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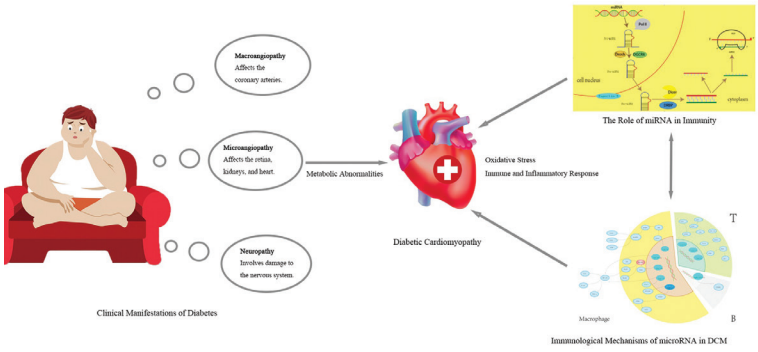
REVIEW ARTICLE

MicroRNAs Have an Immunomodulatory Role in Diabetes Mellitus and Diabetic Cardiomyopathy

Graphical Abstract



Highlights

- The clinical manifestations of diabetes encompass a wide range of symptoms and complications. Microvascular disease affects the coronary arteries, retina, kidneys, and heart, highlighting its systemic nature.
- Immune and inflammatory responses play a critical role in the pathogenesis of diabetes-related conditions.
- Metabolic abnormalities and oxidative stress contribute to the progression of diabetes-related complications.
- Diabetic cardiomyopathy (DCM) is a significant cardiovascular complication of diabetes.
- Immunological mechanisms involving microRNA are crucial in the development and progression of DCM.

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In Brief

Diabetic cardiomyopathy is a complication of diabetes. This article primarily discusses how microRNAs contribute to the development of diabetes and diabetic cardiomyopathy through their immunological effects throughout the body.

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MicroRNAs Have an Immunomodulatory Role in Diabetes Mellitus and Diabetic Cardiomyopathy

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Abstract

Diabetic cardiomyopathy (DCM), an independent diabetes complication, is characterized by abnormalities in myocardial structure, function, and metabolism, including diminished myocardial contractility, myocardial hypertrophy, and fibrosis. Factors such as hyperglycemia, metabolic disorders, microangiopathy, inflammation, oxidative stress, and insulin resistance have been found to play important roles in DCM pathophysiology. Recent research has shown that miRNAs are involved in processes such as myocardial cell proliferation, differentiation, and metastasis, and promote the progression of DCM. Despite these insights, the regulatory effects of miRNAs on immune function in DCM remain inadequately explored. This review synthesizes current advancements in understanding miRNA-mediated immune regulation in DCM. We highlight the need for further research to elucidate the complex interactions between miRNAs and immune pathways in DCM, which might reveal novel therapeutic targets to mitigate this debilitating condition. Targeted regulation of B cells, macrophages, and T cells through immune-associated miRNAs in DCM might open new avenues for therapeutic intervention. Developing efficient delivery systems for miRNA-based therapies might ensure targeted delivery and enhance stability. Additionally, combining existing hypoglycemic drugs with targeted therapies might produce anti-inflammatory and anti-fibrotic effects, thereby improving therapeutic outcomes.

Keywords: Diabetic cardiomyopathy; MicroRNAs; Diabetes mellitus; Immune; Inflammation

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Introduction

Epidemiology of Diabetes Mellitus

Diabetes mellitus (DM), a frequently occurring metabolic disease characterized by chronic hyperglycemia, poses a substantial global public health challenge. Insufficient insulin secretion and/or utilization resulting from multiple underlying factors contribute to the development of DM. According to diabetes epidemiology statistics, the estimated number of people with hyperglycemia in 2021 was 537

million, representing an increase of 74 million individuals since 2019 [1]. Furthermore, on the basis of past trends, more than 780 million individuals have been projected to be affected by DM by the year 2045 worldwide [2]. The etiology, pathophysiology, and clinical manifestations of the main types of diabetes – type 1 DM (T1DM), accounting for approximately 10% of cases, and type 2 DM (T2DM), accounting for approximately 90% of cases – are now well understood [3]. A small percentage of DM cases encompass gestational diabetes and other specific types of diabetes [4]. T1DM is characterized by absolute insulin deficiency resulting from humoral and cellular immune-mediated or idiopathic destruction of pancreatic islet cells, presenting as necrosis and apoptosis of beta-islet cells [5]. In contrast, T2DM is a heterogeneous disease involving insulin resistance and progressive insulin insufficiency attributed to the dysfunction and decompensation of β-islet cells, and influenced by both genetic and environmental factors [6, 7]. Specific types of diabetes are characterized by hyperglycemia with relatively clear etiology, including genetic defects in β-islet cell function such as maturity-onset diabetes of the young (MODY) and mitochondrial gene mutation diabetes, as well as diabetes resulting from pancreatic exocrine disorders, endocrine diseases, drug- or chemical-induced diabetes, infections, and less common immune-mediated forms, such as type 1B diabetes (idiopathic type 1 diabetes) and latent autoimmune diabetes in adults (LADA) [8].

Clinical Manifestations of DM

DM commonly presents with metabolic disorders, clinically described as a pattern of "three more and one less," comprising increased thirst, hunger, and urination, together with unintentional weight loss [9]. Different types of DM exhibit distinct clinical manifestations. Patients with T1DM are often adolescents experiencing acute onset and pronounced symptoms that predispose them to diabetic ketoacidosis (DKA) [10]. In contrast, patients with T2DM are typically adults with insidious onset, mild symptoms, and a low incidence of DKA [11]. Prolonged and chronic hyperglycemia leads to metabolic dysfunction, inflammation, abnormal coagulation function, and various pathological processes culminating in cellular damage. Chronic complications of DM encompass microangiopathy affecting the retina, kidneys, and myocardium; macroangiopathy affecting the coronary arteries; and neuropathy [12]. Notably, the risk of cardiovascular disease (CVD) is significantly elevated and is a leading cause of mortality in patients with DM [13]. A study in 5000 individuals followed for approximately 10 years has indicated that microangiopathy elevates mortality risk in T2DM [14]. Given the substantial detrimental effects of diabetic heart complications on the human body, research focusing on heart microangiopathy has gained attention.

Relationship Between DCM and DM

The concept of DCM was initially proposed by Rubler et al. in 1972, who delineated this condition as a diabetes complication independent of other etiologies, such as coronary atherosclerotic heart disease, valvular heart disease, and hypertension [15]. DCM is a severe cardiovascular complication of DM affecting a substantial proportion of patients with diabetes, particularly those with T2DM. DCM is characterized by widespread abnormalities in myocardial structure, function, and metabolism, and affects approximately 12% of patients with T2DM [16]. The pathological features of DCM include diminished myocardial contractility, myocardial hypertrophy and fibrosis, typically induced by prolonged hyperglycemia and dyslipidemia [17]. Hyperglycemia and dyslipidemia lead to oxidative stress, chronic inflammation, microangiopathy, and mitochondrial dysfunction [18]. These physiological changes subsequently trigger cardiomyocyte apoptosis and damage, thereby impairing cardiac function [17]. Initially, in a hyperglycemic environment, the immune and inflammatory systems are abnormally activated, and a local inflammatory response may cause the development of myocardial disease. Subsequently, the inflammatory response can further trigger inflammation and damage in cardiac cells by activating immune cells to release inflammatory mediators. Inflammation stimulates collagen synthesis, but excessive collagen production in DCM leads to excessive collagen deposition and myocardial fibrosis [19, 20]. Subsequently, impaired cardiomyocyte proliferation further hinders effective repair of fibrotic myocardial regions [21]. Excessive deposition of collagen fibers in

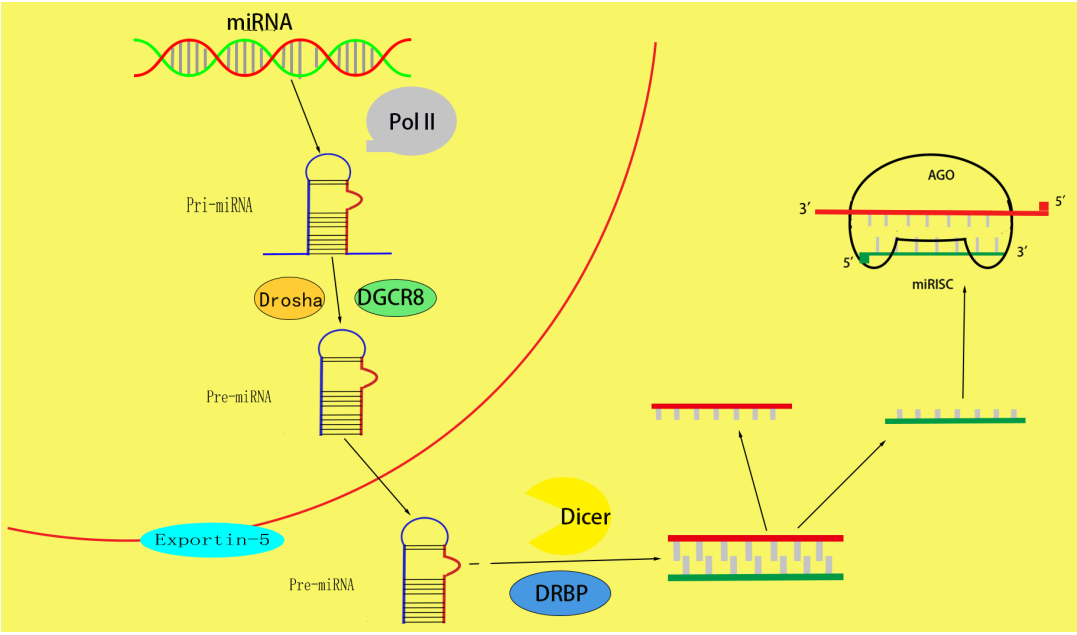

Figure 1 After Transcription, the pri-miRNA is Processed by Enzymes Such as Double-stranded RNA-specific Endoribonuclease (DROSHA) and DiGeorge Syndrome Critical Region 8 (DGCR8), Thus Resulting in the Formation of a Precursor miRNA (pre-miRNA).
The pre-miRNA is then transported into the cytoplasm and further processed by the enzyme DICER into mature miRNAs. These mature miRNAs bind the RNA-induced silencing complex (RISC) and influence gene expression by binding target mRNAs and inhibiting their translation. This class of highly conserved RNA molecules has important biological functions. miRNAs play key roles in post-transcriptional gene regulation in both animals and plants, exerting major effects on various biological processes and contributing to the complex regulatory networks within cells. The precise regulation of miRNA-mediated gene silencing allows for fine-tuning of protein synthesis in different cell types and under different environmental conditions. The ability of miRNAs to regulate gene expression is determined by various factors, including the specific binding between miRNAs and target mRNAs, the location of binding, and the phosphorylation status of AGO proteins in the RISC complex. DRBP, double-stranded RNA binding protein.

myocardial tissue results in stiffening, decreased myocardial muscle contractility, and ultimately structural and functional abnormalities in the myocardium [22]. Diabetes directly affects the three major metabolic pathways of glucose metabolism, lipid metabolism, and protein metabolism. Hyperglycemia primarily affects glucose metabolism and can lead to mitochondrial dysfunction, thus disrupting energy production and the metabolic balance within cardiac muscle cells, and ultimately resulting in cellular damage and apoptosis [23]. Oxidative stress in diabetes is also a major factor in the development of DCM [20]. Reactive oxygen species (ROS) play crucial roles in promoting inflammation, myocardial hypertrophy, and fibrosis, as well as inducing cell death in the diabetic myocardium. Because of the abundance of mitochondria within myocardial cells, the rate of ROS production is significantly elevated in these conditions [24]. Both T1DM and T2DM involve metabolic disorders, characterized by the body's decreased utilization of glucose, increased fat burning, and ketone body production [25, 26]. These factors can lead to myocardial interstitial fibrosis and cardiomyocyte hypertrophy, and ultimately affect heart function.

Physiological and Pathological Roles of MicroRNAs

MicroRNAs (miRNAs), first identified approximately 30 years ago in studies in nematodes, are approximately 22-nucleotide non-coding RNA molecules encoded by endogenous genes in eukaryotes. miRNAs are initially transcribed as primary miRNA (pri-miRNA) molecules and subsequently undergo a series of processing steps to generate mature miRNAs (Figure 1) [27]. Since the discovery

of miRNAs, the field has substantially expanded. Physiological studies have confirmed that miRNAs play critical roles in processes such as cell growth, tissue differentiation, cell proliferation, embryonic development, and cell apoptosis [28]. They play a crucial role in maintaining the normal physiological functions of the nervous system, immune system, cardiovascular system, and metabolic system. miRNAs perturbation or abnormal expression may lead to the onset of various diseases, including neurological disorders, immune system dysregulation, CVD, and metabolic disorders. Numerous diseases in the human body are closely associated with miRNAs, including cancer, vascular diseases, heart diseases, osteocyte differentiation, metabolic diseases, and neuropathic diseases [29–32]. For the cardiac diseases discussed herein, miRNAs have recently been identified as sensitive and specific biomarkers for the diagnosis of heart conditions, particularly coronary artery disease, and therefore may have substantial diagnostic value in clinical practice [33–35].

Aberrant miRNA Expression Leading to Disease Onset

The roles of miRNAs in tumor initiation and progression have garnered substantial attention. Some miRNAs have been recognized as either tumor suppressor genes or promoter genes, and their abnormal expression has been found to regulate important tumor cell properties, such as proliferation, apoptosis, invasion, and metastasis. The study of miRNAs has led to targeted therapy breakthroughs in cancer and has shown considerable promise in the treatment of various other medical conditions. Additionally, miRNAs have major roles in neuromodulation by regulating protein expression and modulating synaptic plasticity, thus affecting the central nervous system's development and physiological functions. Dysregulation of specific miRNAs is associated with neurological disorders such as Parkinson's disease, Alzheimer's disease, and alcohol use disorder [36–38]. Additionally, the dysregulation of specific miRNAs is closely associated with metabolic diseases and CVD. Abnormal expression of miRNAs has pathological roles in the development of metabolic diseases. For instance, miR-33, which is responsible for regulating lipid metabolism, has been associated with metabolic disorders such as atherosclerosis and fatty liver [39]. Similarly, miR-155 has been associated with CVD, including cardiac fibrosis and heart failure. Moreover, miR-155 has been found to promote the formation of cardiac fibrosis by inducing the transformation of fibroblasts into myofibroblasts in mice [40]. In a cross-sectional case-control observational study, elevated levels of miR-155 have been identified in patients with coronary atherosclerosis, thus confirming that miR-155 expression is dysregulated during chronic inflammation [41]. These findings indicate the potential utility of this miRNA as a precise inflammatory biomarker for atherosclerosis. Moreover, miR-126 is involved in the proliferation and angiogenesis of vascular endothelial cells, and its diminished expression is associated with the development of conditions such as coronary heart disease, myocardial infarction, and atherosclerosis [42]. MiR-126 promotes angiogenesis and enhances endothelial repair. Studies in patients with cardiomyopathy have shown that decreased miR-126 leads to severe pulmonary hypertension [43]. Overall, miRNAs exhibit a diverse range of pathological roles, and their dysregulation has been implicated in a wide array of diseases, such as tumors, neurological diseases, metabolic diseases, and CVD, thereby highlighting their potential as targets for therapeutic intervention and diagnostic biomarkers (Table 1).

Roles of miRNAs in Immunity

The immune system comprises a sophisticated network of immune cells and organs critical in safeguarding the body against diseases. This system consists primarily of immune cells such as lymphocytes and monocytes, as well as immune organs including lymphoid structures, the thymus, and the bone marrow. These components intricately collaborate in mounting effective immune responses against pathogens and maintaining homeostasis within the body. Lymphocytes originate from bone marrow pluripotent stem cells and are categorized into various subsets according to their distinct functions and surface markers. These subsets include helper T cells (Th1, Th2, Th17), cytotoxic T cells, regulatory T cells (Treg), and memory T cells. In

Table 1 Roles and Mechanisms of miRNAs in DM and DCM.

miRNA	Function/Role	Mechanism	References
miR-21	Promotes pancreatic β cell apoptosis; reverses insulin resistance	Overexpression promotes pancreatic β cell apoptosis, but can reverse high glucose and high insulin induced insulin resistance in 3T3-L1 adipocytes	[44]
miR-375	Regulates immune cell function and inflammation	Modulates the PI3K-AKT, MAPK, and mTOR signaling pathways, thereby activating T lymphocytes and cytokine production, and exacerbating diabetes progression	[45]
miR-4431	Leads to impaired glucose tolerance, decreased insulin sensitivity, and altered lipid metabolism	Suppresses TRIP10 and PRKD1 expression, thereby affecting glucose metabolism and energy regulation	[46]
Non-specific miRNAs	Affect endothelial cells and fibroblast cells, thereby disrupting vascular endothelium and neovascularization	Affects functions of large blood vessels and microvessels, thereby leading to vascular complications	[47]
miR-155	Promotes cardiac inflammatory responses in patients with DCM	Suppresses SHIP1, thereby enhancing PI3K-Akt pathway activation and increasing pro-inflammatory cytokines; targets TAB2 and TAK1, thereby activating the NF-κB pathway	[48–50]
miR-146a	Inhibits immune cell activation and inflammatory mediator production	Targets signaling pathways involved in immune cell activation; inhibits NF-κB activation, thus decreasing pro-inflammatory cytokines and chemokines; influences T cell and B cell function and differentiation; modulates T cell receptor and cytokine signaling pathways; targets IRAK1 and subsequently attenuates inflammatory responses; regulates migration and infiltration of immune cells by downregulating CXCR4 and CCL2	[44, 51–53]

animal models, miRNA expression is up- or down-regulated, or ectopic expression is observed, in response to allergen stimulation. This regulation is crucial for maintaining the normal function of B and T lymphocytes as well as dendritic cells [54, 55]. The loss of miR17-92 leads to developmental arrest of B lymphocytes by increasing the apoptotic protein Bim [56]. MiR-155 has been shown to enhance the maturation and functionality of dendritic cells, thereby facilitating the presentation of foreign antigens to T cells and subsequently initiating immune responses [57]. Furthermore, the ectopic expression of miRNAs can result in alterations in the numbers of CD4 and CD8 cells. miRNA-mediated gene silencing is a mechanism through which Tregs inhibit inflammatory diseases [58]. miRNAs are involved in regulating the differentiation and function of Tregs, thus exerting direct and indirect control over immune responses. For example, miR-146a has been shown to enhance the immunosuppressive function of Tregs by inhibiting the signaling pathways of interleukin-6 (IL-6) and interleukin-1β (IL-1β). In contrast, miR-155 promotes the proliferation and maintenance of Tregs and plays major roles in autoimmune diseases [59]. Additionally, miRNAs finely tune the immune regulation mediated by Tregs by targeting key genes and signaling pathways in the Treg biological processes. For instance, miR-10a suppresses the differentiation of Th1 cells and promotes the generation of Tregs by targeting Bcl-6 gene expression [60]. Furthermore, miR-21 has been found to enhance the suppressive function of Tregs by inhibiting the gene Programmed Cell Death 4 (PDCD4) [61].

Roles of miRNAs in Diabetes

miRNAs play critical roles in diabetes through various pathological mechanisms, primarily through

participation in pancreatic β-cell proliferation and apoptosis, modulation of the immune response and inflammation, and regulation of insulin resistance. miRNAs contribute to β cell destruction through distinct mechanisms, thereby promoting the development of various complications of diabetes [62]. For example, miR-21 reverses high glucose and high insulin induced insulin resistance in 3T3-L1 adipocytes, but overexpression of miR-21 promotes the apoptosis of pancreatic β cells [63]. miRNAs play critical roles in modulating diabetes progression by exerting regulatory effects on the immune response and inflammation. MiR-375 and miR-146a have been identified as key regulators of immune cell function and inflammation that influence the development and progression of diabetes. MiR-375 has been implicated in modulating the activation of critical signaling pathways such as phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt), mitogen-activated protein kinase (MAPK), and mammalian target of rapamycin (mTOR) [64]. Excessive activation of these pathways has been found to potentiate T lymphocyte activation and cytokine production, thus exacerbating the immune system's assault on islet cells and potentially amplifying the progression of DCM [65]. Furthermore, in inflamed states, miR-146a inhibits the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), thereby blocking the transmission of inflammatory signals. This inhibition decreases the release of inflammatory cytokines, decreases inflammation, and ultimately improves insulin sensitivity and insulin secretion [44]. miRNAs also exert effects on diabetes by targeting specific cell types involved in glucose metabolism and energy regulation. For example, enhanced miR-4431 expression suppresses thyroid hormone receptor interactor 10 (TRIP10) and protein kinase D1 (PRKD1), and ultimately leads to impaired glucose tolerance, decreased insulin sensitivity, and altered lipid metabolism [45]. In addition, miRNAs influence endothelial cells, fibroblasts, and numerous other cell types, which in turn can disrupt the vascular endothelium, impair neovascularization, and affect the function of both large blood vessels and microvessels [46, 66]. Hence, miRNAs exert diverse roles in diabetes through the intricate mechanisms and pathways described above.

MicroRNAs in DCM

In the context of DCM, miRNAs play crucial roles in the immune response by modulating the phenotype and activity of inflammatory cells. Specifically, certain miRNAs regulate the functions of macrophages, T cells, and B cells, thereby influencing their ability to secrete cytokines and chemokines. This regulation is critical in orchestrating the inflammatory response and immune modulation (Figure 2).

Hyperglycemia, metabolic abnormalities, and oxidative stress activate myocardial tissue inflammation and promote the release more inflammatory factors and chemokines, which further aggravate the inflammatory response and promote the development of DCM. In early stages of the inflammatory response, the innate immune system is activated. Innate immune cells such as macrophages, dendritic cells, neutrophils, and natural killer cells recognize pathogen-associated molecular patterns or damage-associated molecular patterns through pattern recognition receptors (such as TLRs) and initiate an inflammatory response. With the development of inflammation, the adaptive immune system gradually intervenes. B and T lymphocytes are the main effector cells of adaptive immunity. miRNAs play important immunomodulatory roles in the inflammatory progression of DCM. For example, miR-155, a crucial inflammatory regulatory miRNA, is upregulated and associated with cardiac inflammatory responses in patients with DCM [47]. MiR-155 suppresses the expression of molecules such as Src homology 2 domain-containing inositol 5-phosphatase 1 (SHIP1), which negatively regulates pro-inflammatory pathways such as the PI3K-Akt pathway. By downregulating SHIP1, miR-155 enhances the activation of the PI3K-Akt pathway, and consequently increases the production of pro-inflammatory cytokines and mediators. Moreover, by targeting SHIP1, miR-155 stimulates the PI3K-Akt signaling activation and increases inflammation [48]. Additionally, miR-155 targets TAB2 and TAK1, thereby facilitating activation of the NF-κB signaling pathway and exacerbating inflammatory processes [49]. MiR-510-3p targets vascular endothelial growth factor A (VEGFA), thereby affecting the PI3K/AKT/eNOS/mTOR signaling axis, and leading to vascular dysfunction.

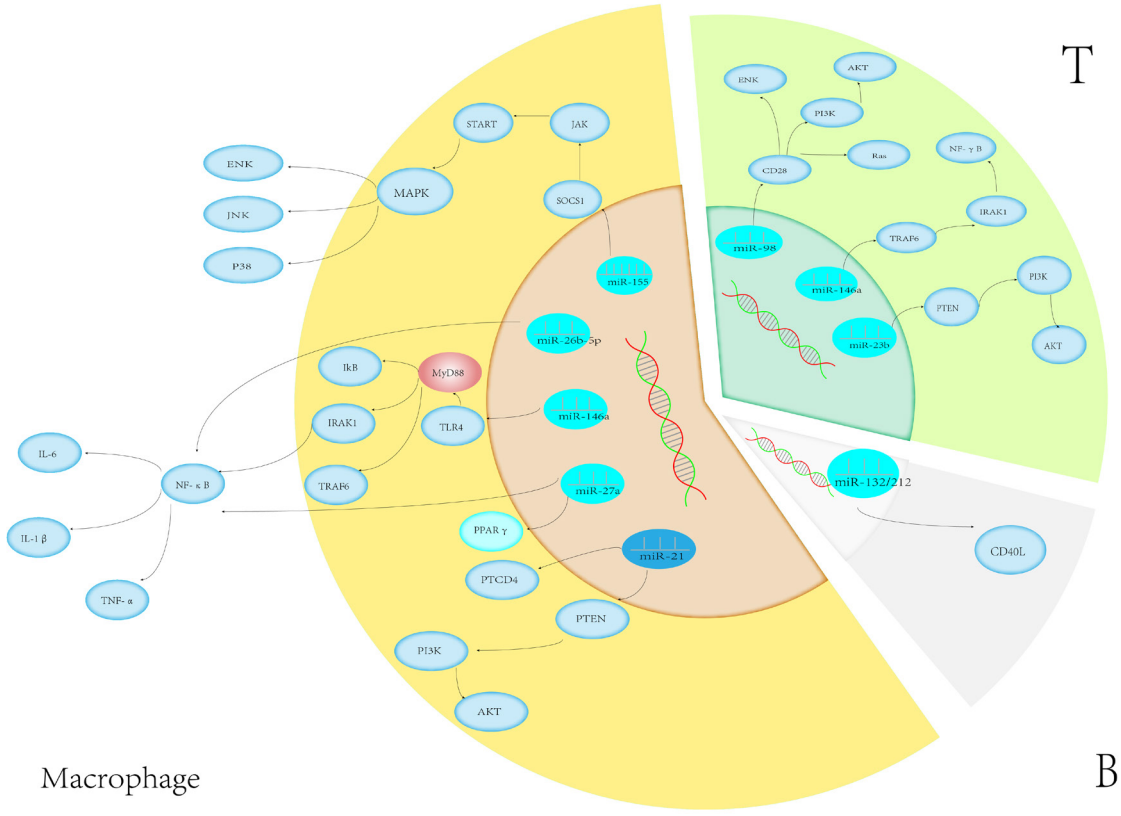

Figure 2 MicroRNAs promote the pathological progression of diabetic cardiomyopathy by differentially regulating key signaling pathways (e.g., NF-κB, PI3K/AKT) in macrophages, B lymphocytes, and T lymphocytes, leading to dysregulated secretion of inflammatory cytokines such as IL-6 and TNF-α. This schematic diagram highlights the representative miRNA-mediated signaling networks in these immune cells.

The administration of anti-miR-510-3p significantly ameliorates vascular damage induced by inflammation [67]. miRNAs also modulate the function of immune cells. For instance, upregulation of miR-146a, an important immunomodulatory miRNA, inhibits immune cell activation and the production of inflammatory mediators [51]. MiR-146 suppresses the activation of these cells by targeting signaling pathways involved in their activation. By inhibiting NF-κB activation, miR-146 decreases the expression of pro-inflammatory cytokines and chemokines, thereby dampening the inflammatory response [68]. Moreover, miR-146 influences the differentiation and function of adaptive immune cells, including T cells and B cells. This miRNA plays a role in regulating T cell activation and differentiation by targeting molecules involved in T cell receptor signaling and cytokine signaling pathways. Additionally, miR-146 modulates the function of Tregs, which play critical roles in maintaining immune homeostasis and suppressing excessive inflammation [69]. Furthermore, miR-146 has been implicated in the regulation of inflammatory signaling pathways within immune cells themselves. This miRNA targets molecules involved in positive feedback loops of inflammatory signaling, thereby dampening prolonged or excessive immune activation. For example, miR-146 targets interleukin-1 receptor-associated kinase 1 (IRAK1), a key mediator of Toll-like receptor signaling, and subsequently leads to the attenuation of inflammatory responses. miRNAs also regulate the migration and infiltration of immune cells. MiR-146a inhibits immune cell migration and infiltration by downregulating the expression of chemokines such as C-X-C chemokine receptor type 4 (CXCR4) and C-C motif chemokine ligand 2 (CCL2) [52, 53]. The sections below describe the macrophage innate immunity and adaptive immunity of T cells and B cells (Table 2).

Table 2 Functions and Mechanisms of MicroRNAs in Immune Cells.

miRNA	Function/Role	Mechanism	References
miR-155	Promotes activation of the M1 macrophage phenotype, thereby leading to increased release of inflammatory mediators; enhances inflammatory responses; promotes Th1 cell differentiation; regulates Treg cell function	Upregulates M1 macrophage activation, thereby enhancing inflammatory mediator release; inhibits SOCS1 and SHIP1; promotes IL-12–mediated Th1 differentiation and inflammatory signaling pathways; regulates Treg cell quantity and functionality	[50, 70–72]
miR-124	Inhibits activation of the M1 macrophage phenotype; facilitates transformation to the M2 phenotype, thereby decreasing inflammatory responses	Inhibits M1 macrophage activation; aids in macrophage transformation to M2 phenotype, thereby decreasing inflammation	[73]
miR-223	Inhibits activation of the M1 macrophage phenotype; facilitates transformation to the M2 phenotype, thereby decreasing inflammatory responses	Inhibits M1 macrophage activation; aids in macrophage transformation to M2 phenotype, thereby decreasing inflammation	[73]
miR-182	Inhibits polarization of M1 macrophages to M2 macrophages, thereby decreasing myocardial inflammation	Isolated from exosomes of C57BL/6 mice; inhibits M1 macrophage polarization, thereby decreasing myocardial inflammation	[74]
miR-17-92	Regulates T cell function and proliferation	Directly inhibits TSC1 and TSC2; activates the mTOR pathway, thereby promoting T cell metabolism and proliferation	[75, 76]
miR-19a/b	Promotes T cell metabolism and proliferation	Part of the miR-17-92 cluster; directly inhibits TSC1 and TSC2; activates the mTOR pathway	[76]
miR-29	Promotes Th1 cell differentiation and function, thereby leading to cardiac fibrosis and ventricular remodeling	Targets T-bet and IFN-γ expression; induces myocardial cells to produce the pro-fibrotic cytokine TGF-β1	[77]
miR-146a	Suppresses inflammatory responses; protects myocardial integrity	Inhibits the NF-κB signaling pathway; decreases the release of inflammatory mediators; regulates Treg cell quantity and functionality	[53, 75]

Macrophage Polarization Imbalance

Monocytes are a crucial subset of immune cells essential for orchestrating immune responses against pathogens and maintaining tissue homeostasis. They can differentiate into diverse immune cell lineages including macrophages and dendritic cells, and consequently substantially contribute to all phases of immune responses. Macrophages function primarily in phagocytosis, clearing pathogens, cellular debris, and foreign substances from the body. Additionally, they play essential roles in immune regulation and the initiation of inflammatory cascades [78]. The two main types of macrophages, M1 and M2, have polarization features that change structurally and functionally depending on the environment [78]. The main polarization states of macrophages are classically activated (M1) and alternatively activated (M2). M1 macrophages are primarily pro-inflammatory, whereas M2 macrophages are mainly anti-inflammatory. In the presence of hyperglycemia, expression of M1 macrophage markers is heightened, whereas expression of M2 macrophage markers is diminished in mice injected with STZ [79]. Moreover, macrophages engage in signaling resulting in restricted cardiac relaxation and increased myocardial interstitial fibrosis [80]. In mouse models of obesity and diabetes (ob/ob mice and db/db mice), activated macrophage aggregates around adipocytes have been observed to form structures known as coronal crown-like structures [81]. These structures activate fibroblasts and promote collagen synthesis, thus suggesting that macrophages influence myocardial fibrosis, a potential contributing factor to DCM [81]. miRNAs influence immune cell phenotype, activation status, and function. For example, miR-155 promotes activation of the M1 phenotype of macrophages, thus leading to increased release of inflammatory mediators [82]. Moreover, miR-124

and miR-223 inhibit activation of the M1 phenotype, facilitate the transformation of macrophages into the M2 phenotype, and decrease inflammatory responses [83]. Furthermore, miR-182 isolated from exosomes of C57BL/6 mice has been found to inhibit the polarization of M1 macrophages into M2 macrophages and to decrease myocardial inflammation [70]. In summary, these findings indicate that microRNA-mediated targeting and regulation of macrophage polarization imbalance, along with an increased proportion of M1 macrophages, contribute to the inflammatory processes that might lead to the development of DCM and cardiac dysfunction.

T Cell Differentiation

T cells have been implicated in the pathogenesis of DCM through modulation of inflammatory and immune responses, among other mechanisms. T cells are categorized into pro-inflammatory and anti-inflammatory subsets, according to their functions and secretion of cytokines. Pro-inflammatory subsets participate primarily in promoting inflammatory responses and immune reactions, thereby exacerbating tissue damage and inflammation. Some pro-inflammatory T cells are known as Th1 cells, which secrete pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor (TNF). Th17 cells are a subset of pro-inflammatory T cells that produce cytokines such as IL-17, and contribute to inflammatory responses and tissue damage. Moreover, anti-inflammatory subsets primarily inhibit inflammatory responses and immune reactions, thus regulating immune balance and mitigating tissue damage. Treg cells achieve suppression of inflammation and autoimmunity by producing inhibitory cytokines such as IL-10 and TGF-β, and directly suppress the activity of other immune cells. Various subtypes of T cells play distinct roles in immune responses. In the context of cardiac inflammation, Th1 and Th17 cells are particularly important pro-inflammatory subsets and are closely associated with CVD [73, 74]. In BALB/c mice, Th17 cells have been shown to cause myocardial inflammation and enhance the accumulation of monocytes [84]. However, Treg cells have been found to induce macrophage transformation into an M2 type, thereby decreasing inflammatory responses [85]. miRNAs in T cells regulate gene expression, thus influencing the functional, polarized states, and metabolic features of T cells, and regulating inflammation and autoimmunity. NF-κB is a crucial transcription factor implicated in modulating the expression of numerous genes encoding inflammatory factors. After activation, NF-κB stimulates the synthesis and secretion of inflammatory mediators such as IL-1β and TNF-α, thereby exacerbating the inflammatory response. MiR-146a inhibits NF-κB activation by targeting critical molecules within the NF-κB signaling cascade, including TRAF6 and IRAK1 [86]. Moreover, miR-155 has been discovered to play an important role in promoting Th1 polarization and regulating the inflammatory response [87]. Additionally, miR-155 boosts the activity of inflammatory signaling pathways by inhibiting negative regulators such as SOCS1 and Src homology 2 domain-containing inositol phosphatase 1 (SHIP1), thereby promoting inflammatory responses [75]. The miR-17-92 cluster has been shown to exert crucial effects on regulating T cell function and proliferation [71]. MiR-19a and miR-19b, members of the miR-17-92 cluster, promote T cell metabolism and proliferation by directly inhibiting the negative regulators TSC1 and TSC2 of mTORC1, thus activating the mTOR pathway, and facilitating T cell metabolism and proliferation [50]. MiR-29 promotes Th1 cell differentiation and function by targeting T-bet and IFN-γ expression. Th1 cells induce myocardial cells to produce the pro-fibrotic cytokine TGF-β1, which in turn heightens inflammatory and immune responses, contributes to interstitial fibrosis and ventricular remodeling, and ultimately fosters the development of DCM [72]. Treg cells decrease the inflammatory response by releasing inhibitory cytokines or directly interacting with other immune cells and inhibiting their activation and function, thereby decreasing the production of inflammatory factors [88]. As previously described, miR-146a, miR-155, miR-21, and various other miRNAs influence DCM progression by modulating Treg quantity and function, alongside other pertinent immune cells and pathways. These miRNAs play critical roles in orchestrating immunoregulatory responses. Extensive research has demonstrated that miR-146a, a well-characterized immunomodulatory microRNA, plays a pivotal role in myocardial protection through its potent

anti-inflammatory effects, primarily mediated by the suppression of NF-κB signaling pathway and subsequent inhibition of pro-inflammatory cytokine release [51]. Emerging evidence highlights the critical role of miR-155 in maintaining immune homeostasis through its regulation of Treg cell expansion and functional differentiation, thereby significantly influencing the pathological progression of DCM as a pivotal modulator of immune tolerance [76].

Overall, miRNAs have been shown to regulate immune responses and T cell functions by modulating gene expression, and influencing T cell polarization, metabolism, and proliferation. These miRNAs affect key signaling pathways such as the NF-κB and mTOR pathways, and consequently affect the balance of pro-inflammatory and anti-inflammatory signals. Thus, miRNAs might contribute to the development of DCM by regulating inflammatory processes, immune dysregulation, and cardiac remodeling.

B Cell-mediated Inflammation

B lymphocytes, also known as B cells, undergo development and maturation in the bone marrow and contribute to humoral immunity by producing antibodies. They play crucial roles in enhancing the body's immune response in B cells and regulating apoptotic pathways. In the hyperglycemic environment, B cells secrete pro-inflammatory cytokines (such as IL-6 and TNF-α), which further activate other immune cells (such as macrophages and T cells), thereby aggravating myocardial inflammation. This inflammatory microenvironment promotes myocardial fibrosis and remodeling, ultimately leading to impaired cardiac function [77]. Accumulating evidence suggests that B lymphocytes play a pivotal role in the pathogenesis of insulin resistance and the development of DCM. In animal studies, B cell inhibition using CD20 monoclonal antibodies has been shown to be effective in attenuating disease progression. Furthermore, in diabetic mouse models, elevated levels of IL-6 are strongly correlated with increased myocardial fibrosis and cardiac dysfunction. Myocardial inflammation and fibrosis in these mice are alleviated by the administration of an IL-6 inhibitor [89]. Clinical studies have shown that elevated TNF-α levels in patients with diabetes positively correlate with the degree of cardiac insufficiency and myocardial fibrosis. In experimental animal models, the administration of TNF-α inhibitors such as etanercept significantly decreases myocardial fibrosis and enhances cardiac function [90]. miRNAs play crucial roles in regulating B cell development [91]. The roles of miRNAs in DCM might involve effects on disease progression through the regulation of B cell function and the expression of related inflammatory factors. However, the specific underlying mechanisms require further investigation.

Conclusion

DCM is a serious complication in both T1DM and T2DM. The persistent hyperglycemic environment characteristic of diabetes leads to a cascade of metabolic disturbances and immune responses. In particular, hyperglycemia activates macrophages and B/T lymphocytes through various immune mechanisms and ultimately results in detrimental outcomes, such as ventricular fibrosis and a reduced left ventricular ejection fraction (LVEF). miRNAs have emerged as critical regulators in the pathogenesis of DCM. These small non-coding RNAs play major roles in controlling the macrophage inflammatory response by modulating M1/M2 macrophage polarization. M1 macrophages are generally pro-inflammatory, whereas M2 macrophages are associated with anti-inflammatory effects and tissue repair. Proper regulation of the M1/M2 ratio is crucial for maintaining cardiac homeostasis and preventing excessive inflammation and fibrosis. Moreover, miRNAs influence the inflammatory response by affecting the differentiation and maturation of T lymphocytes. T cell-mediated immune responses are integral to the inflammatory milieu in diabetic hearts. miRNAs modulate various signaling pathways and transcription factors involved in T cell activation, thereby influencing their roles in cardiac inflammation and remodeling. However, despite advances in understanding of the roles of miRNAs in macrophages and T cells, the specific regulatory roles of miRNAs in B lymphocyte responses to immune inflammation in the context of DCM remain largely unclear. B lymphocytes, known for their antibody production and antigen-presenting abilities, have complex interactions with miRNAs and might influence their behavior during diabetic inflammation. Investigating this area might

reveal novel regulatory mechanisms and therapeutic targets. Numerous miRNAs interact within the human body and collectively maintain homeostasis. However, imbalances in their ratios can lead to disease development. MiR-155 and miR-21 synergistically promote activation of the M1 macrophage phenotype, enhance inflammatory responses, facilitate Th1 cell differentiation, and further augment inflammation [92]. In contrast, miR-223 and miR-124 coordinately facilitate the conversion of M1 to M2 macrophages, thereby mitigating inflammatory responses [93]. Furthermore, different miRNAs with varying targets and pathways exhibit antagonistic effects in DCM. For example, whereas miR-155 enhances inflammatory responses and immune cell activation, miR-146a counteracts these effects by suppressing the NF-κB signaling pathway, thereby decreasing the release of inflammatory mediators. Recent studies have demonstrated that exosomes released from lipid-loaded HL-1 cardiomyocytes have elevated levels of miR-1 and miR-133a; these levels can serve as diagnostic tools for DCM in its subclinical stage [94, 95]. Additionally, miR-320 significantly inhibits the target genes IGF-1, Hsp20, and Ets2 in cardiac endothelial cells, thus preventing their migration; moreover, this miRNA is transferred via exosomes from lipid-loaded HL-1 cardiomyocytes. Therefore, miR-320 shows potential as a therapeutic target for DCM [96]. Given current gaps in knowledge, further research is necessary to elucidate the roles of miRNAs in B lymphocyte-mediated immune responses. Understanding these mechanisms might lead to innovative therapeutic strategies. Targeting B cell function through miRNA manipulation or B cell inhibition presents a promising avenue for the treatment or prevention of DCM. These strategies might help mitigate inflammation, decrease myocardial fibrosis, and improve cardiac function in patients with diabetes, thus offering new hope in the management of this debilitating condition. In conclusion, despite substantial progress in understanding the roles of miRNAs in macrophage and T cell responses, the exploration of miRNAs in B cell regulation remains an important frontier. Addressing this gap might aid in ameliorating DCM through enhancing comprehensive novel therapeutic approaches. miRNA-based therapies are currently emerging as a promising new area of focus. For example, miRNA mimics are used to enhance beneficial miRNAs, whereas inhibitors are used to suppress harmful miRNAs, with the aim of modulating miRNA levels effectively. Second, efficient delivery systems for miRNA-based therapeutics, including lipid nanoparticles, viral vectors, and polymeric nanoparticles, are being developed to achieve targeted delivery and stability [97]. Furthermore, using B-cell inhibitors such as rituximab or gene therapy to adjust levels of miRNA specifically affecting B cell functions, might decrease myocardial inflammation and fibrosis. Therefore, combination therapies that integrate current antidiabetic medications with miRNA-targeted treatments, alongside the use of anti-inflammatory and antifibrotic drugs, might offer pronounced therapeutic benefits. Future research should focus on a comprehensive elucidation of miRNA regulatory networks, particularly in B lymphocytes under hyperglycemic conditions [98]. Clinical studies are necessary to validate the efficacy and safety of miRNA mimics and inhibitors, along with advanced, safe delivery systems. Multi-omic approaches and collaborations among basic scientists, clinicians, and bioengineers will be crucial in developing highly targeted therapeutic modalities. As a promising frontier, the extensive exploration of miRNAs in DCM is likely to open new avenues for effective management and treatment strategies, and might potentially bring new hope to patients with diabetes with this severe cardiac condition. In exploring novel miRNA-based therapeutic strategies, several challenges must be addressed. First, the complexity and diversity of miRNA regulatory networks present a major obstacle. miRNAs are involved in the regulation of a wide array of gene expression within cells. This pleiotropy hinders determination of their precise functions under specific pathological conditions. Furthermore, miRNAs often have multiple targets, thus increasing the risk of off-target effects and potentially leading to unexpected biological outcomes. Therefore, a deep understanding of miRNA targets and pathway specificity is crucial for advancing the development of related therapies. Second, the tissue-specific expression of miRNAs poses another critical challenge. The significant variations in expression profiles of miRNAs among tissues present a major barrier to the development of miRNA therapies that are both efficient and precise. Although current delivery systems, such as lipid

nanoparticles and polymers, can enhance stability and bioavailability in vivo, achieving targeted delivery remains challenging. An urgent need exists for more advanced delivery technologies to improve therapeutic efficacy and safety. From a clinical research and translational perspective, miRNA therapies remain in an early stage. Most studies have been conducted in vitro or in animal models, and human clinical trial data are scarce. The long-term safety and efficacy of miRNA therapies require further validation, and potential immune reactions or adverse effects must be carefully monitored. Rigorous studies must be designed to evaluate the long-term effects of miRNA therapies on patients with diabetes and DCM to enhance clinical translation rates. Additionally, individual variability poses a major challenge in miRNA research. Patients with diabetes show considerable differences in genetic background, disease progression, and treatment response. Thus, personalized miRNA therapeutic strategies may be a viable solution, but their implementation will require substantial scientific and technical hurdles to be overcome. In conclusion, although miRNAs show tremendous potential in research on diabetes and DCM, researchers must overcome challenges associated with target specificity, delivery mechanisms, and clinical safety to achieve clinical application. Through multidisciplinary collaboration and the integration of bioinformatics and clinical practice, future research promises to advance miRNA therapies toward safe and effective precision medicine, and to offer new directions for the treatment of diabetes and its associated complications.

DCM is a serious complication in both T1DM and T2DM. The persistent hyperglycemic environment leads to metabolic disturbances and immune responses, which activate macrophages and B/T lymphocytes, and ultimately result in adverse outcomes such as ventricular fibrosis and reduced left ventricular ejection fraction. miRNAs play major roles as key regulators of the pathogenesis of DCM. miRNA-based therapies are becoming a research focus, and efforts are aimed at exploring and using miRNA mimics to enhance beneficial miRNAs or inhibitors to suppress harmful miRNAs, thereby effectively modulating miRNA levels. Future research should focus on the comprehensive elucidation of miRNA regulatory networks, advancing miRNA therapies toward safe and effective precision medicine, and providing new directions for the treatment of diabetes and its associated complications.

Author Contributions

L.Z. and Y.M. researched data for the article, substantially contributed to discussions of the content, and contributed to writing the article. X.X. and C.M. researched data for the article, discussed its content, wrote the manuscript, and reviewed/edited the manuscript before submission.

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Conflict of Interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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