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Review

microRNAs in Type 1 Diabetes: Roles, Pathological Mechanisms, and Therapeutic Potential

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Abstract : Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by the progressive destruction of pancreatic β-cells, leading to insulin deficiency. The primary drivers of β-cell destruction in T1D involve autoimmune-mediated processes that trigger chronic inflammation and ultimately β-cell loss. Regulatory microRNAs (miRNAs) play a crucial role in modulating these processes by regulating gene expression through post-transcriptional suppression of target mRNAs. Dysregulated miRNAs have been implicated in T1D pathogenesis, serving as both potential diagnostic biomarkers and therapeutic targets. This review explores the role of miRNAs in T1D, highlighting their involvement in disease mechanisms across both rodent models and human patients. While current anti-diabetic therapies manage T1D symptoms, they do not prevent β-cell destruction, leaving patients reliant on lifelong insulin therapy. By summarizing key upregulated and downregulated miRNAs in diabetic models and patients, this review discusses the potential of miRNA-based therapies to restore β-cell function and modify disease progression.

Keywords: type 1 diabetes; autoimmune; β-cells; apoptosis; miRNAs

1. Introduction

Diabetes mellitus, commonly referred to as diabetes, is characterized by chronic hyperglycemia and associated with metabolic dysfunctions in carbohydrates, fats, and proteins [1]. The disease encompasses genetic, pathophysiological, and clinical factors [2]. Diabetes is categorized into several types based on its etiology and pathogenesis: type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes (GD), and other forms [1]. T1D, or insulin-dependent diabetes, results from dysfunction of pancreatic β-cells and accounts for about 5-10% of all diabetes cases [1]. T2D, or non-insulin-dependent diabetes, is primarily caused by insulin resistance and insulin deficiency, making up 90-95% of all cases [1]. GD is diagnosed when glucose intolerance or diabetes develops during pregnancy, typically in the second or third trimester, and affects 1-14% of pregnancies [1]. All forms of diabetes share the common feature of insulin dysregulation, either absolute or relative. Currently, there are no reliable biomarkers for diagnosing diabetes before it develops. Although various tests to assess insulin secretion, such as fasting indices, oral and intravenous glucose tolerance tests, and other provocative challenges, have been proposed, they are not widely used due to their time-consuming nature, expense, and lack of standardization [3]. Furthermore, these methods do not adequately reflect the underlying pathophysiology of β-cell dysfunction, as their correlation with β-cell mass is limited [3].

T1D, also known as one of the most common chronic diseases of childhood, affects approximately 8.4 million patients globally, according to the World Health Organization [4]. T1D results from the loss of pancreatic islet β-cells, often through autoimmune activation, β-cell

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autoantigen release, oxidative and endoplasmic reticulum (ER) stress, and cytokine-mediated damage, leading to β-cell destruction, insulin deficiency, and hyperglycemia through disruption of insulin signaling pathways (Figure 1) [5–8]. Although diverse causes of destruction of pancreatic islet β-cells were identified, the molecular mechanisms of the loss of pancreatic islet β-cells remains controversial. T1D is categorized into T1Da and T1Db [6]. Most patients (70-90%) fall into T1Da, an autoimmune form known as autoimmune T1D while T1Db, or idiopathic T1D, includes a small subset of patients [6].

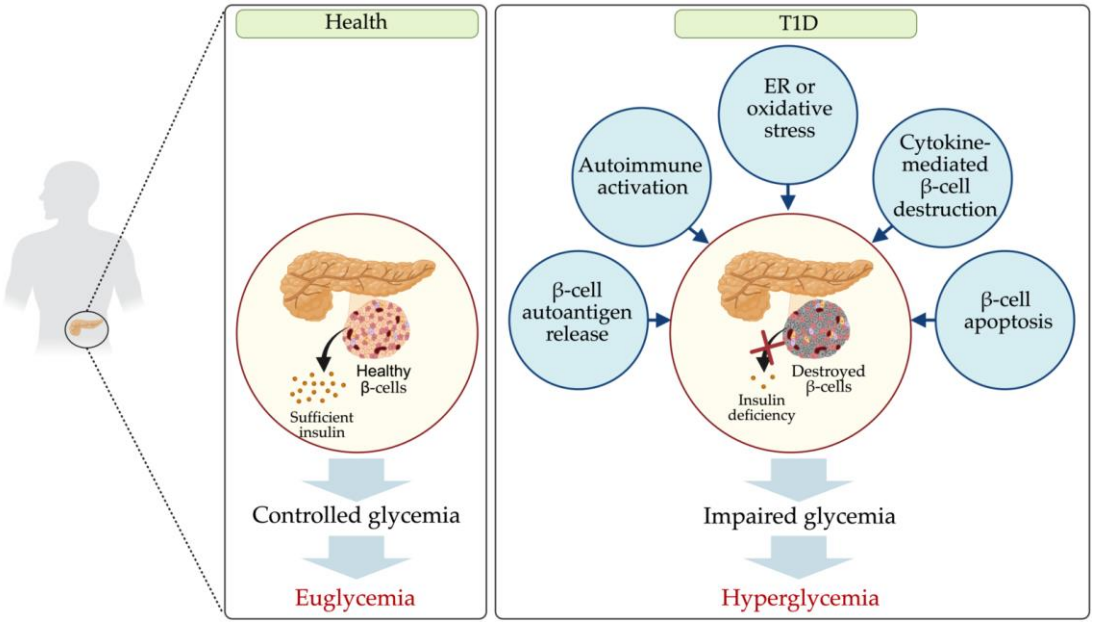

Figure 1. Pathophysiological mechanisms underlying Type 1 diabetes. Type 1 diabetes (T1D) results from the progressive destruction of pancreatic islet β-cells, driven by autoantigen release, autoimmune activation, oxidative and ER stress, cytokine-induced damage, and apoptosis. This cascade of pathological events leads to β-cell loss, insulin deficiency, and hyperglycemia, ultimately disrupting insulin signaling pathways.

There are a few biomarkers available to distinguish T1D from other types of diabetes. In autoimmune T1D, autoantibodies (AAbs) against β-cell antigens are produced early, often before clinical symptoms appear [9]. This early antibody production is often accompanied by genetic mutations associated with the disease, with variations in the human leukocyte antigen (HLA) class II genes being the most common [10]. The presence of two or more AAbs indicates a high risk for T1D, as it signals an active autoimmune response against β-cells [7,8]. Several AAbs targeting islet cells, insulin, tyrosine phosphatases, IA-2 and IA-2β, glutamic acid decarboxylase, and zinc transporter 8 serve as biomarkers for T1D [3,7,8,11,12]. While these AAbs and measurements of T-cell reactivity reliably identify individuals at risk of T1D by assessing β-cell dysfunction due to autoimmune activity, they lack precision in predicting T1D onset and are not effective for monitoring disease progression [3,11,12].

Furthermore, while AAbs are the most common biomarkers for T1D, they are only applicable for identifying T1D in AAbs-positive individuals. Notably, some children in the initial stage may be negative for islet AAbs and some AAbs-positive individuals may not develop T1D [7,8]. Moreover, despite extensive research into the molecular mechanisms underlying T1D pathogenesis, patients with T1D still rely on lifelong insulin therapy, which often has limited tolerance and can lead to adverse effects [13]. Thus, novel biomarkers to assess β-cell dysfunction are essential to predict T1D onset, monitor its progression, and establish effective clinical approaches in T1D therapies.

Sustained high blood glucose levels are associated with several serious diseases, including retinopathy, nephropathy, neuropathy, and cardiovascular conditions such as coronary artery disease, atherosclerosis, hypertension, and stroke [14]. Key pathological factors like hyperglycemia,

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hyperlipidemia, advanced glycation end products (AGEs), growth factors, and inflammatory cytokines/chemokines contribute to the increased risk of these complications [14–16]. Diabetic patients with these complications often require lifelong treatment, and if left unmanaged, can significantly reduce their quality of life [14]. Therefore, understanding the molecular mechanisms underlying the onset of diabetic complications is crucial for developing effective treatments.

