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Review: RNA therapy for type 1 & 2 diabetes

Muhamad Ilham Bintang[1], Aiyi Asnawi[2], Widhiya Agita[3]
[1,2,3]Pharmachy, Bhakti Kencana University, Bandung, Indonesia

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ABSTRACT

Diabetes is a group of metabolic disorders with high blood glucose levels. In type 1 diabetes, blood glucose increases due to damage to pancreatic beta cells. In type 2 diabetes, insulin production is ineffective in glucose uptake into target tissues, increasing glucose levels. Advances in RNA-based technologies indicate that RNA molecules have multiple roles in disease initiation and progression. This review discusses recent developments in RNA therapy for type 1 and type 2 diabetes. RNA therapies, such as mRNA, miRNA, siRNA, lncRNA, and circRNA, show great potential. mRNA and miRNA are important in pancreatic cell development, insulin resistance, insulin sensitivity, and insulin secretion. siRNA improves glucose regulation and improves beta cell dysfunction in T1D and T2D. lncRNAs regulate beta cell responses to inflammation and insulin resistance. circRNA plays a role in M1 macrophage activation associated with T1D pathogenesis and regulation of insulin transcription and secretion. RNA therapy offers revolutionary possibilities in the management and potential cure of type 1 and type 2 diabetes. It is believed to improve and change the clinical approach to diabetes, with research continuing to develop therapies that are safe, effective, and able to change the paradigm of diabetes treatment.

Corresponding Author:

Muhammad Ilham Bintang,
Pharmachy,
Bhakti Kencana University,
Jl. Soekarno Hatta No. 754, Cipadung Kidul, Kec. Panyileukan, Bandung City, West Java 40614, Indonesia
Email: Bintang.ilham0904@gmail.com

INTRODUCTION

One of the main health problems that occurs among Indonesian people is metabolic disease, one of which is diabetes mellitus(Care & Suppl, 2019). According to the International Diabetes Federation (IDF), Indonesia is ranked 7th among 10 countries with a total of 10.7 million sufferers. Indonesia is one of the countries in Southeast Asia on the list(Ministry of Health of the Republic of Indonesia, 2020). Diabetes is a group of metabolic disorders in which blood glucose levels are abnormally high. In type 1 diabetes (T1D), blood glucose levels increase due to destruction of pancreatic beta islet cells through autoimmunity leading to low or no insulin production, most (T1D) patients rely on lifelong insulin replacement therapy(Fan, Pang, Shi, et al., 2022). In type 2 diabetes (T2D), insulin production is unable to stimulate glucose uptake into target tissues such as liver, adipose, and skeletal muscle, thereby increasing blood glucose levels.(Nutter & Kuyumcu-Martinez, 2018).

Additionally due to long-term hyperglycemia, diabetes mellitus will cause severe chronic injury and dysfunction in all types of tissues and organs, imposing tremendous health and economic consequences on patients.(Ilonen et al., 2019; Pang et al., 2020). This defect in insulin-mediated glucose uptake into target tissues causes chronic hyperglycemia in the bloodstream and triggers pathogenic signals including inflammation, hypertension, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum (ER) stress, and(Harcourt et al., 2013; Schneider et al., 2016). Recently, recent advances in RNA-based technologies, given that RNAs molecules have many roles in biological processes such as disease initiation and progression. RNA has emerged as a promising therapeutic candidate for many diseases, one of which is diabetes mellitus(Sullinger & Nair, 2016).

RNA therapy can manipulate gene expression or produce therapeutic proteins, thereby making these drugs suitable for pathologies with defined genetic targets. Currently, protein-coding RNAs have been the most studied, although they account for only a small fraction of all RNA molecules in transcript books. In contrast, the role of non-coding RNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), in disease processes has only begun to emerge in the last 15 years.(Sullinger & Nair, 2016). miRNAs negatively regulate mRNA expression and thereby interfere with post-transcriptional regulation in various diseases(Thum, 2014). Similarly, lncRNAs participate in cellular processes by influencing epigenetic, post-transcriptional and translational pathways(Devaux et al., 2015). These RNA therapies act by targeting RNA or proteins, by encoding missing or damaged proteins, or by mediating RNA editing(Lu & Thum, 2019).

RNA therapies can be designed to specifically target certain genes or mRNAs that play a role in the pathogenesis of diabetes, thereby reducing the side effects that may arise from less specific therapies. RNA can be used for various purposes, such as coding for missing proteins (mRNA)(Qin et al., 2022), inhibits the expression of certain genes (siRNA)(Neumann et al., 2017), or regulate gene expression (miRNA and lncRNA)(Devaux et al., 2015; Latreille et al., 2014).(R. Liu et al., 2022)reported the involvement of miRNAs in T2D by showing that miR-375 plays an important role in insulin secretion and miR-21 promotes apoptosis in mouse and human beta cells(Sims et al., 2017). circRNA is related to T2DM. For example, hsa_circ0054633 in peripheral blood has potential as a diagnostic biomarker of pre-diabetes and T2DM, in addition another circRNA, Cdr1as, regulates insulin transcription and secretion in islet cells via miRNA (miR)-7 and its targets(H. Xu et al., 2015; Z. Zhao et al., 2017).

Regardless of its therapeutic mechanism, it interferes with posttranscriptional RNA programming in diabetes and plays an important role in the development of type 1 and type 2 diabetes. RNA therapy provides new possibilities to improve the management and possibly cure diabetes through highly specific and individualized interventions. Research continues to develop to develop therapies that are safe, effective, and capable of changing the diabetes treatment paradigm. The aim of this review article is to provide guidance regarding recent developments in RNA therapy for type 1 and type 2 diabetes.

RESEARCH METHOD

In the last ten years (2014-2024), scientific articles on RNA therapy for type 1 and 2 diabetes were used as the basis for this review article. The first 120 articles were collected, including 15 main articles and 20 supporting articles. The reference sources used consist of keywords such as "RNA Therapy", "RNA Therapy Diabetic type 1 & 2", "Diabetic type 1", "Diabetic type 2", "RNA Therapy metabolic diseases", "Types of RNA Therapy", "Therapeutic potential of RNA" lncRNA Therapy Diabetic type 1 & 2, circRNA Therapy Diabetic type 1 & 2, mRNA Therapy Diabetic type 1 & 2, miRNA Therapy Diabetic type 1 & 2, and Therapy Diabetic type 1 & 2 siRNA.

RESULTS AND DISCUSSIONS

Type 1 diabetes and type 2 diabetes are heterogeneous diseases whose clinical presentations and disease progression can vary greatly. Classification is important for determining therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis.(Dabelea et al., 2014). A variety of genetic and environmental factors can result in a progressive loss of b-cell mass and/or function that manifests clinically as hyperglycemia. Identification of individualized therapies for diabetes in the future will require better characterization of many of these therapies' pathways to b cell death or dysfunction(Skyler et al., 2017).

Over the past 25 years, the idea of using RNA molecules as therapeutic agents has evolved from a concept to a clinical reality(Burnett & Rossi, 2012; Sullenger & Nair, 2016). Initially, RNA was considered a poor choice for a therapeutic agent, given its relatively short half-life in vivo. RNA molecules have many properties that could potentially make them useful therapeutics. They can fold into complex conformations that allow them to specifically bind proteins, small molecules, or other nucleic acids or even to form catalytic centers.(Cech & Steitz, 2014). The four classes of therapeutic RNA that have received the most attention can be classified according to their mode of action: (i) encoding therapeutic proteins or vaccine antigens (mRNA), (ii) inhibiting the activity of pathogenic RNA [small interfering RNA (siRNA), microRNA (miRNA), and antisense RNA], (iii) can interact with RNA polymerase II and influence the transcription process of circRNA (circular RNA) genes, and (iv) influence various lncRNA (long non-coding RNA) cellular signaling pathways(Sullinger & Nair, 2016).

The mechanism of RNA therapy involves the use of various types of RNA to regulate gene expression and modulate biological pathways relevant to diseases, including diabetes(Zogg et al., 2022). RNA therapy for diabetes involves several types of RNA used to regulate gene expression and modulate disease-relevant biological pathways. The type of RNA used is mRNA (messenger RNA), miRNA (microRNA), siRNA (small interfering RNA), lncRNA (long non-coding RNA) and circRNA (circular RNA). RNA therapy offers a variety of approaches to regulate gene expression and has great potential for the treatment of various diseases. Ongoing research and development will continue to expand its clinical applications for type 1 and type 2 diabetes.

Table 1. Mechanisms of RNA therapy in type 1 and 2 diabetes

Target RNA	Mechanism	Results	Reference
In this study, the targeted RNA therapy is Micro RNA (miRNA) based therapy.	The mechanism of RNA against target proteins involves the role of microRNA (miRNA) in regulating gene expression. By binding to mRNA, miRNA can inhibit protein translation or trigger mRNA degradation, which ultimately reduces the amount of protein produced from the target gene. In this way, miRNAs can directly control the expression of their target proteins, influencing various biological processes in cells, including the regulation of glucose and insulin metabolism in the context of diabetes.	Identification of miRNAs involved in the regulation of glucose metabolism, insulin secretion, pancreatic beta cell proliferation, and diabetes pathogenesis. The discovery that miRNAs can be potential therapeutic targets in the treatment of diabetes by two main approaches: restoring reduced miRNA expression using miRNA mimics, or inhibiting excessive miRNA activity using miRNA inhibitors. Research into certain miRNAs such as miR-375 and miR-143 which have been shown to play a role in the regulation of insulin secretion, adipogenesis, and lipid metabolism.	(Mao et al, 2014)
In this study, the targeted RNA therapy is Circular RNA circPPM1F (circRNA) based therapy.	The mechanism of RNA against target proteins involves various complex molecular processes in the regulation of gene expression	The role of circPPM1F in the regulation of M1 macrophage activation, interactions with target proteins, and its implications in	(C. Zhang et al., 2020)

Target RNA	Mechanism	Results	Reference
	and protein function. The target proteins in this study are HuR (Human antigen R), EIF4A3 and FUS (Fused in Sarcoma)	the pathophysiology of T1DM. These findings may pave the way for the development of therapies targeted at circPPM1F regulation as a new approach in the treatment of type 1 diabetes.	
In this study, the targeted RNA therapy is therapy based on the lncRNA MALAT1 (Metastasis-Associated Lung Adenocarcinoma Transcript 1)	The mechanism of RNA therapy in this study involves the regulation of gene expression and target protein activity through complex interactions between lncRNA, microRNA, and the hormone resistin to reduce insulin resistance in Type 2 Diabetes Mellitus	The complex regulation between MALAT1, miR-382-3p, and resistin may be a potential therapeutic target to reduce insulin resistance in Type 2 Diabetes Mellitus, with physical exercise also playing a role in alleviating insulin resistance through this mechanism	(S. Liu et al., 2019)
In this study, the targeted RNA therapy is circular RNAs (circRNAs) based therapy.	Circular RNAs (circRNAs) can interact with target proteins through several mechanisms. circRNAs can act as sponges for microRNAs (miRNAs), binding to miRNAs and preventing them from interacting with target mRNAs, thereby affecting gene regulation. circRNAs can also regulate host gene expression through cis-acting mechanisms, influencing the transcription and translation levels of associated genes.	Association with Inflammation: IL-6 (Interleukin-6) expression was significantly increased in the T2DM group compared with the control group, and there was a positive correlation between IL-6 and circANKRD36. Interaction of circANKRD36 with miRNAs: circANKRD36 is thought to interact with several miRNAs, including hsa-miR-3614-3p, hsa-miR-498, and hsa-miR-501-5p, which may influence pathways related to inflammation and type 2 diabetes.	(Fang et al., 2018)
In this research, the RNA used is mRNA	Exosomal mRNA can also play a role in the regulation of gene expression. In the context of T1DM, where abnormal interactions between pancreatic beta cells and immune cells, especially T lymphocytes, are the main pathogenic mechanism, exosomes may act as mediators between beta cells and immune cells. Exosomes originating from the islets of Langerhans contain beta cell autoantigens and can be taken up by dendritic cells, which then causes cell activation.	This study identified plasma exosomal mRNA expression profiles in type 1 diabetes (T1DM) for the first time. Significant differences in mRNA expression between T1DM patients and controls were found, with 112 mRNAs being significantly different. These results highlight the potential of exosomal mRNA biomarkers in the diagnosis and understanding of T1DM pathogenesis.	(Fan, Pang, Shi, et al., 2022)
this research focuses on the analysis of lncRNA (long non-coding RNA) in exosomes.	In this study, lncRNA (long non-coding RNA) in exosomes can interact with their action targets through mechanisms such as regulation of gene transcription, modulation of mRNA translation, regulation of chromatin structure, interaction with miRNA as a "sponge", and interaction with proteins. This mechanism allows exosomal lncRNAs to influence biological pathways involved in the pathogenesis of Type 1 Diabetes Mellitus.	Identification of 162 exosomal lncRNAs that differ in expression between Type 1 Diabetes Mellitus (T1DM) patients and control subjects. Of the 162 lncRNAs, 77 of them experienced increased expression, while 85 experienced decreased expression. Although lncRNA sequencing results showed differences in expression, qRT-PCR analysis did not show significant differences between T1DM patients and control subjects.	(Pang et al., 2020)
The type of RNA that is the main basis in this	microRNA (miRNA) works by specifically binding to the 3' UTR	The results of this study indicate that microRNAs (miRNAs) serve	(Nigi et al., 2018)

Target RNA	Mechanism	Results	Reference
journal is microRNA (miRNA).	(Untranslated Region) sequence of the target mRNA. This process causes mRNA degradation or translation inhibition, which ultimately results in effects on gene expression and protein activity involved in the insulin signal transduction pathway. MiRNAs act as negative regulators in controlling gene expression and protein activity involved in the insulin response, thereby having an impact on energy homeostasis and metabolism.	as important regulators in the insulin signaling pathway, with the ability to regulate gene expression and the activity of factors involved in insulin signal transduction. MiRNA regulation of insulin pathway components is tissue or cell level specific, adding complexity to the understanding of this regulation.	
The type of RNA that is the main basis for this journal is modified mRNA encoding VEGF-A.	mRNA functions as a carrier of genetic information that is chemically modified to encode the protein VEGF-A. The mRNA is introduced into cells via intradermal injection and then converted into the VEGF-A protein via a translation mechanism. The resulting VEGF-A protein plays a role in increasing blood flow and local expression of functional VEGF-A protein, which can trigger regenerative angiogenesis in patients with type 2 diabetes	The results of this study indicate that the use of intradermal delivery of modified mRNA encoding VEGF-A in patients with type 2 diabetes is safe and can produce local expression of functional VEGF-A protein. This can increase blood flow and trigger angiogenesis regeneration in the patient's skin.	(Gan et al., 2019)
In this study, the targeted RNA therapy was circRNA-based therapy for diabetic nephropathy (DN) by changing circRNA levels.	circRNAs for diabetic nephropathy (DN) involve the regulation of gene expression through the interaction of circRNAs with specific miRNAs, which then influence signaling pathways involved in the pathogenesis of DN.	The results of this study suggest that circRNA-based therapy may be a promising approach in the treatment of diabetic nephropathy (DN) by altering the expression levels of certain circRNAs to modulate signaling pathways involved in pathological conditions, such as podocyte apoptosis and kidney damage.	(Fan, Pang, Xie, et al., 2022)
In this study, the targeted RNA therapy is small interfering RNA (siRNA) based therapy.	Through the mechanism of RNA interference, siRNA can inhibit the expression of genes responsible for the development of the condition. By suppressing certain genes, siRNA can reduce inflammation, improve glucose regulation, and inhibit the progression of diabetes complications such as retinopathy and nephropathy.	This research shows that the use of siRNA has provided promising results in the treatment of diabetes and other related conditions. By using siRNA to suppress the expression of certain genes, this research was successful in improving wound healing in diabetes patients, regulating glucose homeostasis, managing diabetic nephropathy, retinopathy, and diabetes-related inflammation.	(Pravin & Chirag, 2018)

mRNA in Type 1 and 2 Diabetes Therapy

mRNA is an abbreviation of "messenger RNA" or "messenger ribonucleic acid." which plays a role in transcribing genetic information from DNA and carrying it to ribosomes, the place where proteins are synthesized in cells. mRNA acts as an intermediary molecule that carries the genetic code from DNA to produce certain proteins in a process called translation(Deravi, 2023). mRNA therapy: mRNA therapy involves the introduction of engineered mRNA into the body to produce therapeutic proteins(Pardi et al., 2018; Sahin et al., 2014). mRNA therapy offers an

innovative and potential approach to treating diabetes in a more natural and sustainable way than conventional therapy. This approach also holds promise in terms of gene modification and management of immune and inflammatory responses that contribute to the development of diabetes.

Gene modification in diabetes pathogenesis

Beta cells have a very important role, so their proper differentiation and growth is essential for glucose metabolism.(Fishman et al., 2017)reported that mRNA was used to transfect polyclonal CD8 T cells to express a peptide/b2m/CD3-z construct that can direct T cells against pathogenic CD8 T cells that play a role in diabetes. This mRNA allows reprogramming of T cells to recognize diabetogenic T cells and prevent autoimmune diabetes in NOD mice. Besides that(Wasserfall et al., 2017)found that although levels of mature insulin and C-peptide were very low or undetectable in the pancreas of type 1 diabetes (T1D) patients, proinsulin and INS mRNA were still present, so this condition may indicate a disruption in the properly functioning mechanism of processing proinsulin into insulin in pancreas of type 1 diabetes patients.

The role of mRNA in the pathogenesis of diabetes

Compared with non-diabetic patients, 279 mRNAs were up-regulated and 353 mRNAs were down-regulated in the serum of diabetic patients. Differential genes at nodes of the interaction network were screened, and TLR6, RUNX1, and ST2 were found to be associated with the development of diabetes. Pathway enrichment analysis revealed that the lysosomal pathway plays an important role in the occurrence and development of diabetes. TLR6, RUNX1, and ST2 mRNA expression as well as the lysosomal pathway may be involved in the pathogenesis of diabetes. This study provides insight into the molecular mechanisms of diabetes and associated mRNA levels(W. Zhao et al., 2020).

microRNA in Type 1 and 2 Diabetes Therapy

miRNA-based therapies offer the potential to regulate multiple aspects of diabetes pathophysiology, from beta cell function and regeneration to insulin sensitivity and vascular complications. Modifying the expression of certain miRNAs can provide a precise and effective therapeutic approach to manage type 1 and type 2 diabetes. The use of microRNA (miRNA) as the main basis in this research is due to the fact that miRNAs are important regulators in various biological processes, including glucose metabolism and development. disease. MiRNAs can serve as potential biomarkers due to their stability in blood circulation and their ability to reflect changes in pathological conditions, such as type 1 and type 2 Diabetes. Therefore, miRNA analysis can provide valuable insights in the understanding of diseases and the identification of new biomarkers(Higuchi et al., 2015). Following are the types of miRNA and their role in type 1 and type 2 diabetes.

Pancreatic Beta Cell Development

Pancreatic beta cells are the sole source of insulin production and secretion within the pancreas of the human body, therefore their proper differentiation and growth is essential for glucose metabolism. Research reports that miR activity is closely related to pancreatic islet development(Tattikota et al., 2015). In addition, the expression of miRs can contribute to the differentiation of islets of Langerhans cells which are the main units in insulin secretion(Coskun et al., 2018). Overall, miRs may be associated with the differentiation, proliferation and survival of pancreatic beta cells(LaPierre & Stoffel, 2017). The differentiation of insulin-producing cells from stem cells is influenced by several up-regulated miRs (such as 9-5p, 9-3p, 10a, 99a-3p, 124a, 135a, 138, 149, 211, 342-3p, and 375), while Other miRs were downregulated (such as 31, 127, 143, 302c-3p, 373, 518b, and 520c-3p) in pancreatic islets(Sebastiani et al., 2017). The differentiation of mesenchymal stem cells into cells that produce insulin is also related to the presence of miRs(Bai et

al., 2017). Dysregulation of miRs by intrinsic or extrinsic agents can disrupt normal pancreatic beta cell formation(Engelmann et al., 2017).

miRs and insulin sensitivity/resistance

Insulin sensitivity and resistance depend primarily on the cellular response to circulating insulin. Cellular modifications of insulin sensitivity and resistance are influenced by certain miRs, such as miR-29, miR-221/222, and miR-103/107(Vivacqua et al., 2017).(He et al., 2007)Found that overexpression of miR-29 was found to be strongly associated with insulin resistance, where the expression of miR-29 in skeletal muscle, liver, and adipocytes was compared between healthy mice and Goto-Kakizaki (diabetic) mice, indicating that overexpression of miR-29 in Diabetic animals inhibit glucose uptake, possibly through suppression of AKT (Protein kinase B) activity.(Ling et al., 2009)It was demonstrated that upregulation of miR-320 in adipocytes and vascular endothelial cells induces insulin resistance by suppressing p85 expression and downregulating GLUT-4.(Trajkovski et al., 2011)It was confirmed that miR-103 and miR-107 disrupt glucose homeostasis by downregulating caveolin-1, thereby inducing insulin resistance in liver and adipose tissue. Caveolin-1, a protein component of the membrane layer of caveolae, is known to be a key regulator of insulin receptor signaling; This protein improves glucose homeostasis by increasing insulin receptor activity and inhibiting tyrosine phosphatase 1B.

miRs and insulin production/secretion

An influence of some miRs on insulin gene expression or exocytosis of its storage vesicles is possible. In this context, it is evident that overexpression of miR375 and miR-9 decreases insulin secretion and exocytosis by mechanisms dependent on the transcription factors myotropin and Onecut-2, respectively. In addition, miR-7 regulates insulin exocytosis and impaired beta cell function in conditions of obesity and T2DM, both in animal models and humans.(Hubal et al., 2017). Insulin exocytosis can be reduced by miR-124a and miR-96. In this context, miR-124a reduces glucose-induced insulin release by increasing the expression of Rab3A, SNAP25 (synaptosomal-associated protein 25), and synapsin-1A, whereas miR-96 increases the expression of granulophilin and decreases the expression of Noc2 (Nucleolar complex protein 2), which inhibits the capacity of MIN6B1 cells for insulin secretion(Lovis et al., 2008).(Sebastiani et al., 2015)confirmed these findings and suggested that miR-124 was overexpressed in the pancreatic islets of T2DM patients, thereby negatively impacting insulin secretion.

siRNA in Type 1 and 2 Diabetes Therapy

Small interfering RNA (siRNA) is a ribonucleic acid (RNA) consisting of a single-stranded linear structure that has an important role in the regulation and expression of certain genes and also stores genetic information. RNA structure consists of four ribonucleotide base pairs namely, adenine, guanine, cytosine and uracil where purines like adenine and guanine bind complementary pyridines like uracil and cytosine, respectively. siRNA has great potential to be used in genetic therapy to treat various diseases by inhibiting the expression of genes that play a role in disease pathogenesis(Pravin & Chirag, 2018).

siRNA therapy of pancreatic beta cell dysfunction

Recent studies have demonstrated the identification of islet homeostasis protein (IHoP) present in pancreatic α cells. Research shows that glucagon and IHoP strongly stimulate diabetic islets and regulate IHoP-induced glucagon secretion to regulate glucose homeostasis. Glucagon levels increase when the body lacks normal glucose levels and to regulate normal glucose levels glucagon is secreted. IHoP-siRNA was introduced to suppress IHoP expression in diabetic mice resulting in suppression of DM development(Oh et al., 2017). Gluconeogenesis, a metabolic process that occurs in the liver is responsible for producing glucose and transcription factors play an important role in the regulation of this process. Effective results in diabetes management were observed when knockdown of TORC2 gene with siRNA was performed in mouse models. siRNA

against TORC2 was target specific and delivered with novel lipid nanoparticles(Pravin & Chirag, 2018).

siRNA in the treatment of diabetic nephropathy

The Gremlin siRNA plasmid was optimized, and its effects were examined in a CD-1 mouse model undergoing uninephrectomy and STZ treatment before plasmid injection. It was observed that gremlin siRNA successfully inhibited gremlin gene expression in rat kidney. The level of proteinuria was significantly reduced with an increase in serum creatinine levels and renal hypertrophy was observed. Gremlin siRNA plasmid treatment suppressed apoptosis and proliferation of renal cells as well as the role of BMP-7 in mesangial cells(Pravin & Chirag, 2018). Another study revealed that transforming growth factor-β1 (TGF-β1) is a protein that increases during the development of diabetic nephropathy leading to renal fibrosis and Decreased SnoN gene is associated with increased TGF-β1 that mediates TGF-β1 induction of diabetic nephropathy. Regulation of SnoN patterning was studied in mice subjected to high glucose stress by arcadia silencing achieved by siRNA transfection. The results show that the epithelial mesenchymal transition in renal cells due to high glucose levels is an early phase of renal fibrosis and is successfully inhibited and helps in the management of diabetic nephropathy.(L. Liu et al., 2017).

circRNA in Type 1 and 2 Diabetes Therapy

CirRNA is a single-stranded RNA molecule that differs from linear RNA in that it forms a continuous loop that joins covalently. CirRNAs are formed by a back-splicing mechanism, where the 5' end of the upstream pre-mRNA is spliced non-linearly to an exon downstream of the 3' end(Holdt et al., 2018). CircRNAs have the potential to serve as a source of regulatory signals in a variety of disease conditions, including diabetes. Several studies have shown that circRNAs may play a role in the regulation of diabetes-related gene expression through interactions with miRNAs or proteins.

circRNA in modifying gene expression

Diversified circRNAs have been identified based on their function, such as sponges, decoys, or translatable elements that modify gene or protein expression(Cheng et al., 2015). First, circRNAs can modulate miRNA activity by functioning as sponges. A single circRNA can bind to one or many miRNAs through its circular sequence. A well-studied example of miRNA sponging is circRNA-CDR1as, which was found to have 63 binding sites for miR-7. Second, circRNAs can serve as decoys by interacting with proteins and altering cellular function(Sakshi et al., 2021). CircRNAs have significant gene regulatory capabilities and are disrupted in various diseases, including tumors(R. Zhou et al., 2018). The most important function of CircRNAs is that they can act as endogenous RNAs that compete to interact with miRNAs (Oudkk. 2020). Recently, several databases have been developed as easy-to-use tools for miRNAs-CircRNAs association prediction. For example,(Shan et al., 2017)reported that the novel circRNA circ-HIPK3 significantly increased in diabetic retinas, and may act as an endogenous competing RNA interacting with miR-30a to promote endothelial proliferation and vascular dysfunction.

circRNA as a diabetes biomarker

The role of epigenetic regulation of circRNAs in diabetes is rapidly evolving. Considering the stability of circular RNA in blood samples, many studies have focused on circular RNA as a promising biomarker for early diagnosis of diabetes. Indeed, clinical studies have shown that circulating long non-coding RNA (lncRNA) could be a potential diagnostic biomarker for diabetes (Carter et al., 2015). Therefore, it is reasonable that circular RNA could also be used to predict diabetes. Multiple studies have tested the diagnostic potential of circular RNAs in this context(JR Zhang & Sun, 2020). Specifically, 489 circular RNAs were differentially detected in peripheral blood samples of type 2 diabetics(B. Zhou & Yu, 2017). Of these circular RNAs, hsa_circ_0054633 was found to have the highest diagnostic capacity for pre-diabetes and type 2 diabetes(Z. Zhao et

al., 2017), which is also supported by other findings that hsa_circ_0054633 is significantly increased in gestational diabetes(JR Zhang & Sun, 2020). In addition, the same research group showed that blood levels of hsa-circRNA11783-2 were closely related to the severity of coronary artery disease and type 2 diabetes(C. Li et al., 2018).

Role of circRNAs in pancreatic islet function

Abnormal insulin synthesis and release are closely related to high blood glucose levels and the development of diabetes. Type 1 diabetes is characterized by β-cell loss, insulin deficiency, and sustained high blood glucose levels, whereas type 2 diabetes is caused by β-cell malfunction and insulin resistance.(JR Zhang & Sun, 2020). Therefore, comprehensive elucidation of the mechanisms involved in β-cell function and insulin release may open new avenues for the development of therapies against diabetes. In diabetic conditions, β-cell dysfunction is closely correlated with abnormal expression of protein-coding and non-coding transcripts, including miRNAs and lncRNAs(Motterle et al., 2015, 2016). Recently, evidence for the role of circular RNAs in the maintenance of β-cell function has begun to emerge(Ghasemi et al., 2019; Stoll et al., 2018; Tian et al., 2018; Wong et al., 2018).

lncRNA in Type 1 and 2 Diabetes Therapy

lncRNAs are endogenous RNA molecules with a length of more than 200 nucleotides. LncRNA has a structure similar to mRNA but does not code for protein. Gene expression is regulated by lncRNAs through their influence on mRNA splicing, transcription, translation, and genome imprinting(M. Li et al., 2019). The functional mechanisms of lncRNAs are still under investigation and are more complicated compared to miRNAs that only bind to specific complementary RNA sequences. lncRNAs often take advantage of their large size to form secondary or tertiary structures to carry out their functions. Most lncRNAs reside in the cell nucleus, serving as molecular scaffolds to stabilize nuclear structures or signaling complexes(Suwal et al., 2019).

Implications of lncRNAs in Metabolic Networks

Recently, it has been shown that lncRNAs mediate biological processes in islet cells, such as β-cell differentiation and proliferation, as well as insulin biosynthesis and secretion. A total of 1,128 human islet cell genes have been identified with high confidence through transcriptome mapping, of which 55% are intergenic lncRNAs and 40% are islet-specific antisense lncRNAs(Morán et al., 2012). Many metabolic processes, including lipid synthesis, drug metabolism, the process of which is gluconeogenesis, occur in the liver. In normal liver function, a number of lncRNAs have been identified. In particular, lncLSTR (liver-specific triglyceride regulator lnc) was identified as a liver-specific lncRNA that regulates systemic lipid metabolism(P. Li et al., 2015). Cyp8b1 activity is regulated by this lncRNA through its binding to TDP-43, which alters bile acid levels and affects FXR (farnesoid X receptor), thereby increasing hepatic clearance of triglycerides(P. Li et al., 2015). This initial study revealed the involvement of lncRNAs in normal liver metabolic pathways. Similarly, lipid levels are modulated by lncRNA SRA by regulating the expression of adipose triglyceride lipase (ATGL), which plays an important role in hepatic triacylglycerol hydrolysis.(Chen et al., 2016).

lncRNAs in regulating glucose metabolism

Regarding lncRNAs that regulate glucose and lipid metabolism in adipocytes,(B. Xu et al., 2010)first reported that SRA, a lncRNA, promotes insulin-stimulated glucose uptake by activating PPARγ, leading to increased phosphorylation of downstream targets Akt and Forkhead box protein O1 (FOXO1) in adipocytes. Furthermore, the same group showed that global deletion of SRA protected mice from high-fat diet-induced obesity and improved glucose tolerance throughout the animal's body.(S. Liu et al., 2014). In addition, lncRNAs were also found to regulate glucose and lipid metabolism in certain cancer cells. Increased CRNDE expression in CRC cells

increases glucose metabolism, lactate secretion, and lipid synthesis, and reduces lipid catabolism(Ellis et al., 2014). Regulation of lactate consumption and production via the mTOR–STAT3⁄miR143–HK2 pathway in cancer cells has been reported(Y. Li et al., 2014). In addition to targeting various metabolic processes, including glucose and lipids, some lncRNAs are only involved in the regulation of lipid metabolism(Hu et al., 2014).

lncRNAs in the regulation of insulin secretion and sensitivity

Several recent studies have identified a number of lncRNAs that have the ability to regulate insulin secretion and sensitivity. For example, the positive effects of SRA in improving insulin sensitivity and insulin-stimulated glucose uptake in adipocytes(B. Xu et al., 2010). In addition, increased SRA was also associated with increased insulin-stimulated glucose uptake via Akt and FOXO1 signaling. In contrast, steady depletion of SRA using the lentiviral system inhibits insulin-stimulated glucose uptake and insulin-stimulated phosphorylation of Akt and FOXO1(B. Xu et al., 2010). Additionally, it has been identified that a lncRNA termed Growth Arrest-Specific 5 (Gas5) also functions as a novel regulator of insulin synthesis and secretion in pancreatic β cells. Depletion of Gas5 reduces insulin production by inhibiting the expression of several key transcription factors, including Pdx-1 and MafA(JR Zhang & Sun, 2020).

CONCLUSION

RNA therapy offers revolutionary possibilities in the management and potential cure of type 1 and type 2 diabetes. RNA therapies, such as siRNA, miRNA, mRNA, lncRNA and circRNA, enable targeting of specific genes or molecular pathways involved in diabetes, increasing the potential effectiveness of therapy and reducing the risk drug resistance. Continued research in this area is critical to developing therapies that are safe, effective, and able to change the paradigm of diabetes treatment.

References

Bai, C., Gao, Y., Li, X., Wang, K., Xiong, H., Shan, Z., Zhang, P., Wang, W., Guan, W., & Ma, Y. (2017). MicroRNAs can effectively induce formation of insulin-producing cells from mesenchymal stem cells. Journal of Tissue Engineering and Regenerative Medicine, 11(12), 3457–3468. https://doi.org/10.1002/term.2259

Burnett, J.C., & Rossi, J.J. (2012). RNA-based therapeutics: Current progress and future prospects. Chemistry and Biology, 19(1), 60–71. https://doi.org/10.1016/j.chembiol.2011.12.008

Care, D., & Suppl, S.S. (2019). 2. Classification and diagnosis of diabetes: Standards of medical care in diabetesd2019. Diabetes Care, 42(January), S13–S28. https://doi.org/10.2337/dc19-S002

Cech, T.R., & Steitz, J.A. (2014). The noncoding RNA revolution - Trashing old rules to forge new ones. Cell, 157(1), 77–94. https://doi.org/10.1016/j.cell.2014.03.008

Chen, G., Yu, D., Nian, X., Liu, J., Koenig, R. J., Xu, B., & Sheng, L. (2016). LncRNA SRA promotes hepatic steatosis through repressing the expression of adipose triglyceride lipase (ATGL). Scientific Reports, 6(October), 1–13. https://doi.org/10.1038/srep35531

Cheng, L.J., Chen, J.H., Lin, M.Y., Chen, L.C., Lao, C.H., Luh, H., & Hwang, S.J. (2015). A competing risk analysis of sequential complication development in Asian type 2 diabetes mellitus patients. Scientific Reports, 5(October), 1–11. https://doi.org/10.1038/srep15687

Coskun, E., Ercin, M., & Gezginci-Oktayoglu, S. (2018). The Role of Epigenetic Regulation and Pluripotency-Related MicroRNAs in Differentiation of Pancreatic Stem Cells to Beta Cells. Journal of Cellular Biochemistry, 119(1), 455–467. https://doi.org/10.1002/jcb.26203

Dabelea, D., Rewers, A., Stafford, J.M., Standiford, D.A., Lawrence, J.M., Saydah, S., Imperatore, G., D'Aǵostino, R.B., Mayer-Davis, E.J., & Pihoker, C. (2014). Trends in the prevalence of ketoacidosis at diabetes diagnosis: The search for diabetes in youth study. Pediatrics, 133(4). https://doi.org/10.1542/peds.2013-2795

Deravi, C. (2023). BioGecko BioGecko. Biogecko, 12(01), 316–324.

Devaux, Y., Zangrando, J., Schroen, B., Creemers, E.E., Pedrazzini, T., Chang, C.P., Dorn, G.W., Thum, T., &

Heymans, S. (2015). Long noncoding RNAs in cardiac development and aging. Nature Reviews Cardiology, 12(7), 415–425. https://doi.org/10.1038/nrcardio.2015.55

Ellis, B.C., Graham, L.D., & Molloy, P.L. (2014). CRNDE, a long non-coding RNA responsive to insulin/IGF signaling, regulates genes involved in central metabolism. Biochimica et Biophysica Acta - Molecular Cell Research, 1843(2), 372–386. https://doi.org/10.1016/j.bbamcr.2013.10.016

Engelmann, I., Alidjinou, E.K., Bertin, A., Bossu, J., Villenet, C., Figeac, M., Sane, F., & Hober, D. (2017). Persistent coxsackievirus B4 infection induces microRNA dysregulation in human pancreatic cells. Cellular and Molecular Life Sciences, 74(20), 3851–3861. https://doi.org/10.1007/s00018-017-2567-0

Fan, W., Pang, H., Shi, X., Li, J., Wang, Y., Luo, S., Lin, J., Yu, H., Xiao, Y., Li, Huang, G., Xie, Z., & Zhou, Z. (2022). Plasma-derived exosomal mRNA profiles associated with type 1 diabetes mellitus. Frontiers in Immunology, 13(September), 1–14. https://doi.org/10.3389/fimmu.2022.995610

Fan, W., Pang, H., Xie, Z., & Huang, G. (2022). Circular RNAs in diabetes mellitus and its complications. 2045(August), 1–17. https://doi.org/10.3389/fendo.2022.885650

Fang, Y., Wang, X., Li, W., Han, J., Jin, J., & Su, FEI (2018). Screening of circular RNAs and validation of circANKRD36 associated with inflammation in patients with type 2 diabetes mellitus. 1865–1874. https://doi.org/10.3892/ijmm.2018.3783

Fishman, S., Lewis, MD, Siew, LK, De Leenheer, E., Kakabadse, D., Davies, J., Ziv, D., Margalit, A., Karin, N., Gross, G., & Wong, F.S. (2017). Adoptive Transfer of mRNA-Transfected T Cells Redirected against Diabetogenic CD8 T Cells Can Prevent Diabetes. Molecular Therapy, 25(2), 456–464. https://doi.org/10.1016/j.ymthe.2016.12.007

Gan, L.M., Lagerström-Fermér, M., Carlsson, L.G., Arfvidsson, C., Egnell, A.C., Rudvik, A., Kjaer, M., Collén, A., Thompson, JD, Joyal, J., Chialda, L., Koernicke, T., Fuhr, R., Chien, K.R., & Fritsche-Danielson, R. (2019). Intradermal delivery of modified mRNA encoding VEGF-A in patients with type 2 diabetes. Nature Communications, 10(1), 1–9. https://doi.org/10.1038/s41467-019-08852-4

Ghasemi, H., Sabati, Z., Ghaedi, H., Salehi, Z., & Alipoor, B. (2019). Circular RNAs in β-cell function and type 2 diabetes-related complications: a potential diagnostic and therapeutic approach. Molecular Biology Reports, 46(5), 5631–5643. https://doi.org/10.1007/s11033-019-04937-x

Harcourt, B.E., Penfold, S.A., & Forbes, J.M. (2013). Coming full circle in diabetes mellitus: From complications to initiation. Nature Reviews Endocrinology, 9(2), 113–123. https://doi.org/10.1038/nrendo.2012.236

He, A., Zhu, L., Gupta, N., Chang, Y., & Fang, F. (2007). Overexpression of micro ribonucleic acid 29, highly up-regulated in diabetic rats, leads to insulin resistance in 3T3-L1 adipocytes. Molecular Endocrinology, 21(11), 2785–2794. https://doi.org/10.1210/me.2007-0167

Higuchi, C., Nakatsuka, A., Eguchi, J., Teshigawara, S., Kanzaki, M., Katayama, A., Yamaguchi, S., Takahashi, N., Murakami, K., Ogawa, D., Sasaki, S., Makino, H., & Wada, J. (2015). Identification of circulating miR-101, miR-375 and miR-802 as biomarkers for type 2 diabetes. Metabolism: Clinical and Experimental, 64(4), 489–497. https://doi.org/10.1016/j.metabol.2014.12.003

Holdt, L.M., Kohlmaier, A., & Teupser, D. (2018). Molecular roles and functions of circular RNAs in eukaryotic cells. Cellular and Molecular Life Sciences, 75(6), 1071–1098. https://doi.org/10.1007/s00018-017-2688-5

Hu, YW, Yang, JY, Ma, , L., & Wang, Q. (2014). A lincRNA-DYNLRB2-2/GPR119/GLP-1R/ABCA1-dependent signal transduction pathway is essential for the regulation of cholesterol homeostasis. Journal of Lipid Research, 55(4), 681–697. https://doi.org/10.1194/jlr.M044669

Hubal, MJ, Nadler, E.P., Ferrante, S.C., Barberio, M.D., Suh, J.H., Wang, J., Dohm, G.L., Pories, W.J., Mietus-Snyder, M., & Freishtat, R.J. (2017). Circulating adipocyte-derived exosomal MicroRNAs associated with decreased insulin resistance after gastric bypass. Obesity, 25(1), 102–110. https://doi.org/10.1002/oby.21709

Ilonen, J., Lempainen, J., & Veijola, R. (2019). The heterogeneous pathogenesis of type 1 diabetes mellitus. Nature Reviews Endocrinology, 15(11), 635–650. https://doi.org/10.1038/s41574-019-0254-y

Ministry of Health of the Republic of Indonesia. (2020). Stay Productive, Prevent and Treat Diabetes Mellitus. In the data and information center of the Indonesian Ministry of Health.

LaPierre, M. P., & Stoffel, M. (2017). MicroRNAs as stress regulators in pancreatic beta cells and diabetes. Molecular Metabolism, 6(9), 1010–1023. https://doi.org/10.1016/j.molmet.2017.06.020

Latreille, M., Hausser, J., Stützer, I., Zhang, Q., Hastoy, B., Gargani, S., Kerr-Conte, J., Pattou, F., Zavolan, M., Esguerra, J.L.S. , Eliasson, L., Rülicke, T., Rorsman, P., & Stoffel, M. (2014). MicroRNA-7a regulates pancreatic β cell function. Journal of Clinical Investigation, 124(6), 2722–2735. https://doi.org/10.1172/JCI73066

Li, C., Zhao, L., Jiang, W., Che, L., & Xu, Y. (2018). Correct microarray analysis approaches in 'Hsa-circRNA11783-2 in peripheral blood is correlated with coronary artery disease and type 2 diabetes mellitus.' Diabetes and Vascular Disease Research, 15(1), 92–93. https://doi.org/10.1177/1479164117739435

Li, M., Duan, L., Li, Y., & Liu, B. (2019). Long noncoding RNA/circular noncoding RNA–miRNA–mRNA pathways in cardiovascular diseases. Life Sciences, 233(March), 116440. https://doi.org/10.1016/j.lfs.2019.04.066

Li, P., Ruan, X., Yang, L., Kiesewetter, K., Zhao, Y., Luo, H., Chen, Y., Gucek, M., Zhu, J., & Cao, H. (2015). A liver-enriched long non-coding RNA, lncLSTR, regulates systemic lipid metabolism in mice. Cell Metabolism, 21(3), 455–467. https://doi.org/10.1016/j.cmet.2015.02.004

Li, Y., Lin, X., Zhao, X. J., Xie, J., JunNan, W., Sun, T., & Fu, Z. (2014). Ozone (O3) elicits neurotoxicity in spinal cord neurons (SCNs) by inducing ER Ca2+ release and activating the CaMKII/MAPK signaling pathway. Toxicology and Applied Pharmacology, 280(3), 493–501. https://doi.org/10.1016/j.taap.2014.08.024

Ling, HY, Ou, HS, Feng, SD, Zhang, XY, Tuo, QH, Chen, LX, Zhu, BY, Gao, ZP, Tang, CK, Yin, WD, Zhang, L., & Liao, DF (2009). Changes in microRNA (mir) profile and effects of mir-320 in insulin-resistant 3t3-l1 adipocytes. Clinical and Experimental Pharmacology and Physiology, 36(9), 32–39. https://doi.org/10.1111/j.1440-1681.2009.05207.x

Liu, L., Shi, M., Wang, Y., Zhang, C., Su, B., Xiao, Y., & Guo, B. (2017). SnoN upregulation ameliorates renal fibrosis in diabetic nephropathy. PLOS ONE, 12(3), 1–14. https://doi.org/10.1371/journal.pone.0174471

Liu, R., Liu, C., He, X., Sun, P., Zhang, B., Yang, H., Shi, W., & Ruan, Q. (2022). MicroRNA-21 promotes pancreatic β cell function through modulating glucose uptake. Nature Communications, 13(1), 1–15. https://doi.org/10.1038/s41467-022-31317-0

Liu, S., Sheng, L., Miao, H., Saunders, T.L., Macdougal, O.A., Koenig, R.J., & Xu, B. (2014). SRA gene knockout protects against diet-induced obesity and improves glucose tolerance. Journal of Biological Chemistry, 289(19), 13000–13009. https://doi.org/10.1074/jbc.M114.564658

Liu, S., Zheng, F., Xie, K., Xie, M., Jiang, L., & Cai, Y. (2019). Exercise Reduces Insulin Resistance in Type 2 Diabetes Mellitus via Mediating the lncRNA MALAT1 / MicroRNA-382-3p / Resistin Axis. Molecular Therapy: Nucleic Acids, 18(87), 34–44. https://doi.org/10.1016/j.omtn.2019.08.002

Lovis, P., Gattesco, S., & Regazzi, R. (2008). Regulation of the expression of components of the exocytotic machinery of insulin-secreting cells by microRNAs. Biological Chemistry, 389(3), 305–312. https://doi.org/10.1515/BC.2008.026

Lu, D., & Thum, T. (2019). RNA-based diagnostic and therapeutic strategies for cardiovascular disease. Nature Reviews Cardiology, 16(11), 661–674. https://doi.org/10.1038/s41569-019-0218-x

Manuscript, A. (2014). NIH Public Access. 37–47. https://doi.org/10.1016/j.phrs.2013.06.005.MicroRNAs

Morán, I., Akerman, I., Van De Bunt, M., Xie, R., Benazra, M., Nammo, T., Arnes, L., Nakić, N., García-Hurtado, J., Rodríguez -Seguí, S., Pasquali, L., Sauty-Colace, C., Beucher, A., Scharfmann, R., Van Arensbergen, J., Johnson, P.R., Berry, A., Lee, C., Harkins, T., … Ferrer, J. (2012). Human β cell transcriptome analysis uncovers lncRNAs that are tissue-specific, dynamically regulated, and abnormally expressed in type 2 diabetes. Cell Metabolism, 16(4), 435–448. https://doi.org/10.1016/j.cmet.2012.08.010

Motterle, A., Gattesco, S., Caille, D., Meda, P., & Regazzi, R. (2015). Involvement of long non-coding RNAs in beta cell failure at the onset of type 1 diabetes in NOD mice. Diabeologia, 58(8), 1827–1835. https://doi.org/10.1007/s00125-015-3641-5

Motterle, A., Sanchez-Parra, C., & Regazzi, R. (2016). Role of long non-coding RNAs in the determination of β-cell identity. Diabetes, Obesity and Metabolism, 18(April), 41–50. https://doi.org/10.1111/dom.12714

Neumann, U.H., Ho, J.S.S., Chen, S., Tam, Y.Y.C., Cullis, P.R., & Kieffer, T.J. (2017). Lipid nanoparticle delivery of glucagon receptor siRNA improves glucose homeostasis in mouse models of diabetes. Molecular Metabolism, 6(10), 1161–1172. https://doi.org/10.1016/j.molmet.2017.06.012

Nigi, L., Grieco, G.E., Ventriglia, G., Brusco, N., Mancarella, F., Formichi, C., Dotta, F., & Sebastiani, G. (2018). MicroRNAs as regulators of insulin signaling: Research updates and potential therapeutic perspectives in type 2 diabetes. International Journal of Molecular Sciences, 19(12). https://doi.org/10.3390/ijms19123705

Nutter, C. A., & Kuyumcu-Martinez, M. N. (2018). Emerging roles of RNA-binding proteins in diabetes and their therapeutic potential in diabetic complications. Wiley Interdisciplinary Reviews: RNA, 9(2), 1–17. https://doi.org/10.1002/wrna.1459

Oh, S.H., Jorgensen, M.L., Wasserfall, C.H., Gjymishka, A., & Petersen, B.E. (2017). Suppression of islet protein homeostasis thwarts diabetes mellitus progression. Laboratory Investigation, 97(5), 577–590. https://doi.org/10.1038/labinvest.2017.15

Pang, H., Luo, S., Huang, G., Xia, Y., Xie, Z., & Zhou, Z. (2020). Advances in Knowledge of Candidate Genes Acting at the Beta-Cell Level in the Pathogenesis of T1DM. Frontiers in Endocrinology, 11(March), 1–11. https://doi.org/10.3389/fendo.2020.00119

Pardi, N., Hogan, M.J., Porter, F.W., & Weissman, D. (2018). mRNA vaccines-a new era in vaccinology. Nature Reviews Drug Discovery, 17(4), 261–279. https://doi.org/10.1038/nrd.2017.243

Pravin, S., & Chirag, P. (2018). Ac ce pt ed us cr t. Journal of Drug Targeting, 0(0), 000. https://doi.org/10.1080/1061186X.2018.1476518

Qin, S., Tang, X., Chen, Y., Chen, K., Fan, N., Xiao, W., Zheng, Q., Li, G., Teng, Y., Wu, M., & Song, X. (2022). mRNA-based therapeutics: powerful and versatile tools to combat diseases. Signal Transduction and Targeted Therapy, 7(1). https://doi.org/10.1038/s41392-022-01007-w

Sahin, U., Karikó, K., & Türeci, Ö. (2014). MRNA-based therapeutics-developing a new class of drugs. Nature Reviews Drug Discovery, 13(10), 759–780. https://doi.org/10.1038/nrd4278

Sakshi, S., Jayasuriya, R., Ganesan, K., Xu, B., & Ramkumar, K. M. (2021). Role of circRNA-miRNA-mRNA interaction network in diabetes and its associated complications. Molecular Therapy Nucleic Acids, 26(December), 1291–1302. https://doi.org/10.1016/j.omtn.2021.11.007

Schneider, ALC, Kalyani, R.R., Golden, S., Stearns, S.C., Wruck, L., Yeh, H.C., Coresh, J., & Selvin, E. (2016). Diabetes and prediabetes and risk of hospitalization: The atherosclerosis risk in communities (ARIC) study. Diabetes Care, 39(5), 772–779. https://doi.org/10.2337/dc15-1335

Sebastiani, G., Po, A., Miele, E., Ventriglia, G., Ceccarelli, E., Bugliani, M., Marselli, L., Marchetti, P., Gulino, A., Ferretti, E., & Dotta, F. (2015). MicroRNA-124a is hyperexpressed in type 2 diabetic human pancreatic islets and negatively regulates insulin secretion. Acta Diabetolica, 52(3), 523–530. https://doi.org/10.1007/s00592-014-0675-y

Sebastiani, G., Valentini, M., Grieco, G.E., Ventriglia, G., Nigi, L., Mancarella, F., Pellegrini, S., Martino, G., Sordi, V., Piemonti, L., & Dotta, F. (2017). MicroRNA expression profiles of human iPSCs differentiation into insulin-producing cells. Acta Diabetolica, 54(3), 265–281. https://doi.org/10.1007/s00592-016-0955-9

Shan, K., Liu, C., Liu, BH, Chen, X., Dong, R., Liu, Wu, J. H., Zhao, C., & Yan, B. (2017). Circular noncoding RNA HIPK3 mediates retinal vascular dysfunction in diabetes mellitus. Circulation, 136(17), 1629–1642. https://doi.org/10.1161/CIRCULATIONAHA.117.029004

Sims, E.K., Lakhter, A.J., Anderson-Baucum, E., Kono, T., Tong, X., & Evans-Molina, C. (2017). MicroRNA 21 targets BCL2 mRNA to increase apoptosis in rat and human beta cells. Diabeologia, 60(6), 1057–1065. https://doi.org/10.1007/s00125-017-4237-z

Skyler, JS, Bakris, G.L., Bonifacio, E., Darsow, T., Eckel, R.H., Groop, L., Groop, P.H., Handelsman, Y., Insel, R.A., Mathieu, C., McElvaine, A.T., Palmer , J.P., Pugliese, A., Schatz, D.A., Sosenko, J.M., Wilding, J.P.H., & Ratner, R.E. (2017). Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes, 66(2), 241–255. https://doi.org/10.2337/db16-0806

Stoll, L., Sobel, J., Rodriguez-Trejo, A., Guay, C., Lee, K., Venø, M.T., Kjems, J., Laybutt, D.R., & Regazzi, R. (2018). Circular RNAs as novel regulators of β-cell function in normal and disease conditions. Molecular Metabolism, 9, 69–83. https://doi.org/10.1016/j.molmet.2018.01.010

Sullenger, B. A., & Nair, S. (2016). <Sullenger2016.Pdf>.

Suwal, A., Hao, JL, Liu, XF, Zhou, DD, Pant, OP, Gao, Y., Hui, P., Dai, XX, & Lu, CW (2019). Nonratt021972 long-noncoding rna: A promising lncrna in diabetes-related diseases. International Journal of Medical Sciences, 16(6), 902–908. https://doi.org/10.7150/ijms.34200

Tattikota, S.G., Rathjen, T., Hausser, J., Khedkar, A., Kabra, UD, Pandey, V., Sury, M., Wessels, HH, Mollet, I.G., Eliasson, L., Selbach, M. , Zinzen, R.P., Zavolan, M., Kadener, S., Tschöp, M.H., Jastroch, M., Friedländer, M.R., & Poy, M.N. (2015). miR-184 regulates pancreatic β-cell function according to glucose metabolism. Journal of Biological Chemistry, 290(33), 20284–20294. https://doi.org/10.1074/jbc.M115.658625

Thum, T. (2014). Noncoding RNAs and myocardial fibrosis. Nature Reviews Cardiology, 11(11), 655–663. https://doi.org/10.1038/nrcardio.2014.125

Tian, Y., Xu, J., Du, X., & Fu, X. (2018). The interplay between noncoding RNAs and insulin in diabetes. Cancer Letters, 419, 53–63. https://doi.org/10.1016/j.canlet.2018.01.038

Trajkovski, M., Hausser, J., Soutschek, J., Bhat, B., Akin, A., Zavolan, M., Heim, M. H., & Stoffel, M. (2011).

MicroRNAs 103 and 107 regulate insulin sensitivity. Nature, 474(7353), 649–653. https://doi.org/10.1038/nature10112

Vivacqua, A., Marco, P. De, Belfiore, A., & Maggiolini, M. (2017). Recent Advances on the Role of microRNAs in Both Insulin Resistance and Cancer. Current Pharmaceutical Design, 23(25), 3658–3666. https://doi.org/10.2174/1381612823666170622105123

Wasserfall, C., Nick, H.S., Campbell-Thompson, M., Beachy, D., Haataja, L., Kusmartseva, I., Posgai, A., Beery, M., Rhodes, C., Bonifacio, E. , Arvan, P., & Atkinson, M. (2017). Persistence of Pancreatic Insulin mRNA Expression and Proinsulin Protein in Type 1 Diabetes Pancreata. Cell Metabolism, 26(3), 568-575.e3. https://doi.org/10.1016/j.cmet.2017.08.013

Wong, WKM, Sørensen, AE, Joglekar, MV, Hardikar, AA, & Dalgaard, LT (2018). Non-coding RNA in pancreas and β-cell development. Non-coding RNA, 4(4). https://doi.org/10.3390/ncrna4040041

Xu, B., Gerin, I., Miao, H., Vu-Phan, D., Johnson, CN, Xu, R., Chen, XW, Cawthorn, WP, MacDougald, OA, & Koenig, RJ (2010) . Multiple roles for the non-coding RNA SRA in regulation of adipogenesis and insulin sensitivity. PLOS ONE, 5(12). https://doi.org/10.1371/journal.pone.0014199

Xu, H., Guo, S., Li, W., & Yu, P. (2015). The circular RNA Cdr1as, via miR-7 and its targets, regulates insulin transcription and secretion in islet cells. Scientific Reports, 5(July), 1–12. https://doi.org/10.1038/srep12453

Zhang, C., Han, X., Yang, L., Fu, J., Sun, C., & Huang, S. (2020). Theranostics Circular RNA circPPM1F modulates M1 macrophage activation and pancreatic islet inflammation in type 1 diabetes mellitus. 10(24). https://doi.org/10.7150/thno.48264

Zhang, J.R., & Sun, H.J. (2020). Roles of circular RNAs in diabetic complications: From molecular mechanisms to therapeutic potential. Gene, 763(1800), 145066. https://doi.org/10.1016/j.gene.2020.145066

Zhao, W., Liang, J., Chen, Z., Diao, Y., & Miao, G. (2020). Combined analysis of circRNA and mRNA profiles and interactions in patients with Diabetic Foot and Diabetes Mellitus. International Wound Journal, 17(5), 1183–1193. https://doi.org/10.1111/iwj.13420

Zhao, Z., Li, X., Jian, D., Hao, P., Rao, L., & Li, M. (2017). Hsa_circ_0054633 in peripheral blood can be used as a diagnostic biomarker of pre-diabetes and type 2 diabetes mellitus. Acta Diabetolica, 54(3), 237–245. https://doi.org/10.1007/s00592-016-0943-0

Zhou, B., & Yu, J. W. (2017). A novel identified circular RNA, circRNA_010567, promotes myocardial fibrosis via suppressing miR-141 by targeting TGF-β1. Biochemical and Biophysical Research Communications, 487(4), 769–775. https://doi.org/10.1016/j.bbrc.2017.04.044

Zhou, R., Wu, Y., Wang, W., Su, W., Liu, Y., Wang, