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MicroRNAs in diabetes and heart failure

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Abstract

MicroRNAs (miRNAs) are short, non-coding RNA molecules that play a key role in regulating gene expression at the post-transcriptional level by inhibiting translation or degrading target mRNA. This article discusses their biogenesis, functions, and significance in the pathogenesis of diabetes and heart failure. miRNA dysregulation contributes to the development of pathophysiological mechanisms such as apoptosis, oxidative stress, and fibrosis, which negatively affect cardiac function and metabolism. miRNAs are also being explored as potential diagnostic biomarkers and therapeutic targets for both conditions. Understanding their mechanisms of action may contribute to developing innovative therapies and diagnostic strategies. (Gerontol Pol 2025; 33; 151-157) doi: 10.53139/GP.20253319

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Structure and Biogenesis of miRNAs

MicroRNAs (miRNAs) are a class of short, non-coding RNA molecules 19–24 nucleotides in length that function as regulators of gene expression at the post-transcriptional level. Since their discovery in 1993, miRNAs have been the subject of extensive research due to their involvement in numerous biological processes and diseases.

miRNA genes are transcribed primarily by RNA polymerase II, although some can also be transcribed by RNA polymerase III. The resulting primary miRNA transcripts (pri-miRNA) form a hairpin structure and undergo processing in the cell nucleus. The microprocessor complex, composed of the Drosha enzyme and the DGCR8 protein, converts pri-miRNA into pre-miRNA, a shorter precursor with a specific structure. Pre-miRNA is then exported to the cytoplasm by Exportin-5, where the enzyme Dicer further cleaves it, forming a double-stranded miRNA-miRNA* complex. The mature miRNA strand is incorporated into the RNA-induced silencing complex (RISC), enabling it to bind to target mRNAs and regulate their activity by translation inhibition or degradation [1].

Functions of miRNAs

1. **Translational Control** – miRNAs interact with target mRNAs by binding to their 3’ untranslated regions (3’ UTR), leading to a decrease in protein levels through translational repression or mRNA degradation [1].
2. **Regulatory Networks** – miRNAs participate in complex regulatory networks, controlling the expression of multiple genes simultaneously. Some miRNAs act in clusters, regulating interconnected biological processes such as the cell cycle, apoptosis, and inflammation [2].
3. **Non-canonical Functions** – Beyond their classical cytoplasmic action, some miRNAs can regulate gene transcription in the nucleus or interact directly with proteins [3].

miRNAs play a critical role in the pathogenesis of various diseases, including cancer, cardiovascular diseases, neurodegenerative disorders, and metabolic conditions. In these cases, changes in miRNA expression can lead to dysregulation of key cellular pathways. Due to their stability in biological fluids, miRNAs are being investigated as potential diagnostic and prognostic biomarkers [4].

miRNAs undergo modifications such as nucleotide editing, which alters their ability to bind target mRNAs. Such modifications can significantly impact miRNA function, allowing them to adapt to changing cellular or environmental conditions [5].

miRNAs serve as key regulators of biological processes, extending beyond conventional translational control. Their ability to act in diverse cellular contexts and their role in disease pathogenesis make miRNAs an important

