyocyte-derived sEVs from diabetic hearts have been shown to drive fibrosis through alterations in their miRNA cargo, including miR-194-3p and miR-29b-3p^[129]. These pathogenic vesicles can enhance fibroblast activation and ECM accumulation, suggesting that diabetes-associated alterations in EV cargo contribute to maladaptive remodeling of the cardiac microenvironment. Conversely, MSC-derived EVs exert anti-fibrotic effects by restoring redox homeostasis, suppressing TGF- β signaling, and limiting collagen deposition^[117]. Notably, MSC-derived EVs deliver circNOTCH1, which promotes macrophage M2 polarization and subsequently alleviates myocardial fibrosis and cardiac dysfunction in DCM^[130]. Exercise also remodels the molecular composition of circulating EVs, enriching anti-fibrotic miRNAs such as miR-29b and miR-455, thereby contributing to improved cardiac function and reduced fibrosis^[131-133].

Collectively, myocardial fibrosis in DCM arises from a complex interplay involving hyperglycemia-induced inflammatory signaling, ncRNA regulation, and EV-mediated intercellular communication. LncRNAs, miRNAs, and circRNAs form multilayered regulatory circuits that converge on TGF- β and MAPK pathways, with EVs serving as carriers that can either amplify or attenuate fibrotic responses across cardiac cell types. Accordingly, targeting EV-mediated ncRNA delivery represents a promising therapeutic strategy for modulating diabetic cardiac fibrosis; however, further studies are required to determine whether these approaches can be translated into clinically effective interventions.

EV-MEDIATED COMMUNICATION NETWORKS IN DCM

EV-mediated microvascular dysfunction and angiogenic regulation in DCM

Coronary microvascular dysfunction is a core pathological feature of DCM, particularly in the absence of obstructive epicardial coronary artery disease. Clinical imaging investigations have demonstrated that reduced coronary flow reserve (CFR) is significantly associated with adverse outcomes in patients with diabetes, underscoring the prognostic significance of coronary microvascular impairment^[134]. Hyperglycemia initially damages CMECs, provoking nitric oxide-dependent vasoregulatory defects and barrier disruption. Notably, under acute nutrient stress, cardiomyocytes increase EV secretion and selectively load pro-angiogenic cargo capable of transiently stimulating endothelial migration and tube formation; however, with sustained hyperglycemia, the EV cargo profile shifts toward fibrotic and anti-angiogenic signals that compromise microvascular integrity and perfusion^[135]. CMEC-derived EVs are critical intermediaries in this process: under high-glucose conditions, they become enriched in TGF- β 1 mRNA, which is delivered to cardiomyocytes and fibroblasts, promoting perivascular fibrosis and abnormal angiogenic responses^[120]. Because coronary microvascular dysfunction is increasingly recognized as a major contributor to myocardial ischemia, interstitial fibrosis, and the development of HFpEF in diabetes, preserving microvascular integrity has emerged as an important therapeutic objective in DCM.

The biological effects of EVs on the coronary microcirculation are therefore highly context-dependent and largely determined by their cellular origin and molecular cargo. In type 2 diabetic models, cardiomyocyte-derived EVs enriched in miR-320 have been shown to transfer this anti-angiogenic signal to endothelial cells, suppressing IGF-1, HSP20, and ETS proto-oncogene 2 (ETS2) expression and impairing endothelial proliferation, migration, and tube formation^[32]. Conversely, EV-based therapeutic strategies show context-dependent protective effects in experimental cardiovascular models. In experimental diabetic heart disease models, therapeutic inhibition of miR-320 improves cardiac function and attenuates adverse remodeling, although this effect reflects direct miR-320 suppression rather than anti-miR-320-loaded EV delivery^[80]. MSC-derived exosomal miR-21-5p has been shown to enhance cardiac contractility in human cardiac tissue models, but its therapeutic relevance to DCM requires further validation^[57]. EV-associated regulatory mechanisms have also been implicated in diabetic vascular dysfunction and myocardial repair. Circulating exosomal miR-16-2-3p has been associated with diabetic coronary microvascular dysfunction through regulation of endothelial fatty acid metabolism^[58], whereas dendritic-cell-derived exosomal miR-494-3p promotes angiogenesis after myocardial infarction rather than DCM^[59]. HSP20 has been reported to interact with EV biogenesis machinery and enhance cardiomyocyte-derived EV secretion under diabetic conditions, with associated cardioprotective effects; however, its identity as an EV cargo remains unconfirmed^[112].

Among endothelial regulatory miRNAs, the miR-200 family contributes to microvascular pathology by driving EndMT and impairing vasodilatory function: miR-200b promotes EndMT via p300-dependent transcriptional reprogramming and collagen deposition in diabetic hearts, whereas miR-200c is upregulated in diabetic arteries and suppresses zinc finger E-box binding homeobox 1 (ZEB1), resulting in enhanced cyclooxygenase-2 (COX-2)/prostaglandin E2 (PGE2) signaling and diminished endothelium-dependent vasodilation - mechanisms that collectively accelerate microvascular deterioration^[64,65].

Recent studies have identified miR-550a-5p as an additional contributor to diabetic microvascular pathology. This miRNA, which is elevated in circulating EVs from patients with microvascular dysfunction, targets the Hippo-YAP/endothelial nitric oxide synthase (eNOS) axis, potentially mediating adverse endothelial-cardiomyocyte communication and contributing to myocardial injury^[136].

Although EV-targeted therapies have not yet entered clinical practice, findings from EV-independent interventions that improve coronary microvascular function provide important proof-of-concept for restoring vascular homeostasis in DCM. For example, modulation of non-EV pathways that influence

Table 3. Validated EV-mediated communication pathways involved in diabetic cardiac remodeling

EV source	EV-associated molecule/function	Recipient cell	Target/Pathway	Functional effect	Experimental/Evidence context	Ref.
Pathogenic EV-mediated communication						
Cardiomyocyte-derived EVs	miR-320	Endothelial cells	Not specified in this study	Suppresses endothelial angiogenic responses and contributes to microvascular rarefaction and dysfunction	T2DM rat (Level 2)	[32]
CMEC-derived EVs	MST1 protein	Cardiomyocytes	Daxx-GLUT4 complex	Disrupts GLUT4 membrane translocation and promotes cardiomyocyte IR	DCM model (Level 2)	[26]
CMEC-derived EVs	TGF- β 1 mRNA	Fibroblasts	TGF- β /Smad signaling	Promotes perivascular fibrotic remodeling	HG treated CMEC model (Level 4)	[120]
Macrophage-derived EVs	LncRNA MALAT1	Cardiomyocytes	miR-204-5p/ATG7 axis	Regulates autophagy in cardiomyocytes; involved in diabetic cardiac injury	STZ-induced diabetic rat model (Level 2); H9C2 cells (Level 4)	[54]
Adipocyte-derived sEVs	miR-130b-3p	Cardiomyocytes	PGC-1 α	Promotes mitochondrial oxidative stress, impairs mitochondrial function, and increases cardiomyocyte injury/apoptosis	Diabetic mouse model (Level 2)	[31]
Protective/Therapeutic EV-mediated communication						
Cardiomyocytes	HSP20	Endothelial cells	EV biogenesis machinery (e.g., TSG101)	Increased cardiomyocyte-derived EV release associated with enhanced angiogenesis, reduced oxidative stress, and improved cardiac function	DCM model (level 2)	[112]
Cardiac progenitor cell (CPC)-derived	miR-21	Cardiomyocytes/endothelial cells	PDCD4/NF- κ B-related pathways	Reduces apoptosis and inflammation	Experimental cardiac injury models (level 3)	[56]

Evidence context was categorized as follows: Level 1, human clinical evidence; Level 2, *in vivo* DCM models with confirmed cardiac dysfunction; Level 3, non-diabetic cardiovascular models providing mechanistic relevance; and Level 4, *in vitro* cellular studies. Evidence levels indicate experimental context and translational relevance rather than the strength of causal evidence. EV association criteria: Entries in this table represent EV-mediated communication pathways supported by experimental evidence of EV enrichment, EV cargo detection, EV transfer, and/or EV-mediated functional effects in recipient cells. EV subtype terminology (e.g., sEVs) is used only when the original study characterized the corresponding EV population. Findings derived from non-DCM cardiovascular models are considered mechanistically supportive rather than definitive evidence for DCM-specific mechanisms. $\uparrow$ Indicate upregulated; $\downarrow$ indicate downregulated. ATG7: Autophagy-related gene 7; CFs: cardiac fibroblasts; CMEC: cardiac microvascular endothelial cell; CPC: cardiac progenitor cell; DCM: diabetic cardiomyopathy; Daxx: death domain-associated protein 6; ECM: extracellular matrix; EndMT: endothelial-to-mesenchymal transition; ETC: electron transport chain; EV: extracellular vesicle; GLUT4: glucose transporter 4; HFD: high-fat diet; HG: high glucose; HSP20: heat shock protein 20; IR: insulin resistance; LncRNA: long non-coding RNA; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; MDA: malondialdehyde; MSCs: mesenchymal stem cells; MST1: macrophage stimulating 1; NF- κ B: nuclear factor kappa B; PGC-1 α : peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PDCD4: programmed cell death 4; ROS: reactive oxygen species; sEV: small extracellular vesicle; SOD: superoxide dismutase; STZ: streptozotocin; T2DM: type 2 diabetes mellitus; TGF- β : transforming growth factor beta; TGF- β 1: transforming growth factor beta 1; TSG101: tumor susceptibility gene 101.

microvascular tone also carries translational relevance: mineralocorticoid receptor antagonism with spironolactone improved CFR in individuals with type 2 diabetes, providing support for therapeutic strategies that target microvascular dysfunction in diabetes^[137].

Overall, current evidence indicates that EVs exert divergent effects in DCM depending on their cellular origin and molecular cargo. Pathological EVs released from metabolically stressed cardiac cells may contribute to microvascular injury and adverse remodeling, whereas therapeutic EV platforms have shown potential to deliver protective signals [Table 3].

Beyond microvascular regulation, the bidirectional effects of EV-mediated communication extend across multiple pathological domains of DCM, including metabolic dysfunction, oxidative stress, apoptosis,

hypertrophic remodeling, and fibrosis. As summarized in [Figure 2](#), pathological EVs released from metabolically stressed cardiac cells transfer detrimental cargoes, such as miR-34a, miR-320, and MST1, thereby amplifying these maladaptive processes. Conversely, therapeutic EV-based approaches derived from MSCs or engineered platforms may exert protective effects by modulating metabolic homeostasis, vascular repair, and cardiac remodeling. However, the contribution of individual molecules requires careful interpretation because direct EV-mediated delivery has not been established for all candidate factors. This integrated framework highlights EV-mediated signaling as an important mediator of diabetic cardiac remodeling and provides a conceptual basis for understanding the diverse mechanisms underlying DCM progression.

Emerging evidence for EV-mediated metabolic organ-heart communication

Beyond cardiac resident cells, EVs may represent an additional layer of communication between the diabetic heart and metabolically active peripheral organs. This concept is particularly relevant to DCM, which develops within the context of systemic metabolic disturbances rather than isolated myocardial abnormalities. Diabetes-induced remodeling of adipose tissue, liver, and skeletal muscle is accompanied by alterations in circulating EV abundance and cargo composition, raising the possibility that EVs contribute to metabolic organ-heart communication^[138-140]. However, compared with cardiac intercellular EV signaling, direct evidence establishing organ-specific EV transfer and functional effects in DCM remains limited.

The adipose tissue-heart axis represents one of the most extensively investigated examples of EV-mediated metabolic communication. Adipose-derived EV-associated miRNAs have been implicated in regulating glucose homeostasis, IR, and diabetes-related cardiovascular complications^[138]. Specifically, sEVs released from adipocytes of diabetic or high-fat-fed mice carry miR-130b-3p, which can be transferred to cardiomyocytes and suppress PGC-1 α expression, thereby promoting mitochondrial oxidative stress and cardiomyocyte injury. These findings provide mechanistic evidence that metabolic abnormalities originating from peripheral tissues may influence myocardial homeostasis through EV-mediated signaling. Beyond intracellular cargo transfer, adipocyte-derived sEVs also convey protective signals through surface-associated adiponectin (APN), which interacts with cardiomyocyte AdipoR1 to promote metabolic homeostasis. In diabetes, G protein-coupled receptor kinase 2 (GRK2)-mediated phosphorylation of AdipoR1 disrupts this protective signaling pathway, potentially shifting the adipose-heart axis from an adaptive to a maladaptive communication network^[141]. Furthermore, recent evidence suggests that adipocyte-derived EVs can transfer oxidatively damaged mitochondrial components to cardiomyocytes, impairing myocardial bioenergetics and cell survival^[142]. Together, these findings indicate that diabetes-associated EV dysfunction may involve both altered cargo transfer and impaired surface-mediated signaling.

Other metabolically active organs may also participate in EV-mediated communication with the heart. Metabolic stress associated with hepatic steatosis alters EV release and molecular composition, and liver-derived sEVs have been implicated in inter-organ metabolic and inflammatory regulation^[143]. However, direct evidence linking hepatic EV-mediated communication to DCM remains limited. Although these observations suggest a potential liver-heart communication pathway, direct evidence linking hepatic EVs to DCM progression remains insufficient. Similarly, exercise-induced remodeling of skeletal muscle-derived EV profiles, including enrichment of cargoes related to mitochondrial function and angiogenesis, suggests a possible mechanism through which peripheral metabolic adaptation may influence cardiovascular health^[139]. However, whether skeletal muscle-derived EVs directly regulate myocardial function in diabetic hearts remains to be determined.

Collectively, EV-mediated metabolic organ-heart communication represents an emerging extension of the DCM framework, linking systemic metabolic dysregulation with myocardial injury. Nevertheless, current evidence for EV-mediated inter-organ communication remains substantially less established than that for

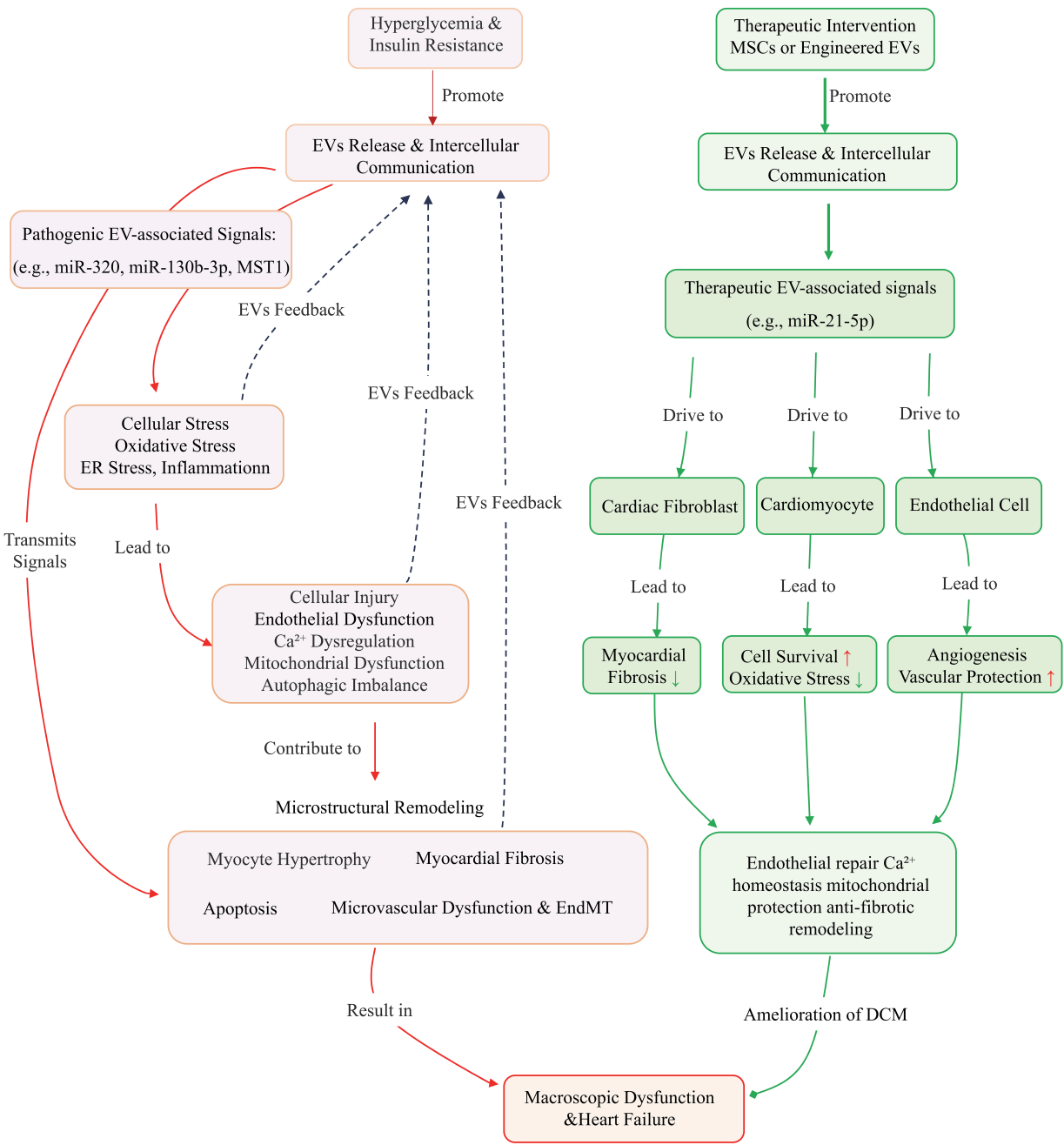


Figure 2. EV-mediated intercellular communication in DCM: pathological mechanisms and therapeutic opportunities. The diabetic milieu characterized by hyperglycemia and IR (center) alters EV release and cargo composition from cardiac cells. EVs function as mediators of communication among cardiomyocytes, endothelial cells, and fibroblasts, thereby regulating multiple pathological processes involved in DCM progression. The left (red) pathway illustrates the pathogenic effects of EVs derived from metabolically stressed cells. These EVs transfer pathological molecular signals, including validated EV-associated cargoes and EV-related regulatory molecules, including miR-320 (cardiomyocyte-derived), miR-130b-3p (adipocyte-derived) and MST1 (CMEC-derived), which promote oxidative stress, fibrosis, apoptosis, microvascular dysfunction, and metabolic impairment, ultimately contributing to cardiac remodeling and HF. The right (green) pathway highlights protective/therapeutic EVs derived from MSCs or engineered platforms. These approaches deliver or modulate cardioprotective molecular signals, including validated EV-associated cargoes and protective regulators, such as miR-21-5p (CPC-derived exosomes), which enhance metabolic homeostasis, preserve vascular function, attenuate fibrosis and apoptosis, and improve cardiac remodeling. The balance between pathogenic and protective EV signaling influences the progression or attenuation of diabetic cardiac injury. Red ↑ indicate upregulated; green ↓ indicate downregulated; Solid arrows indicate established direct interactions, whereas dashed arrows denote putative or indirect regulatory relationships that require further experimental validation. CPC: Cardiac progenitor cell; DCM: diabetic cardiomyopathy; EndMT: endothelial-to-mesenchymal transition; ER: endoplasmic reticulum; EVs: extracellular vesicles; HF: heart failure; IR: insulin resistance; miRNA: microRNA; MSCs: mesenchymal stem cells; MST1: macrophage stimulating 1; CMEC: cardiac microvascular endothelial cell.

cardiac cell-to-cell EV signaling. Future studies incorporating organ-specific EV tracing, functional validation, and longitudinal human cohorts will be essential to determine whether circulating EVs actively contribute to DCM pathogenesis or primarily serve as biomarkers reflecting systemic metabolic disturbances.

TRANSLATIONAL CHALLENGES AND FUTURE PERSPECTIVES OF EV-BASED APPROACHES IN DCM

Although EVs have provided new insights into mechanisms underlying DCM progression, several issues remain unresolved before EV-based biomarkers or therapies can be translated into clinical practice. The most important limitation is that current evidence remains largely derived from experimental models. Although miRNAs, lncRNAs, and proteins have been implicated in IR, mitochondrial dysfunction, inflammation, fibrosis, and microvascular injury, it remains unclear whether these EV alterations represent causal drivers of myocardial injury, compensatory responses, or secondary consequences of systemic metabolic abnormalities. Studies integrating longitudinal EV profiling with detailed clinical phenotyping will be essential to clarify their biological and clinical relevance.

Another major challenge is the considerable methodological heterogeneity in EV studies. Differences in EV isolation procedures, characterization strategies, and functional assays have contributed to inconsistent findings and limited direct comparisons between studies. Adoption of standardized approaches aligned with MISEV2023 recommendations, together with rigorous functional validation, will be critical for improving reproducibility and advancing clinical application.

From a therapeutic perspective, MSC-derived and engineered EV platforms have shown promising cardioprotective effects in experimental models, largely through modulation of inflammation, oxidative stress, metabolism, and tissue remodeling. However, important barriers remain, including production scalability, EV heterogeneity, targeting efficiency, and long-term safety assessment. Further optimization of EV engineering strategies will require balancing enhanced cargo delivery with preservation of biological stability and compatibility.

In addition to exogenous EV administration, pharmacological modulation of EV properties may represent an emerging therapeutic concept. Preliminary experimental evidence suggests that SGLT2 inhibitor exposure can influence EV biology in specific cellular contexts. For example, empagliflozin pretreatment of bone marrow-derived mesenchymal stem cells (BMSCs) alters exosome production and functional properties, enhancing their cardioprotective effects in myocardial ischemia-reperfusion injury models^[144]. However, whether SGLT2 inhibitors directly remodel circulating EV profiles *in vivo* and whether such EV alterations contribute to their cardiovascular benefits remain unclear. Beyond SGLT2 inhibitors, whether other metabolic therapies, including GLP-1 receptor agonists, metformin, and insulin, similarly influence EV secretion or cargo composition remains largely unexplored.

Finally, interpretation of non-coding RNAs requires careful consideration of biological context. The functional consequences of individual miRNAs depend on their cellular origin, target cells, and disease stage. Therefore, changes in EV cargo abundance should not be directly interpreted as therapeutic targets without mechanistic validation. The context-dependent effects observed for several miRNAs, including miR-144 and miR-503, highlight the complexity of EV-mediated regulation in DCM.

Taken together, EV-mediated signaling represents an emerging communication network linking metabolic disturbance, cardiac cellular interactions, and systemic organ crosstalk in DCM. Defining their causal roles, improving methodological consistency, and establishing clinically relevant validation platforms will determine whether EVs can ultimately become useful tools for diagnosis and therapy in diabetic cardiac disease [Table 4].

Table 4. Extracellular vesicle-based therapeutic strategies for DCM and associated challenges

Strategic approach	Specific methodology	Potential benefits	Current status/evidence	Primary challenges & clinical translation barriers	Ref.
Inhibiting pathogenic EV cargo	miRNA antagonists (e.g., antagomirs against miR-320)	Blocks disease-promoting signals; potential to halt or reverse disease progression	Preclinical proof-of-concept (rodent DCM models; <i>in vitro</i> studies)	Delivery: Poor cardiac targeting efficiency; rapid systemic clearance; Safety: Off-target effects; potential toxicity to non-cardiac tissues; Stability: Oligonucleotide degradation in circulation	[32]
Supplementing protective EVs	Administration of naive MSC-derived EVs; Engineered enhancement of EV biogenesis or cardioprotective signaling through HSP20-related pathways	Multi-target synergistic therapy (anti-inflammatory, anti-fibrotic, pro-angiogenic, metabolic restoration); Myocardial repair	Preclinical proof-of-concept (multiple rodent DCM models; porcine models limited)	Manufacturing: Large-scale GMP production; batch-to-batch variability; high cost; Quality control: EV characterization and potency assay standardization; Immunogenicity: Potential immune response to xenogeneic or allogeneic EV proteins; Dosing: Optimal dose and regimen not established	[30,112,115,117]
Engineering & cargo loading	Electroporation, sonication, or transfection to load therapeutic miRNAs	Precise enhancement of protective signals; customizable therapeutic payload	Preclinical optimization (<i>in vitro</i> loading studies; small animal efficacy studies)	Loading efficiency: Inconsistent cargo encapsulation; damage to EV membrane integrity; Scalability: Difficult to achieve large-scale production with consistent loading; Stability: Loaded RNA degradation during storage; Drug capacity: Limited EV cargo space	[115,118]
Targeted delivery	Surface modification with cardiac-targeting peptides or ligands	Improves cardiac enrichment; reduces systemic off-target effects; enables lower dosing	Preclinical exploration (proof-of-concept in small animals; no clinical data in DCM)	Modification complexity: Chemical conjugation may alter EV surface properties and affect biodistribution; Efficiency: Targeting peptide density and orientation not optimized; Scalability: Difficult to maintain surface modification consistency; Safety: Long-term consequences of surface modification unknown	[115,118,145]
Combined technologies	Integration with hydrogel-based sustained-release systems; Combination with existing therapeutics	Prolonged local retention and action; reduced dosing frequency; synergistic therapeutic effects	Preclinical exploration (biomaterial development; <i>in vivo</i> release studies)	Biocompatibility: Host inflammatory response to hydrogel materials; Biodegradability: Unpredictable degradation kinetics; Complexity: System design and validation; Regulatory: Multimodal product requires more complex regulatory review	[115,118]

All strategies listed are at preclinical stages; none have received regulatory approval for DCM treatment. For the “Current Status/Evidence” column: “Preclinical proof-of-concept” indicates evidence in rodent models with functional outcome data; “Preclinical exploration” indicates initial feasibility studies without established therapeutic efficacy. The clinical translation pathway for EV-based therapies remains uncertain, and the barriers listed require systematic investigation before clinical application. DCM in this table refers specifically to diabetic cardiomyopathy. cTnT: Cardiac troponin T; DCM: diabetic cardiomyopathy; EV: extracellular vesicle; GLP-1RA: glucagon-like peptide-1 receptor agonist; GMP: Good Manufacturing Practice; HSP20: heat shock protein 20; miRNA: microRNA; MSC: mesenchymal stem cell; RNA: ribonucleic acid; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

Conclusion

DCM represents a complex metabolic and inflammatory cardiac disorder driven by interconnected processes, including impaired substrate utilization, chronic inflammation, oxidative stress, microvascular

dysfunction, and maladaptive structural remodeling. Over the past decade, EVs have emerged as important regulators of cellular communication, linking cardiomyocytes, endothelial cells, fibroblasts, macrophages, and metabolically active organs. Through their diverse molecular cargo, including miRNAs, lncRNAs, circRNAs, and proteins, EVs regulate pathways involved in insulin sensitivity, mitochondrial homeostasis, fibrosis, hypertrophic remodeling, cell survival, and endothelial integrity.

EV-associated molecular signatures may reflect dynamic alterations in disease states and therapeutic responses that are not fully captured by conventional biomarkers, supporting their potential utility for diagnosis, prognosis, and disease monitoring. Notably, a recent comprehensive review has systematically consolidated the theranostic potential of EV-mediated miRNAs in type 2 diabetes and its complications, highlighting their dual role as both non-invasive biomarkers for early disease detection and promising therapeutic targets^[146]. Preclinical proof-of-concept studies further indicate that MSC-derived and engineered EVs can ameliorate diabetic cardiac injury, providing a foundation for the future development of EV-based therapeutic approaches.

Despite these advances, the field remains in its early stages. Most available evidence remains associative rather than causal, and definitive links between EV cargo and human DCM pathogenesis remain to be established. Technical heterogeneity in EV isolation methods, nomenclature, and characterization criteria continues to limit reproducibility and cross-study comparisons. Whether EV alterations represent primary pathogenic mechanisms, secondary compensatory responses, or nonspecific consequences of metabolic stress remains unresolved. Furthermore, clinical translation of EV-based therapies faces substantial challenges, including manufacturing standardization, tissue-specific delivery, immunocompatibility, and long-term safety evaluation.

Advancing the field will require a transition from descriptive observations toward mechanistically validated and clinically relevant investigations. Key priorities include genetic or pharmacological modulation of EV biogenesis and secretion in DCM models; functional validation of EV cargoes in well-characterized experimental systems; establishment of large, deeply phenotyped clinical cohorts to define biomarker specificity; implementation of MISEV2023-aligned standards; and systematic investigation of how commonly used antidiabetic therapies remodel EV biology. For EV-based interventions to reach clinical application, they must meet rigorous standards for manufacturing consistency, biological activity, safety, and clinical efficacy comparable to other biologic therapies.

The therapeutic potential of EVs in DCM remains highly promising, yet substantial knowledge gaps persist. Bridging these gaps will require sustained research efforts, methodological rigor, and a comprehensive understanding of the complex molecular communication networks connecting EVs, individual cell populations, and metabolically active organs. Further clarification of EV-mediated communication may facilitate the development of improved biomarkers and therapeutic strategies for DCM.

DECLARATIONS

Authors' contributions

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All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tools DeepSeek-V4 Preview (released 2026-04-24) and iFLYTEK Spark (version Xinghuo X2, released 2026-02-11) were used solely for language editing without unsupervised automatic generation. In addition, the AI tool MedKnows (version 3.2.65, released 2026-08-10) was used solely to generate some graphical elements in [Figure 1](#) and the Graphical Abstract; these AI-generated graphical elements were used only as independent icons or schematic components and were subsequently modified, processed, and integrated by the authors into the original scientific illustrations, while the overall conceptual framework, mechanistic pathways, molecular interactions, and composition of the figures were designed by the authors. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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REFERENCES

- Duncan BB, Magliano DJ, Boyko EJ. IDF diabetes atlas 11th edition 2025: global prevalence and projections for 2050. *Nephrol Dial Transplant*. 2025;41:7-9. [DOI PubMed](#)
- Seferović PM, Paulus WJ, Rosano G, et al. Diabetic myocardial disorder. A clinical consensus statement of the Heart Failure Association of the ESC and the ESC Working Group on Myocardial & Pericardial Diseases. *Eur J Heart Fail*. 2024;26:1893-903. [DOI PubMed](#)
- Segar MW, Khan MS, Patel KV, et al. Prevalence and prognostic implications of diabetes with cardiomyopathy in community-dwelling adults. *J Am Coll Cardiol*. 2021;78:1587-98. [DOI PubMed](#)
- Galeone A, Annicchiarico A, Buccoliero C, et al. Diabetic cardiomyopathy: role of cell death, exosomes, fibrosis and epicardial adipose tissue. *Int J Mol Sci*. 2024;25:9481. [DOI PubMed PMC](#)
- Sanganalmath SK, Dubey S, Veeranki S, Narisetty K, Krishnamurthy P. The interplay of inflammation, exosomes and Ca²⁺ dynamics in diabetic cardiomyopathy. *Cardiovasc Diabetol*. 2023;22:37. [DOI PubMed PMC](#)
- Liu S, Pan Z, Chen X, et al. The emerging role of extracellular vesicles in diabetes and complications: mechanistic insights and translational prospects. *Front Endocrinol*. 2025;16:1674028. [DOI PubMed PMC](#)
- Welsh JA, Goberdhan DCI, O'Driscoll L, et al. ; MISEV Consortium. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. *J Extracell Vesicles*. 2024;13:e12404. [DOI PubMed PMC](#)
- Yu Y, Yang X, Yin Y, Qin L, Xiang Q, Yu R. Exosomal microRNA in diabetic myocardial disorder: mechanisms, diagnosis, and treatment. *Biomed Pharmacother*. 2025;193:118761. [DOI PubMed](#)
- Wang M, Chen Y, Xu B, et al. Recent advances in the roles of extracellular vesicles in cardiovascular diseases: pathophysiological mechanisms, biomarkers, and cell-free therapeutic strategy. *Mol Med*. 2025;31:169. [DOI PubMed PMC](#)
- Arya SB, Collie SP, Parent CA. The ins-and-outs of exosome biogenesis, secretion, and internalization. *Trends Cell Biol*. 2024;34:90-108. [DOI PubMed PMC](#)
- Carvalho Ferraz L, Pereira P, Ferreira JV. Molecular mechanisms of extracellular vesicle biogenesis and their impact on the design of custom EVs. *Adv Healthc Mater*. 2025;14:e2501349. [DOI PubMed PMC](#)

12. Lu T, Zheng Y, Chen X, Lin Z, Liu C, Yuan C. The role of exosome derived miRNAs in inter-cell crosstalk among insulin-related organs in type 2 diabetes mellitus. *J Physiol Biochem*. 2024;80:501-10. [DOI PubMed](#)
13. Abbas A, Almaghrbi H, Giordo R, Zayed H, Pintus G. Pathogenic mechanisms, diagnostic, and therapeutic potential of microvesicles in diabetes and its complications. *Arch Biochem Biophys*. 2024;761:110168. [DOI PubMed](#)
14. Renu K. A molecular perspective on the intricate interplay among exosomes, bioenergetic metabolism, and the pathogenesis of diabetic cardiomyopathy. *J Cardiovasc Transl Res*. 2025;18:1707-22. [DOI PubMed](#)
15. Zhang W, Song M, Fang Z, et al. Role of extracellular vesicles in insulin resistance: Signaling pathways, bioactive substances, miRNAs, and therapeutic potential. *Cell Biochem Funct*. 2024;42:e4013. [DOI PubMed](#)
16. Rohm TV, Cunha E Rocha K, Olefsky JM. Metabolic messengers: small extracellular vesicles. *Nat Metab*. 2025;7:253-62. [DOI PubMed](#)
17. Malin SK, Erdbrügger U. Extracellular vesicles in metabolic and vascular insulin resistance. *J Vasc Res*. 2024;61:129-41. [DOI PubMed PMC](#)
18. Paneru BD, Hill DA. The role of extracellular vesicle-derived miRNAs in adipose tissue function and metabolic health. *Immunometabolism*. 2023;5:e00027. [DOI PubMed PMC](#)
19. Marchand A, Atassi F, Mougenot N, et al. miR-322 regulates insulin signaling pathway and protects against metabolic syndrome-induced cardiac dysfunction in mice. *Biochim Biophys Acta*. 2016;1862:611-21. [DOI PubMed](#)
20. Lark DS, Stemmer K, Ying W, Crewe C. A brief guide to studying extracellular vesicle function in the context of metabolism. *Nat Metab*. 2024;6:1839-41. [DOI PubMed](#)
21. Liu L, An Z, Zhang H, et al. Bone marrow mesenchymal stem cell-derived extracellular vesicles alleviate diabetes-exacerbated atherosclerosis via AMPK/mTOR pathway-mediated autophagy-related macrophage polarization. *Cardiovasc Diabetol*. 2025;24:48. [DOI PubMed PMC](#)
22. Zhang T, Gao Z, Chen K. Exosomal microRNAs: potential targets for the prevention and treatment of diabetic cardiomyopathy. *J Cardiol*. 2022;80:423-31. [DOI PubMed](#)
23. Horie T, Ono K, Nishi H, et al. MicroRNA-133 regulates the expression of GLUT4 by targeting KLF15 and is involved in metabolic control in cardiac myocytes. *Biochem Biophys Res Commun*. 2009;389:315-20. [DOI PubMed](#)
24. Blumensatt M, Greulich S, Herzfeld de Wiza D, et al. Activin A impairs insulin action in cardiomyocytes via up-regulation of miR-143. *Cardiovasc Res*. 2013;100:201-10. [DOI PubMed](#)
25. Lu H, Buchan RJ, Cook SA. MicroRNA-223 regulates Glut4 expression and cardiomyocyte glucose metabolism. *Cardiovasc Res*. 2010;86:410-20. [DOI PubMed](#)
26. Hu J, Wang S, Xiong Z, et al. Exosomal Mst1 transfer from cardiac microvascular endothelial cells to cardiomyocytes deteriorates diabetic cardiomyopathy. *Biochim Biophys Acta Mol Basis Dis*. 2018;1864:3639-49. [DOI PubMed](#)
27. Zhu Y, Pereira RO, O'Neill BT, et al. Cardiac PI3K-Akt impairs insulin-stimulated glucose uptake independent of mTORC1 and GLUT4 translocation. *Mol Endocrinol*. 2013;27:172-84. [DOI PubMed PMC](#)
28. Xing Z, Schocken DD, Zgibor JC, Alman AC. Course and trajectories of insulin resistance, incident heart failure and all-cause mortality in nondiabetic people. *Endocrine*. 2025;87:530-42. [DOI PubMed](#)
29. Witteles RM, Tang WH, Jamali AH, Chu JW, Reaven GM, Fowler MB. Insulin resistance in idiopathic dilated cardiomyopathy: a possible etiologic link. *J Am Coll Cardiol*. 2004;44:78-81. [DOI PubMed](#)
30. Sun Y, Shi H, Yin S, et al. Human mesenchymal stem cell derived exosomes alleviate type 2 diabetes mellitus by reversing peripheral insulin resistance and relieving β -cell destruction. *ACS Nano*. 2018;12:7613-28. [DOI PubMed](#)
31. Gan L, Zhao J, Yao P, et al. Adipocyte-derived small extracellular vesicles exacerbate diabetic ischemic heart injury by promoting oxidative stress and mitochondrial-mediated cardiomyocyte apoptosis. *Redox Biol*. 2025;79:103443. [DOI PubMed PMC](#)
32. Wang X, Huang W, Liu G, et al. Cardiomyocytes mediate anti-angiogenesis in type 2 diabetic rats through the exosomal transfer of miR-320 into endothelial cells. *J Mol Cell Cardiol*. 2014;74:139-50. [DOI PubMed PMC](#)
33. Zhu Y, Yang X, Zhou J, et al. miR-340-5p mediates cardiomyocyte oxidative stress in diabetes-induced cardiac dysfunction by targeting Mcl-1. *Oxid Med Cell Longev*. 2022;2022:3182931. [DOI PubMed PMC](#)
34. Das S, Kohr M, Dunkerly-Eyring B, et al. Divergent effects of mir-181 family members on myocardial function through protective cytosolic and detrimental mitochondrial microRNA targets. *J Am Heart Assoc*. 2017;6:e004694. [DOI PubMed PMC](#)
35. el Azzouzi H, Leptidis S, Dirks E, et al. The hypoxia-inducible microRNA cluster miR-199a-214 targets myocardial PPAR δ and impairs mitochondrial fatty acid oxidation. *Cell Metab*. 2013;18:341-54. [DOI PubMed](#)
36. Tang Q, Len Q, Liu Z, Wang W. Overexpression of miR-22 attenuates oxidative stress injury in diabetic cardiomyopathy via Sirt 1. *Cardiovasc Ther*. 2018;36:1-11. [DOI PubMed](#)
37. Yu M, Sun Y, Shan X, et al. Therapeutic overexpression of miR-92a-2-5p ameliorated cardiomyocyte oxidative stress injury in the development of diabetic cardiomyopathy. *Cell Mol Biol Lett*. 2022;27:85. [DOI PubMed PMC](#)

38. Yu M, Liu Y, Zhang B, Shi Y, Cui L, Zhao X. Inhibiting microRNA-144 abates oxidative stress and reduces apoptosis in hearts of streptozotocin-induced diabetic mice. *Cardiovasc Pathol*. 2015;24:375-81. [DOI PubMed](#)
39. Su M, Wang J, Wang C, et al. MicroRNA-221 inhibits autophagy and promotes heart failure by modulating the p27/CDK2/mTOR axis. *Cell Death Differ*. 2015;22:986-99. [DOI PubMed PMC](#)
40. Miao Y, Wan Q, Liu X, et al. miR-503 is involved in the protective effect of phase II enzyme inducer (CPDT) in diabetic cardiomyopathy via Nrf2/ARE signaling pathway. *Biomed Res Int*. 2017;2017:9167450. [DOI PubMed PMC](#)
41. Baseler WA, Thapa D, Jagannathan R, Dabkowski ER, Croston TL, Hollander JM. miR-141 as a regulator of the mitochondrial phosphate carrier (Slc25a3) in the type 1 diabetic heart. *Am J Physiol Cell Physiol*. 2012;303:C1244-51. [DOI PubMed PMC](#)
42. Wang S, Duan J, Liao J, et al. LncRNA H19 inhibits ER stress induced apoptosis and improves diabetic cardiomyopathy by regulating PI3K/AKT/mTOR axis. *Aging*. 2022;14:6809-28. [DOI PubMed PMC](#)
43. Yin Z, Zhao Y, He M, et al. MiR-30c/PGC-1 β protects against diabetic cardiomyopathy via PPAR α . *Cardiovasc Diabetol*. 2019;18:7. [DOI PubMed PMC](#)
44. Duan Q, Chen C, Yang L, et al. MicroRNA regulation of unfolded protein response transcription factor XBP1 in the progression of cardiac hypertrophy and heart failure in vivo. *J Transl Med*. 2015;13:363. [DOI PubMed PMC](#)
45. Bai Y, Zhang Y, Han B, et al. Circular RNA DLGAP4 ameliorates ischemic stroke outcomes by targeting miR-143 to regulate endothelial-mesenchymal transition associated with blood-brain barrier integrity. *J Neurosci*. 2018;38:32-50. [DOI PubMed PMC](#)
46. Ren L, Wang Q, Chen Y, Ma Y, Wang D. Involvement of microRNA-133a in the protective effect of hydrogen sulfide against ischemia/reperfusion-induced endoplasmic reticulum stress and cardiomyocyte apoptosis. *Pharmacology*. 2019;103:1-9. [DOI PubMed](#)
47. Li J, Xie Y, Zheng S, et al. Targeting autophagy in diabetic cardiomyopathy: From molecular mechanisms to pharmacotherapy. *Biomed Pharmacother*. 2024;175:116790. [DOI PubMed](#)
48. Yan M, Zhang S, Liang P, et al. Research hotspots and frontier trends of autophagy in diabetic cardiomyopathy from 2014 to 2024: a bibliometric analysis. *J Multidiscip Healthc*. 2025;18:837-60. [DOI PubMed PMC](#)
49. Zhuo C, Jiang R, Lin X, Shao M. LncRNA H19 inhibits autophagy by epigenetically silencing of DIRAS3 in diabetic cardiomyopathy. *Oncotarget*. 2017;8:1429-37. [DOI PubMed PMC](#)
50. Feng Y, Xu W, Zhang W, Wang W, Liu T, Zhou X. LncRNA DCRF regulates cardiomyocyte autophagy by targeting miR-551b-5p in diabetic cardiomyopathy. *Theranostics*. 2019;9:4558-66. [DOI PubMed PMC](#)
51. Chen D, Zhang M. GAS5 regulates diabetic cardiomyopathy via miR-221-3p/p27 axis-associated autophagy. *Mol Med Rep*. 2021;23:135. [DOI PubMed PMC](#)
52. Qian LB, Jiang SZ, Tang XQ, et al. Exacerbation of diabetic cardiac hypertrophy in OVE26 mice by angiotensin II is associated with JNK/c-Jun/miR-221-mediated autophagy inhibition. *Oncotarget*. 2017;8:106661-71. [DOI PubMed PMC](#)
53. Xiao C, Chen MY, Han YP, Liu LJ, Yan JL, Qian LB. The protection of luteolin against diabetic cardiomyopathy in rats is related to reversing JNK-suppressed autophagy. *Food Funct*. 2023;14:2740-9. [DOI PubMed](#)
54. Shyu KG, Wang BW, Pan CM, Fang WJ. Macrophage-derived exosomal MALAT1 regulates autophagy through miR-204-5p/ATG7 axis in H9C2 cardiomyocytes and diabetic rat heart. *Acta Cardiol Sin*. 2025;41:346-60. [DOI PubMed PMC](#)
55. XiaoTian L, QiNan W, XiaGuang G, WuQuan D, Bing C, ZiWen L. Exenatide activates the APPL1-AMPK-PPAR α axis to prevent diabetic cardiomyocyte apoptosis. *J Diabetes Res*. 2016;2016:4219735. [DOI PubMed PMC](#)
56. Xiao J, Pan Y, Li XH, et al. Cardiac progenitor cell-derived exosomes prevent cardiomyocytes apoptosis through exosomal miR-21 by targeting PDCD4. *Cell Death Dis*. 2016;7:e2277. [DOI PubMed PMC](#)
57. Mayourian J, Ceholski DK, Gorski PA, et al. Exosomal microRNA-21-5p mediates mesenchymal stem cell paracrine effects on human cardiac tissue contractility. *Circ Res*. 2018;122:933-44. [DOI PubMed PMC](#)
58. Liu Y, Zhong C, Chen S, et al. Circulating exosomal mir-16-2-3p is associated with coronary microvascular dysfunction in diabetes through regulating the fatty acid degradation of endothelial cells. *Cardiovasc Diabetol*. 2024;23:60. [DOI PubMed PMC](#)
59. Liu H, Zhang Y, Yuan J, et al. Dendritic cell-derived exosomal miR-494-3p promotes angiogenesis following myocardial infarction. *Int J Mol Med*. 2021;47:315-25. [DOI PubMed PMC](#)
60. Gao L, Wang X, Guo S, et al. LncRNA HOTAIR functions as a competing endogenous RNA to upregulate SIRT1 by sponging miR-34a in diabetic cardiomyopathy. *J Cell Physiol*. 2019;234:4944-58. [DOI PubMed](#)
61. Zheng D, Ma J, Yu Y, et al. Silencing of miR-195 reduces diabetic cardiomyopathy in C57BL/6 mice. *Diabetologia*. 2015;58:1949-58. [DOI PubMed PMC](#)
62. Biao K, Dongli S, Tao R, Guohui Z. [Inhibition of microRNA195 attenuates high-glucose induced neonatal cardiomyocytes hypertrophy in vitro]. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2015;43:712-7. [DOI](#)
63. Kuwabara Y, Horie T, Baba O, et al. MicroRNA-451 exacerbates lipotoxicity in cardiac myocytes and high-fat diet-induced cardiac hypertrophy in mice through suppression of the LKB1/AMPK pathway. *Circ Res*. 2015;116:279-88. [DOI PubMed](#)

64. Zhang H, Liu J, Qu D, et al. Inhibition of miR-200c restores endothelial function in diabetic mice through suppression of COX-2. *Diabetes*. 2016;65:1196-207. [DOI PubMed](#)
65. Feng B, Cao Y, Chen S, Chu X, Chu Y, Chakrabarti S. miR-200b mediates endothelial-to-mesenchymal transition in diabetic cardiomyopathy. *Diabetes*. 2016;65:768-79. [DOI PubMed](#)
66. Qiao Y, Zhao Y, Liu Y, et al. miR-483-3p regulates hyperglycaemia-induced cardiomyocyte apoptosis in transgenic mice. *Biochem Biophys Res Commun*. 2016;477:541-7. [DOI PubMed](#)
67. Wahlquist C, Jeong D, Rojas-Muñoz A, et al. Inhibition of miR-25 improves cardiac contractility in the failing heart. *Nature*. 2014;508:531-5. [DOI PubMed PMC](#)
68. Sabzevari Rad R, Shirvani H, Mahmoodzadeh Hosseini H, Shamsoddini A, Samadi M. Micro RNA-126 promoting angiogenesis in diabetic heart by VEGF/Spred-1/Raf-1 pathway: effects of high-intensity interval training. *J Diabetes Metab Disord*. 2020;19:1089-96. [DOI PubMed PMC](#)
69. Feng B, Liu J, Wang E, Su Z, Chakrabarti S. Endothelial derived miRNA-9 mediated cardiac fibrosis in diabetes and its regulation by ZFAS1. *PLoS One*. 2022;17:e0276076. [DOI PubMed PMC](#)
70. Duan Y, Zhou B, Su H, Liu Y, Du C. miR-150 regulates high glucose-induced cardiomyocyte hypertrophy by targeting the transcriptional co-activator p300. *Exp Cell Res*. 2013;319:173-84. [DOI PubMed](#)
71. Zhao L, Li W, Zhao H. Inhibition of long non-coding RNA TUG1 protects against diabetic cardiomyopathy induced diastolic dysfunction by regulating miR-499-5p. *Am J Transl Res*. 2020;12:718-30. [PubMed PMC](#)
72. Wang C, Liu G, Yang H, et al. MALAT1-mediated recruitment of the histone methyltransferase EZH2 to the microRNA-22 promoter leads to cardiomyocyte apoptosis in diabetic cardiomyopathy. *Sci Total Environ*. 2021;766:142191. [DOI PubMed](#)
73. Zhou X, Zhang W, Jin M, Chen J, Xu W, Kong X. lncRNA MIAT functions as a competing endogenous RNA to upregulate DAPK2 by sponging miR-22-3p in diabetic cardiomyopathy. *Cell Death Dis*. 2017;8:e2929. [DOI PubMed PMC](#)
74. Zhao SF, Ye YX, Xu JD, et al. Long non-coding RNA KCNQ1OT1 increases the expression of PDCD4 by targeting miR-181a-5p, contributing to cardiomyocyte apoptosis in diabetic cardiomyopathy. *Acta Diabetol*. 2021;58:1251-67. [DOI PubMed](#)
75. Zou G, Zhong W, Wu F, Wang X, Liu L. Catalpol attenuates cardiomyocyte apoptosis in diabetic cardiomyopathy via Neat1/miR-140-5p/HDAC4 axis. *Biochimie*. 2019;165:90-9. [DOI PubMed](#)
76. Li X, Wang H, Yao B, Xu W, Chen J, Zhou X. lncRNA H19/miR-675 axis regulates cardiomyocyte apoptosis by targeting VDAC1 in diabetic cardiomyopathy. *Sci Rep*. 2016;6:36340. [DOI PubMed PMC](#)
77. Chen R, Chen H, Yang Z, et al. Danlou tablet inhibits high-glucose-induced cardiomyocyte apoptosis via the miR-34a-SIRT1 axis. *Heliyon*. 2023;9:e14479. [DOI PubMed PMC](#)
78. Wang X, Zhang Z, Wang M. MiR-29a regulates cardiomyocyte apoptosis by targeting Bak1 in diabetic cardiomyopathy. *J Biochem*. 2022;171:663-71. [DOI PubMed](#)
79. Tao L, Huang X, Xu M, et al. Value of circulating miRNA-21 in the diagnosis of subclinical diabetic cardiomyopathy. *Mol Cell Endocrinol*. 2020;518:110944. [DOI PubMed](#)
80. Ghosh N, Fenton S, van Hout I, et al. Therapeutic knockdown of miR-320 improves deteriorated cardiac function in a pre-clinical model of non-ischemic diabetic heart disease. *Mol Ther Nucleic Acids*. 2022;29:330-42. [DOI PubMed PMC](#)
81. Pan L, Huang BJ, Ma XE, et al. MiR-25 protects cardiomyocytes against oxidative damage by targeting the mitochondrial calcium uniporter. *Int J Mol Sci*. 2015;16:5420-33. [DOI PubMed PMC](#)
82. Żarek-Starzewska A, Klimczak-Tomaniak D, Mądrecka A, Sygitowicz G, Janiszewski M, Kuch M. From type 2 diabetes mellitus to diabetic cardiomyopathy - a systematic review on the role of microRNA. *Curr Diab Rep*. 2025;25:42. [DOI PubMed PMC](#)
83. Li X, Du N, Zhang Q, et al. MicroRNA-30d regulates cardiomyocyte pyroptosis by directly targeting foxo3a in diabetic cardiomyopathy. *Cell Death Dis*. 2014;5:e1479. [DOI PubMed PMC](#)
84. Knezevic I, Patel A, Sundaresan NR, et al. A novel cardiomyocyte-enriched microRNA, miR-378, targets insulin-like growth factor 1 receptor: implications in postnatal cardiac remodeling and cell survival. *J Biol Chem*. 2012;287:12913-26. [DOI PubMed PMC](#)
85. Cheng Y, Zhang D, Zhu M, et al. Liver X receptor α is targeted by microRNA-1 to inhibit cardiomyocyte apoptosis through a ROS-mediated mitochondrial pathway. *Biochem Cell Biol*. 2018;96:11-8. [DOI PubMed](#)
86. Kim OH, Noh SW, Choi JS, Jung Y, Oh BC. The SERCA-PLN-DWORF axis in cardiometabolic disease: mechanisms and therapeutic perspectives. *Cardiovasc Diabetol*. 2025;25:17. [DOI PubMed PMC](#)
87. Deng S, Tayefi F, Jin Y. Metabolic-stress-induced mitochondrial calcium dysregulation: a central hub in diabetic cardiomyopathy pathogenesis and treatment. *Front Endocrinol*. 2025;16:1696344. [DOI PubMed PMC](#)
88. Ma X, Mei S, Wuyun Q, Zhou L, Sun D, Yan J. Epigenetics in diabetic cardiomyopathy. *Clin Epigenetics*. 2024;16:52. [DOI PubMed PMC](#)
89. Cha MJ, Jang JK, Ham O, et al. MicroRNA-145 suppresses ROS-induced Ca²⁺ overload of cardiomyocytes by targeting CaMKII δ . *Biochem Biophys Res Commun*. 2013;435:720-6. [DOI PubMed](#)

90. Fu L, Zhang J, Lin Z, Li Y, Qin G. CircularRNA circ_0071269 knockdown protects against from diabetic cardiomyopathy injury by microRNA-145/gasdermin A axis. *Bioengineered*. 2022;13:2398-411. [DOI PubMed PMC](#)
91. Wang C, Zhang C, Liu L, et al. Macrophage-derived mir-155-containing exosomes suppress fibroblast proliferation and promote fibroblast inflammation during cardiac injury. *Mol Ther*. 2017;25:192-204. [DOI PubMed PMC](#)
92. Ding M, Shi R, Du Y, et al. O-GlcNAcylation-mediated endothelial metabolic memory contributes to cardiac damage via small extracellular vesicles. *Cell Metab*. 2025;37:1344-63.e6. [DOI PubMed](#)
93. Messenger SW, Woo SS, Sun Z, Martin TFJ. A Ca²⁺-stimulated exosome release pathway in cancer cells is regulated by Munc13-4. *J Cell Biol*. 2018;217:2877-90. [DOI PubMed PMC](#)
94. Che H, Wang Y, Li H, et al. Melatonin alleviates cardiac fibrosis via inhibiting lncRNA MALAT1/miR-141-mediated NLRP3 inflammasome and TGF- β 1/Smads signaling in diabetic cardiomyopathy. *FASEB J*. 2020;34:5282-98. [DOI PubMed](#)
95. Qi Y, Wu H, Mai C, et al. LncRNA-MIAT-mediated miR-214-3p silencing is responsible for IL-17 production and cardiac fibrosis in diabetic cardiomyopathy. *Front Cell Dev Biol*. 2020;8:243. [DOI PubMed PMC](#)
96. Liu Y, Zhu Y, Liu S, Liu J, Li X. NORAD lentivirus shRNA mitigates fibrosis and inflammatory responses in diabetic cardiomyopathy via the ceRNA network of NORAD/miR-125a-3p/Fyn. *Inflamm Res*. 2021;70:1113-27. [DOI PubMed](#)
97. Dai W, Lee D. Interfering with long chain noncoding RNA ANRIL expression reduces heart failure in rats with diabetes by inhibiting myocardial oxidative stress. *J Cell Biochem*. 2019;120:18446-56. [DOI PubMed](#)
98. Huang ZW, Tian LH, Yang B, Guo RM. Long noncoding RNA H19 acts as a competing endogenous RNA to mediate CTGF expression by sponging miR-455 in cardiac fibrosis. *DNA Cell Biol*. 2017;36:759-66. [DOI PubMed](#)
99. Yan SM, Li H, Shu Q, Wu WJ, Luo XM, Lu L. LncRNA SNHG1 exerts a protective role in cardiomyocytes hypertrophy via targeting miR-15a-5p/HMGA1 axis. *Cell Biol Int*. 2020;44:1009-19. [DOI PubMed](#)
100. Tao H, Zhang JG, Qin RH, et al. LncRNA GAS5 controls cardiac fibroblast activation and fibrosis by targeting miR-21 via PTEN/MMP-2 signaling pathway. *Toxicology*. 2017;386:11-8. [DOI PubMed](#)
101. Peng T, Liu M, Hu L, et al. LncRNA Airn alleviates diabetic cardiac fibrosis by inhibiting activation of cardiac fibroblasts via a m6A-IMP2-p53 axis. *Biol Direct*. 2022;17:32. [DOI PubMed PMC](#)
102. Lai Y, He S, Ma L, et al. HOTAIR functions as a competing endogenous RNA to regulate PTEN expression by inhibiting miR-19 in cardiac hypertrophy. *Mol Cell Biochem*. 2017;432:179-87. [DOI PubMed](#)
103. de Gonzalo-Calvo D, Kenneweg F, Bang C, et al. Circulating long-non coding RNAs as biomarkers of left ventricular diastolic function and remodelling in patients with well-controlled type 2 diabetes. *Sci Rep*. 2016;6:37354. [DOI PubMed PMC](#)
104. Chavali V, Tyagi SC, Mishra PK. MicroRNA-133a regulates DNA methylation in diabetic cardiomyocytes. *Biochem Biophys Res Commun*. 2012;425:668-72. [DOI PubMed PMC](#)
105. Feng B, Chen S, George B, Feng Q, Chakrabarti S. miR133a regulates cardiomyocyte hypertrophy in diabetes. *Diabetes Metab Res Rev*. 2010;26:40-9. [DOI PubMed](#)
106. Hu H, Wang X, Yu H, Wang Z. Extracellular vesicular microRNAs and cardiac hypertrophy. *Front Endocrinol*. 2024;15:1444940. [DOI PubMed PMC](#)
107. Shen E, Diao X, Wang X, Chen R, Hu B. MicroRNAs involved in the mitogen-activated protein kinase cascades pathway during glucose-induced cardiomyocyte hypertrophy. *Am J Pathol*. 2011;179:639-50. [DOI PubMed PMC](#)
108. Raut SK, Kumar A, Singh GB, et al. miR-30c mediates upregulation of Cdc42 and Pak1 in diabetic cardiomyopathy. *Cardiovasc Ther*. 2015;33:89-97. [DOI PubMed](#)
109. Raut SK, Singh GB, Rastogi B, et al. miR-30c and miR-181a synergistically modulate p53-p21 pathway in diabetes induced cardiac hypertrophy. *Mol Cell Biochem*. 2016;417:191-203. [DOI PubMed](#)
110. Singh GB, Raut SK, Khanna S, et al. MicroRNA-200c modulates DUSP-1 expression in diabetes-induced cardiac hypertrophy. *Mol Cell Biochem*. 2017;424:1-11. [DOI](#)
111. Huang XH, Li JL, Li XY, et al. miR-208a in cardiac hypertrophy and remodeling. *Front Cardiovasc Med*. 2021;8:773314. [DOI PubMed PMC](#)
112. Wang X, Gu H, Huang W, et al. Hsp20-mediated activation of exosome biogenesis in cardiomyocytes improves cardiac function and angiogenesis in diabetic mice. *Diabetes*. 2016;65:3111-28. [DOI PubMed PMC](#)
113. Midan HM, Wasfey EF, Doghish AS, Kamal MM, Kassem DH. Harnessing exosomal long non-coding RNAs as a new frontier for molecular diagnostics and therapeutics in diabetes mellitus. *Cell Commun Signal*. 2026;24:215. [DOI PubMed PMC](#)
114. Jiao YR, Chen KX, Tang X, et al. Exosomes derived from mesenchymal stem cells in diabetes and diabetic complications. *Cell Death Dis*. 2024;15:271. [DOI PubMed PMC](#)
115. Pan W, Li S, Li K, Zhou P. Mesenchymal stem cells and extracellular vesicles: therapeutic potential in organ transplantation. *Stem Cells Int*. 2024;2024:2043550. [DOI PubMed PMC](#)

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116. Yin X, Wei Y, Liu Y, et al. Reparative effects of VCAM-1 high-performance MSC-derived exosomes on aged diabetic cardiomyocyte injury: a focus on ferroptosis suppression. *Apoptosis*. 2026;31:9. DOI PubMed
117. Gao S, Dong Y, Yan C, Yu T, Cao H. The role of exosomes and exosomal microRNA in diabetic cardiomyopathy. *Front Endocrinol*. 2023;14:1327495. DOI PubMed PMC
118. Rayat Pisheh H, Sani M. Mesenchymal stem cells derived exosomes: a new era in cardiac regeneration. *Stem Cell Res Ther*. 2025;16:16. DOI PubMed PMC
119. Zhang Y, Zhang YY, Li TT, et al. Ablation of interleukin-17 alleviated cardiac interstitial fibrosis and improved cardiac function via inhibiting long non-coding RNA-AK081284 in diabetic mice. *J Mol Cell Cardiol*. 2018;115:64-72. DOI PubMed
120. Zhang Y, Zhu Z, Wang T, Dong Y, Fan Y, Sun D. TGF- β 1-containing exosomes from cardiac microvascular endothelial cells mediate cardiac fibroblast activation under high glucose conditions. *Biochem Cell Biol*. 2021;99:693-9. DOI PubMed
121. Zhang Y, Zhang L, Li P, et al. Extracellular vesicles from adipose-derived stem cell alleviate diabetic cardiomyopathy by regulating Chit1/NLRP3/Caspase-1-Mediated pyroptosis. *Int Immunopharmacol*. 2025;146:113860. DOI PubMed
122. Bernardo BC, Yildiz GS, Kiriazis H, et al. In vivo inhibition of miR-34a modestly limits cardiac enlargement and fibrosis in a mouse model with established type 1 diabetes-induced cardiomyopathy, but does not improve diastolic function. *Cells*. 2022;11:3117. DOI PubMed PMC
123. Rawal S, Munasinghe PE, Nagesh PT, et al. Down-regulation of miR-15a/b accelerates fibrotic remodelling in the Type 2 diabetic human and mouse heart. *Clin Sci*. 2017;131:847-63. DOI PubMed
124. Chen S, Puthanveetil P, Feng B, Matkovich SJ, Dorn GW 2nd, Chakrabarti S. Cardiac miR-133a overexpression prevents early cardiac fibrosis in diabetes. *J Cell Mol Med*. 2014;18:415-21. DOI PubMed PMC
125. Zhang Y, Wang JH, Zhang YY, et al. Deletion of interleukin-6 alleviated interstitial fibrosis in streptozotocin-induced diabetic cardiomyopathy of mice through affecting TGF β 1 and miR-29 pathways. *Sci Rep*. 2016;6:23010. DOI PubMed PMC
126. Ren L, Chen X, Nie B, Qu H, Ju J, Bai Y. Ranolazine inhibits pyroptosis via regulation of miR-135b in the treatment of diabetic cardiac fibrosis. *Front Mol Biosci*. 2022;9:806966. DOI PubMed PMC
127. Wang W, Zhang S, Xu L, et al. Involvement of circHIPK3 in the pathogenesis of diabetic cardiomyopathy in mice. *Diabetologia*. 2021;64:681-92. DOI PubMed
128. Ding H, Yao J, Xie H, et al. MicroRNA-195-5p downregulation inhibits endothelial mesenchymal transition and myocardial fibrosis in diabetic cardiomyopathy by targeting Smad7 and inhibiting transforming growth factor beta 1-Smads-Snail pathway. *Front Physiol*. 2021;12:709123. DOI PubMed PMC
129. Li Y, Du Y, Liu Y, et al. Cardiomyocyte-derived small extracellular vesicle: a new mechanism driving diabetic cardiac fibrosis and cardiomyopathy. *Theranostics*. 2024;14:5926-44. DOI PubMed PMC
130. Zhen J, Bai J, Liu J, Men H, Yu H. Ginsenoside RG1-induced mesenchymal stem cells alleviate diabetic cardiomyopathy through secreting exosomal circNOTCH1 to promote macrophage M2 polarization. *Phytother Res*. 2024;38:1745-60. DOI PubMed
131. Chaturvedi P, Kalani A, Medina I, Familtseva A, Tyagi SC. Cardiosome mediated regulation of MMP9 in diabetic heart: role of mir29b and mir455 in exercise. *J Cell Mol Med*. 2015;19:2153-61. DOI PubMed PMC
132. Lew JK, Pearson JT, Saw E, et al. Exercise regulates microRNAs to preserve coronary and cardiac function in the diabetic heart. *Circ Res*. 2020;127:1384-400. DOI PubMed
133. Zygmunciak P, Stróżna K, Błażowska O, Mrozikiewicz-Rakowska B. Extracellular vesicles in diabetic cardiomyopathy-state of the art and future perspectives. *Int J Mol Sci*. 2024;25:6117. DOI PubMed PMC
134. Aljizeeri A, Ahmed AI, Suliman I, Alfari MA, Elneama A, Al-Mallah MH. Incremental prognostic value of positron emission tomography-derived myocardial flow reserve in patients with and without diabetes mellitus. *Eur Heart J Cardiovasc Imaging*. 2023;24:563-71. DOI PubMed
135. Garcia NA, Ontoria-Oviedo I, González-King H, Diez-Juan A, Sepúlveda P. Glucose starvation in cardiomyocytes enhances exosome secretion and promotes angiogenesis in endothelial cells. *PLoS One*. 2015;10:e0138849. DOI PubMed PMC
136. Ding X, Bai G, Liu X, et al. Circulating exosomal miR-550a-5p/miR-665 identify coronary microvascular dysfunction and drive endothelial-myocyte crosstalk in type 2 diabetes. *Front Cell Dev Biol*. 2026;14:1744708. DOI PubMed PMC
137. Garg R, Rao AD, Baimas-George M, et al. Mineralocorticoid receptor blockade improves coronary microvascular function in individuals with type 2 diabetes. *Diabetes*. 2015;64:236-42. DOI PubMed PMC
138. Thomou T, Mori MA, Dreyfuss JM, et al. Adipose-derived circulating miRNAs regulate gene expression in other tissues. *Nature*. 2017;542:450-5. DOI PubMed PMC
139. Whitham M, Parker BL, Friedrichsen M, et al. Extracellular vesicles provide a means for tissue crosstalk during exercise. *Cell Metab*. 2018;27:237-51.e4. DOI PubMed
140. Sljukic A, Green Jenkinson J, Niksic A, Prior N, Huch M. Advances in liver and pancreas organoids: how far we have come and where we go next. *Nat Rev Gastroenterol Hepatol*. 2026;23:44-64. DOI PubMed

141. Zhang Z, Zhu D, Liu C, et al. Small extracellular vesicle external surface adiponectin-mediated adipocytes/cardiomyocytes communication in diabetic ischemic heart failure. *Circulation*. 2026;Epub ahead of print. [DOI PubMed PMC](#)
142. Ji H, Cao T, Tan Z, et al. Adipocyte extracellular vesicle mitochondrial cargo is linked to cardiomyocyte dysfunction in type 2 diabetes-related heart failure with preserved ejection fraction. *Free Radic Biol Med*. 2026;244:435-51. [DOI PubMed](#)
143. Chen X, Chen S, Pang J, et al. Hepatic steatosis aggravates atherosclerosis via small extracellular vesicle-mediated inhibition of cellular cholesterol efflux. *J Hepatol*. 2023;79:1491-501. [DOI PubMed](#)
144. Jing Y, Cai Y, Li Q, et al. Empagliflozin-pretreated BMSC exosomes attenuate myocardial ischemia-reperfusion injury by enhancing atad3a/pink1-dependent mitophagy. *Stem Cell Res Ther*. 2025;16:595. [DOI PubMed PMC](#)
145. Chae CW, Choi G, Yoon T, Kwon YW. Exosome-based therapy in cardiovascular diseases: a new frontier in cardiovascular disease treatment. *Korean Circ J*. 2025;55:461-80. [DOI PubMed PMC](#)
146. Vukelić I, Sefedini A, Detel D, et al. Exosomal microRNAs as theranostic tools in type 2 diabetes and its complications: mechanistic insights and clinical implications. *Diabetol Metab Syndr*. 2026;18:79. [DOI PubMed PMC](#)

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