MicroRNAs (miRNAs) can serve as biomarkers and therapeutic targets in various human diseases. miRNAs are small, noncoding RNA molecules, typically 21 to 23 nucleotides in length, that regulate gene expression. They do so by binding to the 3' untranslated regions of target messenger RNAs (mRNAs), forming the RNA-induced silencing complex [8,17]. This complex directly modulates the translation of mRNAs into proteins [8,17]. An increasing number of studies suggest miRNAs hold significant potential as biomarkers for pathogenic conditions, and as therapeutic agents for medical intervention in nearly all human disease, including T1D and T2D. Studies have shown that changes in specific miRNA expression are associated with T1D and hyperglycemia, suggesting their potential as biomarkers for T1D. miR-125b-5p and miR-365a-3p showed positive correlation with hemoglobin A1C levels [18], whereas let-7a-5p, let-7c-5p, miR-5190, and miR-770-5p exhibited negative correlations [18,19]. These miRNAs significantly influence glycosaminoglycan biosynthesis, axon guidance signaling, Rap1 signaling, focal adhesion, and neurotrophin signaling [18,20].

Recent studies have emphasized the therapeutic potential of miRNA-based strategies, such as using miRNA mimics to restore downregulated miRNAs or employing miRNA inhibitors to counteract overexpressed miRNAs, thereby achieving protein homeostasis [21,22]. The safety of prolonged treatment with specific miRNAs has also been demonstrated in preclinical models [23]. With six FDA-approved siRNA drugs (Patisiran, Givosiran, Lumasiran, Inclisiran, Vutrisiran, and Nedosiran) now in clinical use for genetic and metabolic disorders, ongoing research on miRNAs—mimicked by these siRNAs—continues to expand their applications in both preclinical and clinical settings. However, several critical challenges remain to fully harness the potential of miRNA-based therapies. These include identifying key signature miRNAs, elucidating their mechanisms of action, optimizing their use through RNAi, ensuring efficient delivery to target tissues, and validating their efficacy in vivo. Although several miRNA-based therapeutics have entered clinical trials [24], none have yet achieved FDA approval.

Numerous studies have identified dysregulated miRNAs in both T1D rodent models and patients. This review explores differentially expressed miRNAs in T1D, emphasizing their interactions with target genes involved in T1D-related pathways to uncover the molecular mechanisms underlying β-cell dysfunction in rodents and humans. Furthermore, it highlights commonly upregulated and downregulated miRNAs shared between T1D rodent models and patients. These insights aim to advance the development of diagnostic and therapeutic strategies for T1D.

2. Dysregulated miRNAs in T1D Patients

Tissue-specific gene expression patterns are crucial for tissue development, defining cell type characteristics, functions, and transcriptional regulation [25,26]. miRNAs, which exhibit both tissue- and developmental stage-specific features, play an essential role in tissue identity and function [26–28]. Numerous studies have demonstrated correlations between tissue-specific miRNAs and various human diseases [26]. Circulating miRNAs, influenced by tissues such as the heart, liver, pancreas, kidney, colon, and lung, have also been shown to play key roles in disease processes, with many originating from blood cells [29]. These circulating miRNAs are easily accessible, relatively stable, and exhibit disease-specific profiles [30].

Dysregulated miRNAs in Various Samples from T1D Patients

Over the past decades, numerous studies have documented the dysregulation of miRNAs in various specimens, including serum, plasma, peripheral blood, PBMCs, isolated T-cells, urine, and

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exosomes from T1D patients. Table 1 provides a summary of dysregulated miRNAs identified across these sample types. In T1D patients, miRNAs exhibit differential upregulation and downregulation depending on the sample type, with certain miRNAs consistently dysregulated across multiple specimens.

Table 1. Altered miRNA profiles in various blood and urine sample types from T1D patients.

Source				Detection method	miRNA profile		Ref.
Sample	T1D patient characteristic				Expression	miRNA	
	Diagnosis	Age (years)	n				
Serum	21 to 42 days	9.0 ± 1.8	10	qPCR	Up	let-7e/g-5p miR-18a-5p miR-23b-3p miR-25-3p miR-30e-5p miR-93-5p miR-103a-2-5p miR-125a-3p miR-140-5p miR-144-5p miR-182-5p miR-183-5p miR-192-5p miR-214-5p miR-221-3p miR-222-3p miR-324-3p/5p miR-331-3p miR-345-5p miR-377-3p miR-454-3p miR-500a-5p miR-502-3p miR-1468	[19]
					Down	miR-100-5p miR-154-3p miR-490-5p miR-630 miR-636 miR-639 miR-675-3p miR-720	

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	12 months		404	Sequencing qPCR	Up	miR-10a miR-21 miR-24 miR-25 miR-26a/b miR-27a/b miR-29a/b miR-30a-5p miR-103 miR-125b miR-148a miR-152 miR-181a miR-199a miR-200a/c miR-210 miR-222 miR-320a miR-340	[31]
	<6 months or 2 to 5 yrs		26	qPCR	Up	miR-10a miR-21 miR-27a miR-92a miR-100 miR-148a miR-200a miR-208 miR-212 miR-323-3p miR-346 miR-451 miR-886-3p	[32]
					Down	miR-16-5p miR-125a-5p miR-126 miR-146a miR-155 miR-197 miR-342-3p miR-374 miR-454 miR-518d	
	15.71 ± 11.33 yrs	33.57 ± 8.17	15	qPCR	Up	miR-21-5p miR-148a	[33]
Plasma	<5 yrs	19.2 ± 6.4	16	Microarray qPCR	Up	miR-15b-5p miR-21-3p/5p miR-25-3p miR-29a-3p miR-101-3p miR-103a-3p miR-133a-5p miR-148a-3p miR-148b-3p	[34]

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						miR-155-5p miR-200a/c-3p miR-210-3p miR-222-3p miR-320 miR-342 miR-1275	
					Down	miR-29b-3p miR-146a-5p miR-181a-5p miR-338-3p	
	≥5 yrs	19.9 ± 4.6	17	Microarray qPCR	Up	miR-26b-5p miR-146a-5p miR-148b-3p miR-338-3p miR-340-5p miR-1275	[34]
					Down	miR-15b-5p miR-103a-3p miR-126-3p miR-148a-3p miR-155-5p miR-181a-5p miR-200a/c-3p miR-210-3p miR-222-3p	
	< 1 yr	12.93 ± 3.34	16	qPCR	Up	miR-21 miR-210	[35]
	-	25.9 ± 5.7	16	qPCR	Up	miR-21 miR-24 miR-29a miR-30d miR-34a miR-126 miR-146a miR-148a miR-375 miR-376a	[3]
	-	37	95	qPCR	Up	miR-125b-5p miR-365a-3p miR-770-5p	[18]
					Down	miR-5190	
	< 1 yr	31.0±10.2	34	qPCR	Down	miR-409-3p	[36]
Peripheral blood	-	26.93 ± 9.62	12	Sequencing qPCR	Up	let-7i-5p miR-26b-5p miR-99b-5p miR-342-3p miR-501-3p miR-652-3p	[37]
					Down	miR-15a-5p miR-15b-3p/5p miR-16-5p miR-16-2-3p	

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						miR-17-5p miR-21-5p miR-25-3p miR-26a/b-5p miR-27b-3p miR-30e-5p miR-93-5p miR-98-5p miR-100-5p miR-101-3p miR-103a-5p miR-107 miR-106b-3p/5p miR-126-3p/5p miR-130a/b-3p miR-143-3p miR-144-3p/5p miR-181a-5p miR-185-5p miR-221-3p miR-363-3p miR-532-5p	
PBMCs	-	23.5 ± 3.9	11	Microarray	Up	let-7f/g miR-7 miR-10a miR-15b miR-16 miR-18b miR-19a miR-20a miR-20b miR-21 miR-26b miR-27b miR-30e miR-32 miR-33a miR-98 miR-101 miR-126 miR-148a/b miR-186 miR-195 miR-199a-3p miR-301a miR-335 miR-338-3p miR-340 miR-424 miR-450a miR-454 miR-542-3p	[20]

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					miR-548c-3p	
				Down	miR-140-3p miR-324-5p miR-342-3p/5p miR-423-5p miR-720 miR-766 miR-940 miR-1275	
Newly diagnosed T1D patients	17.50 ± 3.68	60	Microarray	Up	miR-320b miR-486-5p miR-652 miR-1275 miR-1301	[38]
				Down	miR-15b miR-19b miR-22 miR-23a miR-25 miR-28-5p miR-29a miR-30b/c miR-146a miR-146b-5p miR-200c miR-221 miR-342-5p	
-	-	20	qPCR	Up	miR-22	[39]
				Down	miR-150	
-	-	78	qPCR	Down	miR-146a miR-150 miR-424	[40]
≥10 yrs	37.35 ± 12.82	31	Sequencing qPCR	Up	miR-133a-3p miR-142-5p miR-144-5p miR-145-3p miR-193a-5p miR-199a-5p miR-382-5p miR-409-5p miR-486-5p miR-543 miR-873-5p miR-1249-3p miR-1299 miR-3150b-3p miR-4531	[41]
				Down	miR-16-5p miR-144-3p miR-409-5p miR-501-3p miR-1271-5p miR-4485-3p	

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T-cells and Tregs isolated from peripheral blood	-	-	5	qPCR	Up	miR-510	[42]
					Down	miR-191 miR-342	
Urine	< 1 yrs	12.93 ± 3.34	68	qPCR	Up	miR-21 miR-210	[35]
					Down	miR-126	
Plasma-derived exosome	25.3 ± 15.9 yrs	46.1 ± 14.4	12	Microarray qPCR	Up	miR-25-3p	[43]
					Down	miR-16 miR-302d-3p miR-378e miR-570-3p miR-574-5p miR-579	
Urine-derived exosome	30.7 ± 6.3 yrs	57.9 ± 3.7	12	qPCR	Up	miR-130a miR-145	[44]
					Down	miR-155 miR-424	

Recent research has identified 138 upregulated and 93 downregulated miRNAs that are consistently altered in T1D patients compared to healthy donors (Table 1). Among them, five miRNAs in various specimens were reported to be dysregulated in T1D patients: miR-21 [3,20,31–35] and miR-148a [3,20,31–34] were upregulated, while miR-126 [32,34,35,37] was downregulated. miR-25-3p [19,34,37,43] and miR-1275 [20,34,38] had different dysregulated patterns in various specimens. miR-21 and miR-148a regulate inflammation and apoptosis. In patients with T1D, increased expression of miR-21 and miR-148a regulates PI3K/AKT signaling and contributes to apoptosis in β-cells leading to dysregulated insulin release through impaired glucose-stimulated insulin secretion through PTEN and SOX6 [33,45–47]. Conversely, decreased expression of miR-25-3p, miR-126, and miR-1275 targets IL-1β and IRS-1, promoting β-cell death [48–52].

Notably, one interesting study [34] found that both miR-148a-3p and miR-148b-3p levels in plasma were increased in newly diagnosed T1D patients (<5 years of diagnosis) but were decreased in later-stage T1D patients (≥5 years of diagnosis). These miRNAs are regulated with the Wnt, FOXO, and insulin signaling pathway [33,34]. In the early stages of T1D, pancreatic β-cell damage progresses due to autoimmunity [5]. During this stage, the increased expression of miR-148a/b-3p show to regulate the Wnt and insulin signaling pathways, protecting the remaining pancreatic cells or modulating inflammatory responses. In the later stages, as pancreatic β-cell damage worsens, pancreatic function is lost, and chronic inflammation leads to fibrosis [1,5], the role of miR-148a/b-3p diminishes, and its expression levels decrease. These miRNAs may serve as valuable resources for identifying novel biomarkers across different stages of T1D.

Dysregulated miRNAs in Serum and Plasma

Circulating miRNAs, found in nearly all biological fluids such as serum and plasma, represent promising sensitive biomarkers for a range of conditions, as their profiles provide an accurate representation of the physiological state of the organism [53–55]. In particular, miRNAs expressed in serum exhibit changes in expression levels in response to disease states and physiological changes [55–58]. They exhibit altered expression profiles in various pathological conditions, including metabolic diseases (e.g., diabetes), cancer, cardiovascular diseases, and inflammatory disorders [53,54,58–61]. These changes make them valuable biomarkers for early disease diagnosis, prognosis evaluation, and monitoring therapeutic responses.

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Research into the expression of these miRNA markers suggests their potential application in the early diagnosis of various diseases, frequently preceding the manifestation of clinical symptoms [57,62–66]. Additionally, these markers may play a crucial role in evaluating patient responses to therapeutic treatments, thus aiding in formulating personalized treatment approaches [67,68].

The analysis of miRNA profiles in T1D patients highlights distinct patterns of dysregulation in both serum and plasma, underscoring their potential as biomarkers for the disease. Specifically, 15 miRNAs were upregulated and 7 were downregulated in serum, while 18 miRNAs were upregulated and 3 miRNAs were down regulated in plasma (Table 1). Notable examples include the downregulation of miR-10b-5p, miR-146a-5p and miR-409-3p [19,33,69], and the upregulation of miR-21, miR-126, and miR-155-5p [18,70–72], which are associated with key pathways in T1D pathogenesis. These findings suggest that miRNAs can provide insights into T1D disease mechanisms and can serve as a foundation for developing diagnostic and therapeutic tools for T1D.

Dysregulated miRNAs in Blood Cells

Approximately 80% of all human genes are expressed in peripheral blood cells, including peripheral blood mononuclear cells (PBMCs). These cells are highly responsive to environmental changes, which can significantly impact their gene expression profiles [20,73]. In the context of T1D, hundreds of miRNAs have been reported to exhibit differential expression in PBMCs [8]. The dysfunction of PBMCs, particularly T-cells and B-cells, plays a critical role in the pathogenesis of autoimmune diseases such as T1D. Therefore, the distinct miRNA expression patterns in PBMCs hold promise as valuable biomarkers for the diagnosis and monitoring of T1D.

The evidence presented highlights the critical role of dysregulated miRNAs in the pathogenesis and progression of T1D. Studies by Takahashi et al. [20], Yang et al. [38], and Massaro et al. [41] collectively demonstrate that specific miRNA expression patterns can distinguish T1D patients, implicating these molecules in key pathways such as immune regulation, insulin signaling, and diabetic complications. Notably, miR-146a/b-5p emerge as central players in the autoimmune imbalance underlying the onset of T1D, with their persistent downregulation linked to immune dysregulation and T-cell response (Table 1). Furthermore, the target genes of miR-146a/b-5p, such as TRAF6, BCL11A, STX3 and NUMB, were upregulated in PBMCs from newly diagnosed T1D patients and those treated with insulin [38]. These target genes are involved in immune regulation and T-cell responses. For instance, TRAF6 regulates TLR signaling to maintain immunological balance [38,70], and NUMB inhibits the Notch signaling pathway, which plays a critical role in T helper cell immune responses [38,74]. STX3 involved in chemokine production by human mast cells [38,75] and BCL11A, related to plasmacytoid dendritic cells differentiation, are also key immune-related genes [38,76]. Additionally, distinct miRNA signatures associated with complications such as neuropathy, nephropathy, and retinopathy further underscore the potential of miRNAs as biomarkers for disease progression and therapeutic targets [44,52,77–92]. These findings pave the way for future research into miRNA-targeted therapies aimed at mitigating both the autoimmune aspects of T1D and its associated complications.

Dysregulated miRNAs in T-Cells

T1D is characterized by the loss of functional insulin producing β-cells of pancreatic islets via the destruction of pancreatic β-cells. This phenomenon is caused by islet infiltrating self-reactive $CD4^+$ and $CD8^+$ T-cells [93]. Simultaneously, regulatory T-cells (Tregs) suppress these autoreactive T-cells [94]. Although, the most self-reactive T-cells are eliminated in the thymus via central tolerance induction mechanism, which strengthens immune tolerance to self-antigens under normal condition, a few remaining autoreactive T-cells are released to the peripheral circulation by avoiding this mechanism [94]. This phenomenon implies that these impaired functions of T-cells and Tregs cause the onset of autoimmune T1D through decreased tolerance to islet antigens leading to uncontrolled T-cells mediated autoimmune destruction of pancreatic β-cells [42,94].

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miR-191, miR-342, and miR-510 were dysregulated in Tregs isolated from peripheral blood of T1D patients [42]. Specifically, miR-191 was downregulated in Tregs of T1D patients, contrasting with its upregulation in various cancers, including myeloid leukemia, breast cancer, and colorectal cancer [42,95–97]. miR-342, abundantly expressed in Tregs of healthy donors, was significantly downregulated in T1D patients [42]. This miRNA was also shown to be downregulated in human leukocytes during lipopolysaccharide-induced inflammation [42,98]. miR-342 targets key molecules such as BMPR2 and PDGFRA in cytokine signaling and EP300 in MAPK and NF-kB signaling pathways [42,98]. These observations suggest that the downregulation of miR-342 in Tregs of T1D patients may impair their functionality, contributing to autoimmune destruction in T1D [42,95–97].

Dysregulated miRNAs in Exosomes Derived from Plasma and Urine

Exosomes are lipid-based carriers with potential for disease-specific diagnostics, since they originate from cellular multivesicular bodies that contain specific miRNAs [43,99]. Exosomal miRNAs are tissue-specific and remain stable in plasma, whereas RNAs in blood are prone to degradation by ribonucleases [43,99,100]. miRNAs expression patterns dynamically change throughout diseases progression. Pancreatic β-cells spread exosomes containing miRNAs [101]. Thus, miRNAs derived from exosomes in plasma hold promise as candidates for early detection tools.

Dysregulated exosomal miRNAs play a critical role in T1D pathophysiology, influencing β-cell function [31,43,102], insulin resistance [43,103], and metabolic regulation [43]. Notably, miR-302d-3p, miR-378e, and miR-574-5p are downregulated, while miR-25-3p is upregulated (Table 1). Barutta et al. [44] analyzed urinary exosomal miRNA expression in T1D patients with and without early diabetic nephropathy (DN). Patients with microalbuminuria exhibited increased miR-130a and miR-145 but decreased miR-155 and miR-424 in urinary exosomes compared to non-diabetic controls and normoalbuminuric T1D patients (Table 1). In vivo, miR-145 levels were elevated in both urinary exosomes and glomeruli of STZ-induced diabetic mice compared to controls. Similarly, in vitro, miR-145 expression increased in mesangial cells and mesangial cell-derived exosomes under high-glucose conditions (Table 1) [44]. Urinary exosomal miRNAs, such as miR-145 and miR-155, show a strong association with DN, underscoring their potential as biomarkers for diabetic complications [44].

3. Dysregulated miRNAs in T1D Rodents

As previously noted, understanding tissue-specific miRNAs is essential for deciphering normal tissue development [104] and T1D progression [105]. Table 2 summarizes dysregulated miRNAs in T1D murine models across various studies. These miRNAs are categorized by species, diabetic models, tissue sources, detection methods, and expression patterns, offering valuable insights into their roles in T1D pathogenesis.

Table 2. Altered miRNA profiles across various cells and tissues in T1D rodent models.

Species	Diabetic Animal Models	Source	Detection Methods	miRNA Expression Alteration		Ref.
				Expression	miRNAs	
Mice	Akita spontaneous mutation (*Ins2*^{Akita}) mice	Retina	Microarray qPCR	Up	miR-7a miR-28 miR-124 miR-186 miR-199a-3p miR-200b miR-369-5p miR-410 miR-429	[77]
				Down	miR-184	

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				miR-296-5p miR-467b miR-539 miR-1196 miR-1224	
Pre-diabetic non-obese diabetic (NOD) mice	Pancreatic islet, cultured islet, infiltrating lymphocytes	qPCR	Up	miR-29a miR-29b miR-29c miR-142-5p miR-155	[106,107]
			Down	miR-142-3p miR-150	
	Pancreatic β-cells	qPCR	Up	miR-142-5p	[107]
			Down	miR-150 miR-155	
Diabetic NOD mice	Pancreatic islet/plasma	qPCR	Up	miR-21	[108]
		Microarray qPCR	Down	miR-126a-3p miR-126a-5p miR-155 miR-188-3p miR-204 miR-218 miR-409-3p	[36]
C57BL/6J mice induced with Streptozotocin (STZ)	Pancreatic tissue	Microarray	Up	miR-154-3p miR-296-3p miR-323-3p miR-491-5p miR-669m-3p miR-670-5p miR-697 miR-881-3p miR-3058-3p miR-5119 miR-5130 miR-5622-3p	[109]
			Down	miR-7a-5p miR-7b-5p let-7a-5p let-7f-5p miR-10b-5p miR-16-5p miR-17-5p miR-26b-5p miR-28a-5p miR-28c miR-101a-3p miR-101b-3p miR-101c miR-126-3p miR-126-5p miR-143-3p miR-151-5p	

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			miR-184-3p miR-410-5p miR-451a miR-466 miR-467c-3p miR-467f miR-467g miR-467h miR-669 miR-1187 miR-3086-3p miR-5625-5p	
Pancreatic islet	qPCR	Up	miR-21	[108]
Full-thickness skin lesion	qPCR	Up	miR-29	[110]
		Down	miR-16 miR-21 miR-23a miR-24 miR-27b miR-31 miR-132 miR-195 miR-497	
Glomeruli	qPCR	Up	miR-145	[44]
Heart	Microarray	Up	miR-21 miR-24 miR-142-3p miR-195 miR-199a-3p miR-208 miR-221 miR-499-3p miR-700 miR-705	[111]
		Down	miR-1 miR-20a miR-29a miR-143 miR-220b miR-373	
FVB mice induced with STZ	Heart	qPCR	Up	miR-107 miR-122 miR-125b-3p miR-134 miR-139-5p miR-141 miR-185 miR-193b miR-197 miR-200c miR-208-b miR-221 miR-222	[78]

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					miR-295 miR-298 miR-329 miR-346 miR-409-3p miR-431 miR-466g miR-467a miR-541 miR-542-5p miR-666-3p miR-702 miR-770-3p	
				Down	miR-302a miR-882 miR-883-5p	
Rats	Sprague-Dawley or Wistar rats induced with STZ	Retina	Microarray qPCR	Up	miR-29b miR-34 miR-203 miR-216 miR-410	[79] [80]
				Down	miR-212	
		Kidney	qPCR	Up	miR-146a	[112]

Various miRNAs have been implicated in T1D pathogenesis within pancreatic islet-related sources, including pancreatic islets, pancreatic β-cells, the whole pancreas, cultured islets, infiltrating lymphocytes, serum, and blood from T1D rodent models. Among these, 39 miRNAs were upregulated [36,106–109,113], while 47 were down regulated [36,106–109,113]. Additionally, miRNAs play a significant role in T1D-related complications. In diabetic retinopathy, for example, 13 miRNAs were upregulated in the retina, while seven were downregulated (Table 2) [77,79,80].

Among the dysregulated miRNAs implicated in T1D pathogenesis, specific miRNAs exhibit more direct roles in disease mechanisms. F[36,106–109,113or example, miR-200b, significantly upregulated in the retina of *Ins2*^{Akita} mice (Table 2), targets Oxr1 and regulates oxidative stress in diabetic retinopathy [77]. In prediabetic non-obese diabetic (NOD) mice, the miR-29 family affects insulin biosynthesis, while miR-142-3p, miR-142-5p and miR-155 are linked to apoptosis and inflammation [106,107]. Additionally, miR-21, upregulated in β-cells of both NOD and streptozotocin (STZ)-induced T1D mice (Table 2), contributes to islet inflammation and β-cell dysfunction [108]. Other notable findings include the downregulation of miR-409-3p in pancreatic islets and plasma from NOD mice [36], as well as the identification of 64 upregulated and 72 downregulated miRNAs in STZ-induced T1D mice, with key roles in β-cell autoantigen release and apoptosis [109]. Human studies further demonstrate dysregulation of miR-24, miR-29a, miR-148a and miR-200a in newly diagnosed T1D patients, with miR-375 correlating with β-cell injury and miR-21 with islet inflammation [3,31,114]. Notably, overlapping miRNA patterns across diabetes subtypes, including T1D, T2D, latent autoimmune diabetes in adults (LADA), and prediabetes, suggest their potential as biomarkers for distinguishing between different forms of diabetes [3]. These findings underscore the fundamental role of miRNA dysregulation in T1D pathogenesis, influencing β-cell autoantigen release, apoptosis, and immune activation. The identification of tissue-specific and circulating miRNAs provides insights into the molecular mechanisms of T1D and highlights their potential as biomarkers for both disease progression and therapeutic intervention.

4. Dysregulated miRNAs in Diabetic Cardiomyopathy and Nephropathy

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The dysregulation of miRNAs in T1D play a significant role in disease pathophysiology and its complications. Diabetes induces vascular and renal dysfunction, contributing to conditions such as diabetic cardiomyopathy (DC) [81] and DN [82], the leading cause of mortality in T1D. Microalbuminuria, the earliest clinical manifestation of DN, has a lifetime incidence of approximately 50% in T1D, with a particularly heightened risk for cardiovascular complications. Although much of the research on diabetes-related DC focuses on T2D, its impact on T1D is even more pronounced. After adjusting for age, the relative risk of cardiovascular complications in T1D remains significantly higher than in T2D [115–117].

Recent studies have identified altered miRNA expression patterns involved in the pathophysiology of DC and DN, where these miRNAs regulate key pathways related to cardiomyocyte hypertrophy, oxidative stress, fibrosis, and apoptosis [82–84]. In DC, miR-21 [85], miR-34a [86], miR-141 [78], miR-142-3p [87], miR-195 [81], and miR-199a-3p [87] are upregulated, while miR-133a [92], miR-143 [87], miR-150 [88], and miR-499 [92] are downregulated (Figure 2). Similarly, in DN, miR-21 [89], miR-130a [44], and miR-145 [44] are upregulated, while miR-15a-5p [90], miR-25 [91], miR-155 [44], and miR-424 [44] are downregulated (Figure 2). These miRNAs regulate genes and pathways implicated in diabetes-related cardiac and renal dysfunctions, highlighting their potential as diagnostic biomarkers and therapeutic targets for managing T1D complications. Their identification opens new avenues for intervention and improved patient outcomes.

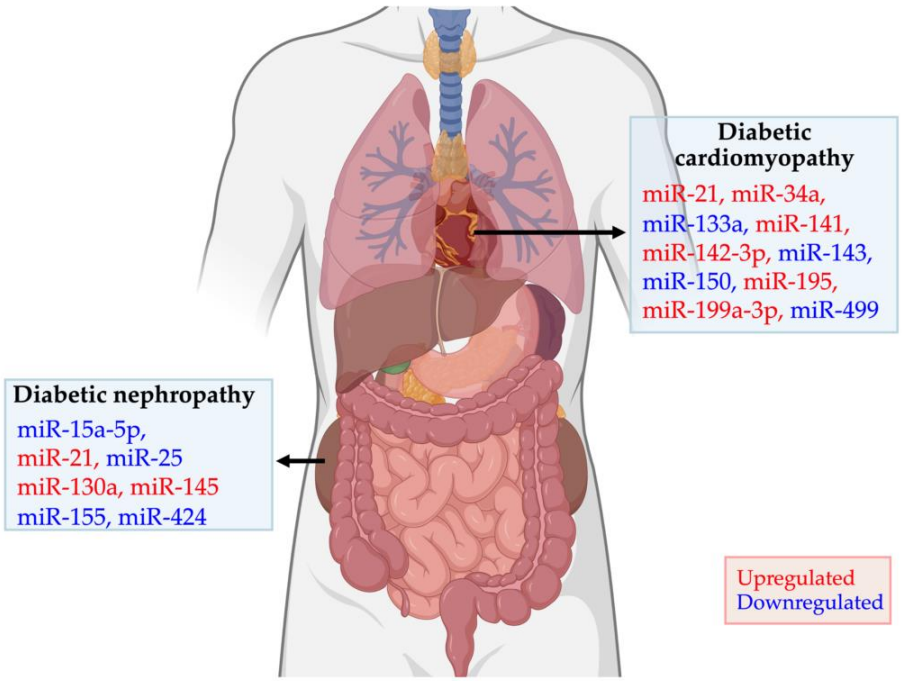

Figure 2. Dysregulated miRNAs in diabetes-related cardiomyopathy and nephropathy. .In T1D patients, diabetic cardiomyopathy and diabetic nephropathy are closely associated. Dysregulated miRNAs contribute to disease progression, with downregulated miRNAs shown in blue and upregulated miRNAs in red.

5. Dysregulated miRNAs in T1D and Their Potential Targets

miRNAs play a vital role in maintaining glucose homeostasis in both humans and diabetic animal models by regulating β-cell development, apoptosis, insulin secretion, and insulin action in target tissues. T1D results from the progressive loss of pancreatic islet β-cells, driven by autoimmune activation, β-cell autoantigen release, oxidative and ER stress, and cytokine-mediated damage, ultimately leading to β-cell destruction. This loss disrupts insulin signaling pathways, causing insulin

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deficiency and hyperglycemia (Figure 1). Table 3 summarizes dysregulated miRNAs and their associated pathways in T1D from various studies.

Table 3. Altered miRNAs and their associated pathways in T1D.

Group	Pathway	Upregulated miRNAs	Downregulated miRNAs
Apoptosis	β-cell apoptosis	miR-21-5p [33,118] miR-24 [119] miR-34a [120] miR-155 [34,121] miR-181a-5p [8] miR-195 [81] miR-200a-3p [34,122] miR-375 [123] miR-424 [20]	miR-100-5p [42] miR-126 [124] miR-146a-5p [34,40] miR-150-5p [40] miR-320a-3p [125] miR-324-5p [20,109] miR-342-3p [42] miR-424 [40]
	TP53 signaling	miR-145 [126]	miR-324-5p [20] miR-342-3p [20] miR-423-5p [20]
	Wnt signaling	miR-143-3p [127] miR-144-5p [19] miR-148a-3p [33,34] miR-365a-3p [18]	miR-140-3p [20] miR-324-5p [20] miR-342-3p [20] miR-766 [20] miR-940 [20]
	TGF-β signaling	miR-26b [34,128] miR-382-5p [41]	miR-10b-5p [129]
	mTOR signaling	miR-323-3p [109]	
ER or oxidative stress	FOXO signaling	miR-21-5p [33] miR-148a-3p [34] miR-323-3p [109] miR-486-5p [32,130]	
	NF-κB signaling	miR-24-3p [131,132] miR-155-5p [34]	miR-146a-5p [34] miR-342 [133]
	NRF2	miR-21-5p [134] miR-144-5p [134]	
	Notch signaling		miR-140-3p [20] miR-146a-5p [34] miR-324-5p [20] miR-423-5p [20] miR-1275 [20]
	Endocytosis	miR-21-5p [118,135] miR-29a-3p [34,136]	miR-324-5p [20] miR-342-3p [20,42]
Immune system activation	Immune system-related	miR-103a-3p [34] miR-155-5p [34] miR-200a-3p [34]	
	T-cell regulation		miR-31 [42] miR-342 [42]
	Chemokine signaling [20]	miR-18b miR-20b miR-33a miR-101 miR-186 miR-338-3p	miR-940

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β-cell autoantigen release	Jak-STAT signaling	miR-21-5p [8] miR-24-3p [8,105] miR-125b-5p [18,137] miR-181-5p [8] miR-323-3p [109] miR-210-5p [8]	
	MAPK signaling	miR-199a [20] miR-342 [34] miR-450a [20] miR-548c-3p [20]	miR-100-5p [8] miR-150-5p [8]
β-cell insulin release	Insulin signaling	miR-21 [20] miR-26b [37] miR-32 [20] miR-103a-3p [34] miR-143-3p [37] miR-148a [20] miR-155-5p [34] miR-200a-3p [34] miR-210-3p [34] miR-320c [138] miR-424 [20] miR-1225-5p [138]	miR-29a-3p [139] miR-146a-5p [34] miR-324-5p [20] miR-342-3p [20] miR-423-5p [20]
	Axon guidance [20]	miR-21 miR-26b miR-32 miR-126 miR-424	miR-766 miR-940
	Focal adhesion [20]	miR-7 miR-19a miR-27b miR-98 miR-148b miR-195 miR-301a miR-335 miR-454 miR-542-3p	miR-1275

β-Cell Autoantigen Release

In T1D pathogenesis, the release of β-cell autoantigens plays a pivotal role in triggering and sustaining the autoimmune response. Autoantigens such as insulin, GAD65, IA-2, and ZnT8 are released from stressed or damaged β-cells due to inflammatory insults, oxidative stress, or viral infections. Antigen-presenting cells (APCs), including dendritic cells and macrophages, process these autoantigens and present them to autoreactive T-cells in lymphoid tissues. This activation of autoreactive T-cells drives targeted β-cell destruction, creating a self-perpetuating cycle of immune-mediated damage. The continuous release of autoantigens further amplifies β-cell loss, ultimately leading to insulin deficiency and hyperglycemia.

Growing evidence suggests that dysregulated miRNAs contribute to β-cell autoantigen release and immune activation by regulating key processes such as apoptosis, inflammation, and stress responses. Research indicates significant miRNA dysregulation in T1D patients, particularly in the early stages of the disease. Notably, miR-24, miR-29a, miR-148a, and miR-200a were found to be altered in the serum of newly diagnosed T1D children, implicating their role in β-cell regulatory

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networks [31,114]. These findings underscore the critical role of miRNAs in modulating β-cell autoantigen release and suggest that targeting specific miRNAs may offer therapeutic strategies to preserve β-cell function and slow T1D progression. Furthermore, understanding miRNA-controlled regulatory networks could facilitate the development of precise diagnostic tools for differentiating diabetes subtypes based on miRNA expression profiles.

Autoimmune Activation

In T1D, autoimmune activation is a key driver of disease onset. Normally, the immune system distinguishes between self and non-self, protecting the body from harmful pathogens. However, in T1D, this system mistakenly targets insulin-producing β-cells in the pancreas as threats, triggering an autoimmune response. T-cells attack and destroy β-cells, progressively reducing insulin production. This immune activation is influenced by genetic predisposition and environmental factors, such as viral infections [5]. Once initiated, the autoimmune cascade leads to sustained β-cell destruction, ultimately resulting in insulin deficiency. As insulin levels decline, blood glucose rises, leading to the hallmark symptoms and complications of T1D.

At a molecular level, several miRNAs have been implicated in this autoimmune process. In recently diagnosed patients (<5 years), miR-21-5p, miR-103a-3p, miR-148b-3p, miR-155-5p, and miR-210-3p are upregulated in plasma, while miR-146a-5p is downregulated [34]. These expression patterns appear specific to the early disease stages, as no significant differences are observed beyond five years post-diagnosis [34]. Among these, miR-155-5p is notably increased in activated B and T-cells, macrophages, and dendritic cells through the NF-κB and JNK pathways, underscoring its critical role in both innate and adaptive immunity [34,140–142]. Upregulated miR-155-5p also modulates immune responses by reducing NF-κB activation via IKK downregulation [34,140,142]. In T1D, this regulatory function contributes to the autoimmune destruction of β-cells [34].

Additionally, miR-200 promotes a pro-apoptotic genetic signature in pancreatic islets of diabetic mice by increasing TP53 expression, which suppresses anti-apoptotic and stress-resistance networks in β-cells [34,143]. miR-210-3p, upregulated in the plasma, serum, and urine of pediatric T1D patients, downregulates FOXP3, a key regulator of Treg function, impairing immune tolerance and exacerbating autoimmunity [34,144]. This miRNA also targets genes involved in mitochondrial metabolism, angiogenesis, DNA repair, and cell survival, linking it to various cancers and cardiovascular diseases [34,69,145]. Notably, miR-21, miR-126, and miR-210 are crucial in the pathophysiology of diabetes [29]. In T1D patients, miR-21 and miR-210 levels are significantly elevated in both plasma and urine, whereas miR-126 is reduced in urine but remains unchanged in plasma [35]. Given their involvement in DN, a leading cause of ESRD, these miRNAs hold promise as noninvasive biomarkers for T1D-associated renal dysfunction [35,146–150].

Furthermore, research has shown that miRNA expression patterns in T1D evolve with disease progression, influencing immunological processes in the early stages. For example, miR-10b-5p, miR-17-5p, miR-30e-5p, miR-93-5p, miR-99a-5p, miR-125b-5p, miR-423-3p, and miR-497-5p exhibit significant temporal alterations based on disease duration [151]. Two distinct expression patterns were identified [151]. The first group—miR-17-5p, miR-30e-5p, miR-93-5p, and miR-423-3p—showed reduced expression within the first 12 months post-diagnosis but increased between one and five years. The second group—miR-10b-5p, miR-99a-5p, miR-125b-5p, and miR-497-5p—displayed elevated expression in the first 12 months, followed by a decline over the subsequent five years. Additionally, miR-30e-5p, miR-93-5p, and miR-423-3p maintained consistently higher expression levels throughout the study, whereas miR-10b-5p, miR-17-5p, miR-99a-5p, miR-125b-5p, and miR-497-5p exhibited persistently lower expression relative to the overall sample average at all time points [151]. These findings underscore the dynamic nature of miRNA regulation in T1D and its potential role in disease progression.

Guay et al. [107] demonstrated that rodent and human T lymphocytes release exosomes containing miR-142-5p, which can be transferred to pancreatic β-cells. Suppression of these miRNAs in recipient β-cells blocked exosome-mediated apoptosis and prevented diabetes development in

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NOD mice, leading to improved insulin levels, reduced insulitis scores, and diminished inflammation. Additionally, exosomes from T lymphocytes induced apoptosis and upregulated Ccl2, Ccl7, and Cxcl10 expression, activating chemokine signaling specifically in β-cells. This process recruited immune cells, potentially exacerbating β-cell destruction during the autoimmune attack [107].

Ventriglia et al. [36] demonstrated that miR-409-3p is significantly downregulated in both recently diabetic NOD mice and newly diagnosed T1D patients. Notably, miR-409-3p expression inversely correlated with insulitis severity and blood glucose levels, reflecting disease progression in NOD mice [36].

To investigate the relationship between miR-409-3p expression and immune system differentiation or metabolic status, including glucose homeostasis, its plasma levels were monitored in recently diabetic NOD mice following anti-CD3 antibody (anti-CD3 Ab) treatment [36]. Anti-CD3 Ab was known to modulate the islet immune response and slow disease progression [152,153]. In anti-CD3-treated NOD mice, plasma miR-409-3p levels were associated with T-cell dynamics and the proinflammatory environment in the islets but not with blood glucose levels [36]. These findings suggest that miR-409-3p plays a role in the primary pathogenesis of T1D by influencing immune system activity.

Taken together, autoimmune activation in T1D is a complex, multifactorial process driven by genetic predisposition and environmental triggers. Key miRNAs, including miR-155-5p, miR-200a-3p, and miR-210-3p, play pivotal roles in the autoimmune destruction of β-cells, underscoring their potential as biomarkers and therapeutic targets for disease management and progression.

Endoplasmic Reticulum and Oxidative Stress

In T1D, endoplasmic reticulum (ER) and oxidative stress are key contributors to the progressive destruction of insulin-producing β-cells. Due to their high insulin production demands and exposure to an inflammatory environment caused by autoimmune attacks, β-cells are particularly vulnerable to these stressors [154]. Oxidative stress in T1D arises from an imbalance between reactive oxygen species (ROS) production and the cell's antioxidant defenses. Excessive ROS generation, driven by chronic inflammation, cytokine release (e.g., IL-1β, IFN-γ), and immune cell infiltration, leads to cellular damage affecting proteins, lipids, and DNA, ultimately promoting β-cell dysfunction and apoptosis [155]. The transcription factors FOXO and NRF2 play crucial roles in the antioxidant response, but their reduced activity in T1D exacerbates oxidative stress [156].

Several miRNAs regulate ER and oxidative stress mechanisms in T1D. miR-200a-3p targets KEAP1, a negative regulator of NRF2, and its downregulation in T1D impairs NRF2 activation, increasing β-cell susceptibility to oxidative damage [157]. miR-146a modulates inflammatory and stress responses by targeting TRAF6 and IRAK1, key components of the NF-κB signaling pathway [158,159]. Its dysregulation in T1D leads to increased NF-κB activity, exacerbating both ER and oxidative stress and promoting β-cell apoptosis [158]. Additionally, miR-21 influences oxidative stress by targeting PTEN, a negative regulator of the PI3K/Akt pathway. While miR-21 overexpression enhances pro-survival Akt signaling, it also contributes to oxidative stress by inhibiting genes responsible for ROS detoxification. Its dysregulation in T1D is associated with increased oxidative damage and impaired β-cell function [160,161].

These miRNAs and their target genes form critical regulatory networks that modulate ER and oxidative stress responses in β-cells. Disruptions in these pathways accelerate β-cell destruction and T1D progression. Understanding these mechanisms provides potential therapeutic targets for preserving β-cell function and delaying disease onset.

Apoptosis

Apoptosis, a tightly regulated process of programmed cell death, is essential for maintaining cellular homeostasis by eliminating compromised cells. However, in T1D, excessive apoptosis of β-cells is a key driver of disease progression. Cytotoxic T-cells, which typically target pathogens,

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mistakenly attack β-cells, releasing cytotoxic molecules such as granzyme B and perforin that trigger apoptosis.

Several molecular pathways mediate β-cell apoptosis in T1D. Anti-apoptotic proteins like BCL-2 and MCL-1 help preserve mitochondrial integrity under normal conditions, but the pro-inflammatory environment of T1D—dominated by cytokines such as IL-1β, TNF-α, and IFN-γ—disrupts the balance between pro- and anti-apoptotic signals, tipping the scale toward cell death. This imbalance promotes mitochondrial dysfunction, cytochrome c release, and caspase activation, culminating in β-cell apoptosis.

miRNAs play a crucial role in regulating apoptotic pathways in T1D. miR-15a-5p, miR-16-5p, miR-21-5p, miR-30e-5p, miR-34a, miR-146a influence genes involved in apoptosis [8,90,118,162,163], while miR-100-5p and miR-150-5p impact the PI3K/Akt pathway, which regulates β-cell survival and growth [8]. Chronic inflammation and oxidative stress impair PI3K/Akt signaling, weakening its protective effects on β-cells and increasing their vulnerability to apoptosis. The cyclin-dependent kinase inhibitor P21, which regulates cell cycle progression, can also induce apoptosis under inflammatory conditions. miR-21-5p, miR-100-5p, and miR-375 modulate the Cyclin-CDK complex, influencing β-cell proliferation and survival. Additionally, KLF11 and the TGF-β pathway contribute to β-cell apoptosis, with miRNAs such as miR-10b-5p, miR-21-5p, and miR-424 modulating these pathways [129,164–166].

Certain miRNAs are notably upregulated in T1D. For example, miR-24, which is involved in inflammation and TGF-β signaling, is implicated in both T1D and T2D pathogenesis [31,167–169]. miR-25, associated with apoptosis regulation and cancer pathology, is elevated in the serum of T1D children and negatively correlated with β-cell function [31,170–175]. However, in DN models, miR-25 is downregulated in the kidneys, affecting NADPH expression under hyperglycemia, underscoring its diverse role in pancreatic endocrine cell proliferation and disease pathology [31,176]. Additionally, miR-21-5p and miR-148a, which are elevated in T1D patients, contribute to apoptosis through pathways such as FoxO and TGF-β, with miR-148a specifically targeting BCL2L11 to promote β-cell death [33,177]

miRNAs in T1D also exhibit complex, context-dependent roles. For example, miR-200b promotes apoptosis by downregulating Oxr1 under oxidative stress, whereas its inhibition confers protection against apoptosis [77].The miR-29 family reduces glucose-stimulated insulin secretion and proinsulin mRNA levels but paradoxically mitigates cytokine-induced apoptosis in β-cells [106]. Similarly, miR-21, upregulated in early T1D, promotes apoptosis by suppressing BCL-2 [108]. Collectively, these findings underscore the intricate involvement of miRNAs in T1D pathophysiology, offering potential therapeutic targets for preserving β-cell function and slowing disease progression.

Insulin signaling

The pathogenesis of diabetes is closely linked to impaired insulin secretion, with both T1D and T2D involving disruptions in insulin signaling. Numerous studies have elucidated the molecular mechanisms underlying these impairments, highlighting the roles of insulin and the insulin receptor in disease progression [178].

miR-103a-3p is upregulated in both the liver of T2D patients [71] and the plasma of T1D patients [34]. This miRNA plays a critical role in insulin signaling by targeting CAV1, a key regulator of the insulin receptor in both forms of diabetes [72]. Additionally, miR-103a-3p influences miRNA biosynthesis by regulating Dicer, suggesting that its upregulation could lead to the downregulation of other miRNAs [179]. Interestingly, studies have also linked miR-103a-3p to cellular proliferation and apoptosis in cancer cell lines, indicating its broader role in cellular homeostasis [180].

Ferraz et al. investigated the effects of nuclear and mitochondrial dysfunctions on T1D dysregulation, identifying 41 dysregulated miRNAs in T1D patients (Table 3) [37]. Among these, miR-21-5p had the highest number of target genes, including SOCS and AKT, which are involved in key T1D-related pathways such as insulin signaling and apoptosis [8,34] [37]. Their findings suggest

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that these 41 miRNAs, particularly miR-21-5p and miR-26b-5p, contribute to nuclear and mitochondrial dysfunctions, ultimately exacerbating T1D dysregulation [37].

Figure 3 illustrates dysregulated miRNAs in T1D that target key proteins, contributing to regulatory T-cell dysfunction, impaired immune tolerance, reduced β-cell proliferation, and heightened apoptosis—ultimately driving autoimmune β-cell destruction. miR-146a-5p, downregulated in T1D [181], normally inhibits STAT1 [182]. Its reduction activates STAT1 in regulatory T-cells, impairing immune tolerance [182]. miR-10b-5p, downregulated in late T1D [151], increases KLF11 expression [129], enhancing TGF-β signaling [183]. However, impaired TGF-β signaling in T1D disrupts regulatory T-cell function [184,185]. miR-210-3p, upregulated in T1D [34], suppresses FOXP3 [144], further contributing to immune dysregulation. miR-216a, crucial for pancreatic β-cells [186], is downregulated in T1D [187]. This reduction increases PTEN, inhibiting β-cell proliferation [187]. miR-21-5p, upregulated in T1D [8,118], suppresses the anti-apoptotic protein BCL2, leading to increased β-cell apoptosis [108]. miR-16-5p enhances β-cell proliferation by inhibiting apoptosis [162]. However, its downregulation in T1D upregulates CXCL10, promoting β-cell death [162]. Collectively, these dysregulated miRNA pathways drive β-cell destruction in T1D.

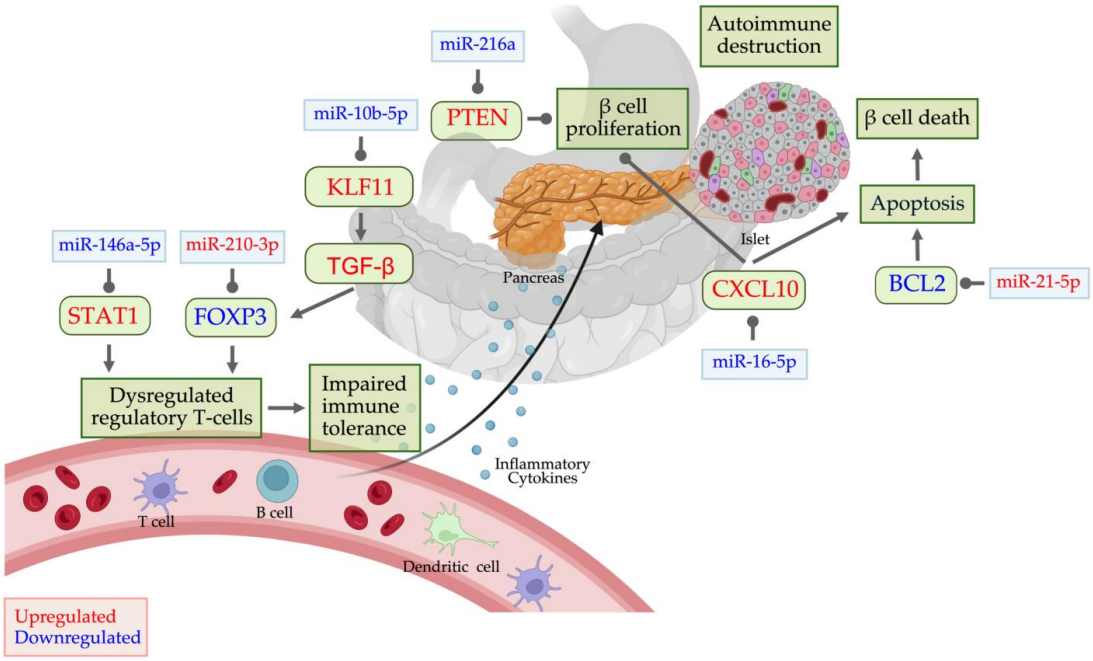

Figure 3. miRNA regulation in T1D pathogenesis and their target pathways. Dysregulated miRNAs play a pivotal role in T1D pathogenesis by modulating key immune and apoptotic processes. Upregulated miRNAs and their target genes are highlighted in red, while downregulated ones are shown in blue. These miRNAs contribute to regulatory T-cell dysfunction, impaired immune tolerance, inhibition of β-cell proliferation, and apoptosis, ultimately driving autoimmune β-cell destruction.

6. miRNA-Based Therapeutic Strategies for T1D

miRNA-based therapeutics represent an innovative approach to disease treatment by regulating gene expression at the post-transcriptional level. Given that miRNA expression is altered in various diseases, modulating their levels—either by introducing miRNAs or inhibiting their function—offers a promising therapeutic strategy. This concept parallels antisense mRNA and RNA interference (RNAi) techniques. miRNA-based therapeutics primarily follow two strategies: antisense inhibition of mature miRNAs and miRNA replacement. The choice of approach depends on whether the therapeutic goal is to suppress overexpressed miRNAs or restore downregulated miRNAs to regain lost function.

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A comprehensive analysis of T1D pathogenesis and its associated complications has identified a range of consistently dysregulated miRNAs. As summarized in Figure 4, miRNA expression patterns in T1D patients and animal models show considerable overlap. In T1D patients, 138 miRNAs are upregulated, while 93 are downregulated. Similarly, T1D animal models exhibit 66 upregulated and 63 downregulated miRNAs. Notably, miR-21, miR-29a, miR-142-5p, miR-145, miR-146a, miR-186, miR-195, miR-199a-3p, miR-208, and miR-323-5p are consistently upregulated in both T1D patients and murine models. Conversely, miR-10b-5p, miR-16-5p, miR-17-5p, miR-23a, miR-126-5p, miR-143-3p, miR-150, miR-155, and miR-409-3p are consistently downregulated in both populations.

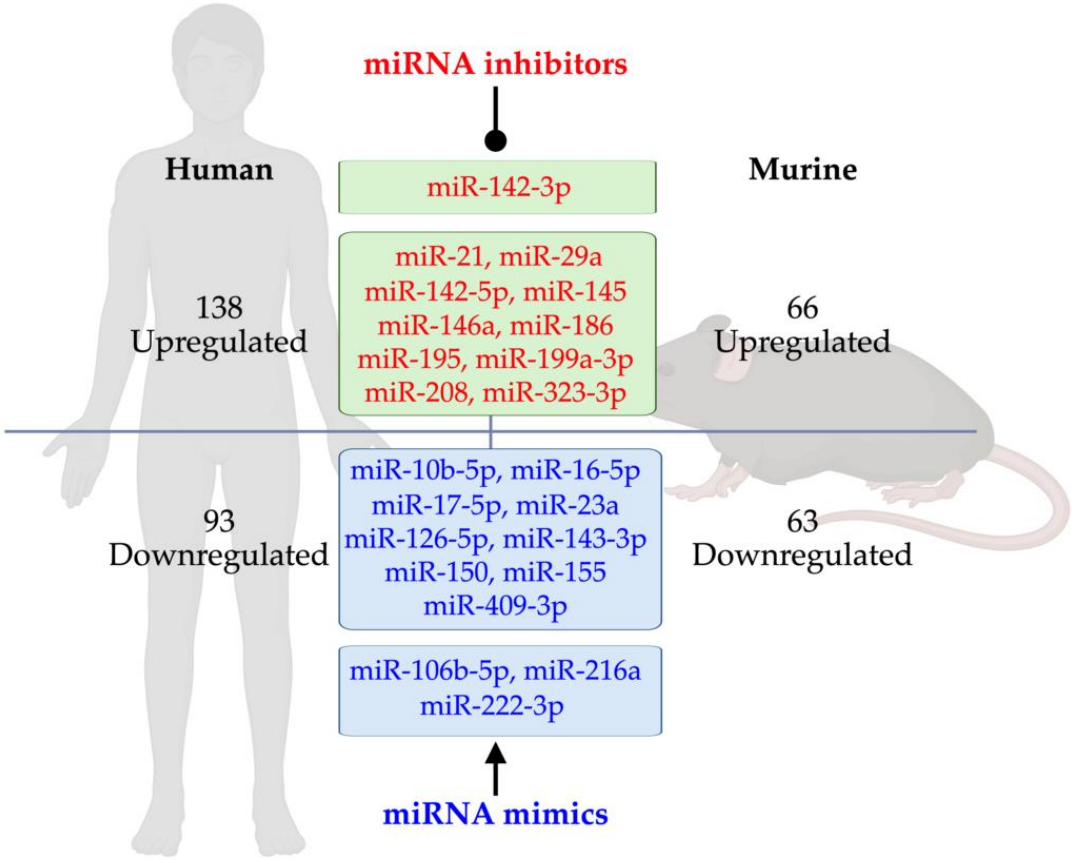

Figure 4. Conserved dysregulated miRNAs in T1D patients and murine models, and therapeutic strategies.In T1D patients, 134 miRNAs are upregulated and 96 downregulated, while T1D animal models exhibit 67 upregulated and 77 downregulated miRNAs. Ten miRNAs (miR-21, miR-29a, miR-142-5p, miR-145, miR-146a, miR-186, miR-195, miR-199a-3p, miR-208, and miR-323-3p) are consistently upregulated in both humans and animal models. Conversely, nine miRNAs (miR-10b-5p, miR-16-5p, miR-17-5p, miR-23a, miR-106b, miR-126-5p, miR-143-3p, miR-150, miR-155, miR-222-3p, and miR-409-3p) are consistently downregulated in both. miR-106b-5p and miR-222-3p currently under investigation in preclinical and clinical trials for their therapeutic potential in T1D. As therapeutic strategies, ungulated miRNAs may be targeted with inhibitors, while downregulated miRNAs can be restored using mimics.

Additionally, miR-106b-5p and miR-222-3p have emerged as potential therapeutic targets due to their roles in pancreatic β-cell function. Tsukita et al. [113] found that bone marrow transplantation (BMT) restored pancreatic islets in STZ-induced diabetic mice while increasing miR-106b and miR-222 levels in serum exosomes and islets. Exosomal miRNA analysis showed elevated miR-106b-5p and miR-222-3p in the culture media of bone marrow cells from STZ-BMT mice. Notably, administering miR-106b-5p and miR-222-3p mimics enhanced β-cell proliferation and improved hyperglycemia by downregulating the Cip/Kip family, promoting β-cell regeneration [113]. A miR-216a mimic nanodrug has been also shown to enhance β-cell proliferation via PTEN inhibition,

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leading to increased insulin production [187]. Another study identified miR-142-3p as a key regulator of islet autoimmunity in NOD mice. Inhibiting miR-142-3p with an LNA-miRNA inhibitor enhanced regulatory T-cell stability by targeting TET2, reducing islet autoimmunity in diabetic mice [188].

Furthermore, miR-21 [33,45–47] and miR-146a [38,70,74–76,158,159]—both implicated in inflammatory and autoimmune responses—have emerged as potential therapeutic targets. Modulating these dysregulated miRNAs through inhibitors or mimics (Figure 4) may help reduce immune-mediated β-cell destruction and inflammation in T1D. Targeting these pathways could slow disease progression and potentially prevent its onset. As research advances, miRNA-based therapies offer a novel approach to preserving β-cell function and improving T1D outcomes.

7. Conclusion and Future Study

T1D results from the loss of pancreatic β-cells through autoimmune or idiopathic processes, yet the precise molecular mechanisms driving β-cell destruction remain incompletely understood. Furthermore, no therapeutics have been developed to effectively reverse disease progression in T1D.

miRNA-based therapeutics offer a unique advantage, as a single miRNA can regulate the expression of multiple genes, ranging from tens to hundreds. These therapies operate through two primary strategies: miRNA mimics, which restore deficient miRNAs to recover protein synthesis, and miRNA inhibitors, which suppress overactive miRNAs to reduce pathological gene expression. Additionally, because miRNAs are endogenous molecules, they exhibit low immunogenicity, reducing the likelihood of immune rejection.

Although no miRNA-based therapies have received FDA approval to date, numerous clinical trials, as reviewed by Singh et al. [24] are exploring their therapeutic potential. These studies demonstrate the broad applicability of miRNA therapeutics in various diseases, including diabetes and autoimmune disorders. This review highlights key preclinical studies investigating miRNA-based therapies in T1D, detailing their therapeutic efficacy, dysregulated miRNAs in T1D patients and murine models, and their associated pathways and target genes.

Despite their promise, miRNA therapeutics face several challenges. First, miRNA mimics and inhibitors are highly susceptible to degradation in circulation, limiting their stability and therapeutic efficacy. Second, intracellular delivery remains inefficient, as many miRNAs become sequestered in endosomes rather than reaching their target sites in the cytoplasm. Developing advanced delivery systems and enhancing endosomal escape mechanisms are crucial for improving gene silencing efficiency. Lastly, miRNAs can induce off-target effects by regulating multiple genes across different pathways and cell types, potentially leading to unintended gene silencing. Strategies such as sequence optimization, chemical modifications, and targeted delivery approaches can enhance specificity and minimize off-target effects, thereby improving the safety and efficacy of miRNA-based therapies.

Although current miRNA-based therapeutics face obstacles, rapidly advancing preclinical and clinical research, along with interdisciplinary innovations, may soon overcome these challenges. Given their remarkable therapeutic potential, miRNA-based treatments hold promise not only for T1D but for a broad spectrum of diseases.

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Abbreviations

T1D, type 1 diabetes; T2D, type 2 diabetes; GD, gestational diabetes; ER, endoplasmic reticulum; AAbs, autoantibodies; HLA, human leukocyte antigen; AGEs, advanced glycation end products; miRNAs, microRNA; mRNAs, messenger RNAs; PBMCs, peripheral blood mononuclear cells; Treg**,** regulatory T-cell; NOD mice, non-obese diabetic mice; STZ, Streptozotocin; LADA, latent autoimmune diabetes in adults; DC, diabetic cardiomyopathy; DN, diabetic nephropathy; APCs, Antigen-presenting cells; ROS, reactive oxygen species; BMT, bone marrow transplantation.

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