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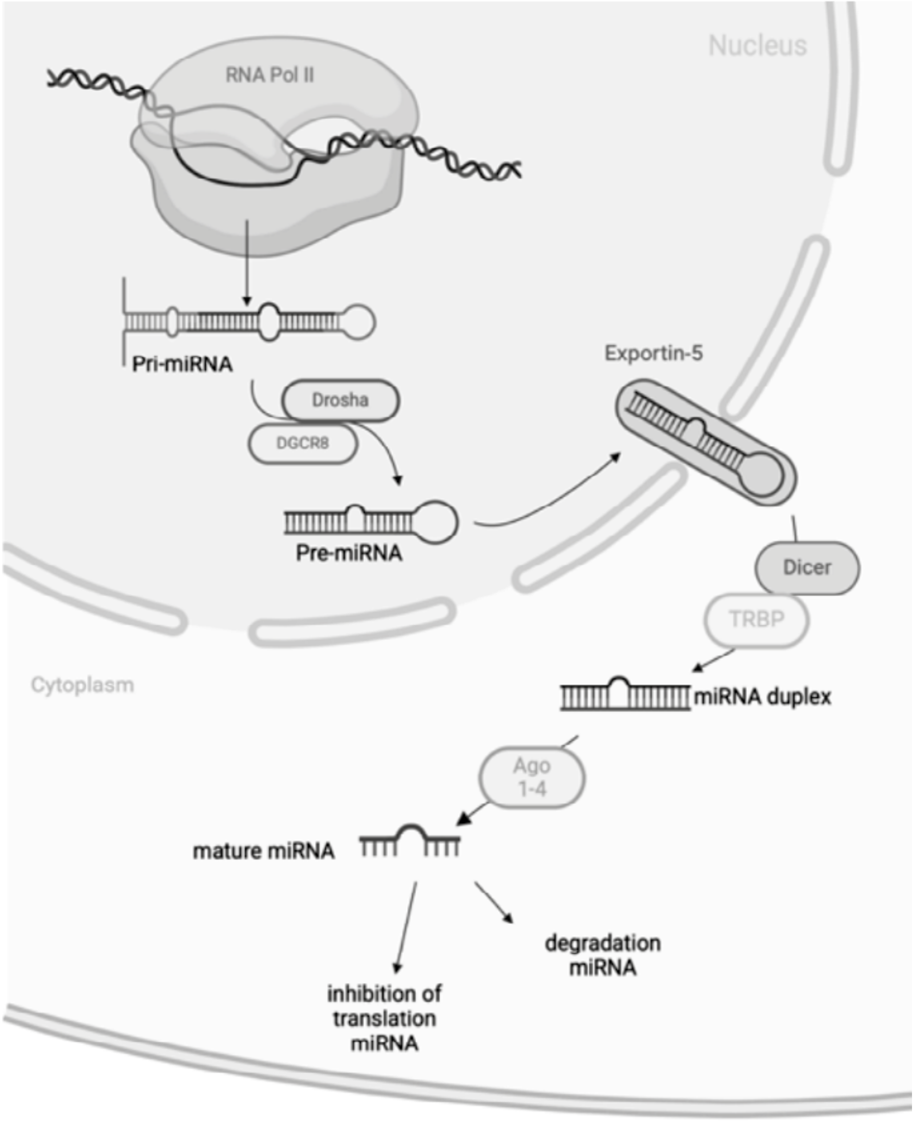

Figure 1. Schematic of biogenesis of miRNAs

focus of biomedical research. With growing knowledge of their mechanisms of action, miRNAs may become the foundation for innovative therapies and diagnostic tools [1-3].

Diabetes

Diabetes is a chronic metabolic disease characterized by persistent hyperglycemia resulting from impaired insulin secretion, cellular insulin resistance, or a combination of these factors. Chronic excess glucose in the blood leads to various pathophysiological changes, including oxidative stress, inflammation, and endothelial dysfunction. This condition results in long-term damage to multiple organs, including the eyes, kidneys, nerves, and cardiovascular system [6,7].

Type 1 diabetes results from the autoimmune destruction of pancreatic beta cells, leading to absolute insulin deficiency. Individuals with this type of diabetes often require insulin therapy [7].

Type 2 diabetes is characterized by insulin resistance and an inadequate compensatory insulin secretion response. It is the most common form of diabetes, accounting for approximately 90% of cases [7].

Diabetes is associated with multiple pathogenic processes, ranging from autoimmune beta-cell destruction to insulin resistance. Insulin dysfunction leads to disturbances in carbohydrate, lipid, and protein metabolism [6,7]. In type 2 diabetes, obesity, adipose tissue function, gut microbiota, and beta-cell activity are intensively studied as factors contributing to disease development [8].

Chronic hyperglycemia in diabetes leads to severe complications such as retinopathy, nephropathy, peripheral and autonomic neuropathy, and an increased risk of cardiovascular diseases [6, 7]. Diabetes is also associated with hypertension and lipoprotein metabolism disorders [7].

Role of miRNAs in Diabetes

In diabetes, miRNAs are involved in various pathophysiological processes, including pancreatic beta-cell function and insulin resistance, making them potential biomarkers and therapeutic targets for this disease.

Table I. Role of miRNAs in Diabetes

miR-375	Essential for beta-cell function. Dysregulation leads to impaired insulin secretion [9].
miR-34a miR-146a	Influence inflammatory processes and beta-cell apoptosis, impairing insulin production [10].
miR-21 miR-29	Modulate signaling pathways associated with oxidative stress and fibrosis, worsening diabetes progression [11].

miRNAs as Biomarkers and Therapeutic Targets in Diabetes

Systematic analyses have shown that patients with type 2 diabetes exhibit altered expression of multiple miRNAs, such as miR-126 and miR-122, which affect glucose metabolism and insulin sensitivity [12].

Table II. miRNAs as Biomarkers and Therapeutic Targets in Diabetes

miR-126	Important biomarker for insulin resistance and endothelial dysfunction [13].
miR-690	Enhances insulin sensitivity in animal models [14].
miR-320	Inhibition improves angiogenesis and cardiac function [15].

Meta-analyses indicate miRNAs' high sensitivity and specificity in detecting early metabolic changes [16].

miRNA profiling in diabetic patients enables personalized treatment tailored to individual genetic and metabolic profiles [17].

Heart Failure

Heart failure (HF) is a complex clinical syndrome resulting from the heart's inability to effectively pump blood, leading to inadequate oxygen and nutrient supply to tissues [18].

HF affects approximately 64 million people worldwide, with its prevalence increasing with the aging population. Major risk factors include ischemic heart disease, hypertension, diabetes, obesity, and atrial fibrillation. In developed countries, HF with preserved ejection fraction (HFpEF) predominates, whereas in developing countries, HF related to infections and valvular diseases is more frequently diagnosed [19].

Heart failure was recognized as an epidemic as early as 1997 and remains a significant public health concern. While HF prevalence has stabilized or even declined in certain populations, the incidence of HFpEF continues to rise, largely due to increasing obesity rates and population aging [19].

The Role of miRNA in Heart Failure

In heart failure (HF), miRNA dysfunction plays a critical role in pathological processes such as cardiac remodeling, fibrosis, and apoptosis. Research on miRNA presents new opportunities for the diagnosis and treatment of heart failure.

Table III. Role of mi RNA in Heart Failure

miR-1	Biomarker for acute heart failure; its reduced levels correlate with disease progression [20].
miR-21 miR-29	Key regulators of fibrosis through TGF-β and collagen pathways [21].
miR-34a	Promotes cardiomyocyte apoptosis, worsening heart dysfunction [22].
miR-126	Supports angiogenesis and cardiac regeneration [23].
miR-30d	Involved in extracellular remodeling leading to HF [24].

miRNAs as Therapeutic Targets in Heart Failure

Table IV. miRNAs as Therapeutic Targets in Heart Failure

miRNA Inhibitors (antagomirs)	Effectively reduce miR-21 expression, decreasing fibrosis and improving heart function [25].
Gene Therapies	Increasing miR-126 levels supports angiogenesis [23].
Exosome-based miRNA Delivery	Emerging as a promising therapeutic strategy [26].

The Relationship Between Diabetes and Heart Failure

Diabetes, both type 1 and type 2, significantly increases the risk of developing heart failure (HF). Meta-analyses indicate that individuals with diabetes have a 2 to 4 times higher risk of HF compared to the general population, with this risk being greater in women than in men. This is due to chronic hyperglycemia, which leads to myocardial damage and metabolic disturbances [27].

Diabetes affects the heart through multiple mechanisms:

1. **Diabetogenic myocardial damage:** hyperglycemia, insulin resistance, and oxidative stress contribute to the development of diabetic cardiomyopathy. This results in myocardial wall thickening, fibrosis, and impaired systolic and diastolic function [28].
2. **Metabolic disturbances:** excessive lipid accumulation in the myocardium leads to lipotoxicity, which damages cardiac cell structures. Additionally, chronic inflammation induces the activation of pro-inflammatory cytokines [29].
3. **Vascular damage:** hyperglycemia promotes atherosclerosis and microangiopathy, reducing blood flow to the myocardium and exacerbating its dysfunction [30].

The relationship between diabetes and HF is bidirectional:

- Diabetes increases the risk of HF through myocardial damage.
- HF can lead to secondary metabolic disorders, exacerbating hyperglycemia and insulin resistance, creating a vicious pathophysiological cycle [29].

Diabetes and heart failure are closely linked through complex pathophysiological mechanisms. Understanding this relationship is crucial for early detection and implementation of effective therapies that can improve prognosis and patient quality of life.

The Role of miRNA in Diabetes and Heart Failure

MicroRNA (miRNA) plays a crucial role in gene expression regulation and is involved in many biological processes, including the development of diabetes and heart failure. In these conditions, miRNA dysregulation contributes to worsening cardiac function, inducing oxidative stress, and promoting myocardial fibrosis.

miRNA such as miR-340-5p play a significant role in oxidative stress and cardiomyocyte apoptosis. Diabetes leads to increased levels of miR-340-5p, causing mitochondrial damage and cardiac dysfunction by inhibiting the Mcl-1 protein [31].

miR-133a affects myocardial contractility, and its deficiency is associated with impaired systolic function in diabetic hearts [32].

miRNA profiling has revealed that "hyperglycemic memory" remains active even after glucose levels are stabilized, contributing to persistent myocardial damage. miR-34a and miR-146a have been identified as key regulators of this process [33].

miR-30d-5p and miR-126a-5p, found in exosomes, have been linked to HF with preserved ejection fraction in type 1 diabetic rats. These miRNAs modulate inflammatory processes and angiogenesis [34].

miR-320 is a pro-apoptotic miRNA, whose overexpression contributes to worsening cardiac function. Its inhibition improves angiogenesis and myocardial contractile function [15].

miRNA as Biomarkers and Therapeutic Targets

miRNA present in serum, such as miR-126, can serve as diagnostic markers for early detection of diabetic cardiomyopathy and heart failure [35].

Therapies targeting miRNA, such as inhibitors of miR-320 or miR-340-5p, may help mitigate diabetes--induced cardiac damage. Additionally, the use of exosomes as therapeutic carriers opens new possibilities for treating cardiovascular complications [36].

This table highlights the most important miRNA dysregulated in diabetes and heart failure, as well as their significance in disease pathogenesis. Proposed therapeutic approaches, such as miRNA inhibitors or mimetics, hold the potential to revolutionize clinical care for these conditions.

Table V. Key miRNA in Diabetes and Heart Failure

miRNA	Target (mRNA)	Biological Function
miR-340-5p	Mcl-1	Regulation of oxidative stress in cardiomyocytes [31].
miR-133a	Tyrosine hydroxylase, TAT	Regulation of myocardial contractility [32].
miR-208	α-MyHC, β-MyHC	Regulation of muscle protein gene expression in response to stress [37].
miR-30d-5p	Undefined	Marker in HF with preserved ejection fraction [34].
miR-126a-5p	VEGF	Regulation of angiogenesis and endothelial function [34].
miR-29	Kolagen	Inhibition of myocardial fibrosis [38].
miR-221/222	p27Kip1	Regulation of cardiac muscle cell proliferation [39].
miR-21	PTEN	Modulation of apoptosis and inflammatory processes [40].
miR-15a/b	Bcl-2	Regulation of apoptosis in cardiomyocytes [24].
miR-146a	IRAK1, TRAF6	Modulation of the inflammatory response [25].

Conclusion

The article discusses the critical role of microRNAs (miRNAs) in the pathogenesis of diabetes and heart failure, highlighting their potential as diagnostic biomarkers and therapeutic targets. miRNA dysregulation in both conditions is associated with various pathophysiological processes, including oxidative stress, apoptosis, and fibrosis, which negatively impact cardiac function and metabolism. For example, miR-375 and miR-34a regulate the function of β-cells, which are essential for glucose homeostasis, while miR-21 and miR-29 are involved in fibrosis in heart failure.

One of the key aspects discussed in the study is the bidirectional relationship between diabetes and heart failure. Chronic hyperglycemia in diabetes induces myocardial damage and metabolic disturbances, thereby increasing the risk of heart failure. Conversely, heart failure exacerbates hyperglycemia and insulin resistance, creating a pathological feedback loop.

The authors highlight the growing interest in miRNAs as therapeutic targets. For instance, miR-21 inhibitors can reduce fibrosis, while modulation of miR-126 promotes angiogenesis and cardiac regeneration. Additionally, the use of exosomes as therapeutic carriers presents new opportunities for treating cardiovascular complications.

The article presents miRNAs as a crucial component in the advancement of targeted therapies and precision diagnostics. However, to fully exploit the potential of miRNAs in medicine, further research is needed to elucidate their mechanisms of action and optimize their clinical applications.

Conflict of interest
None

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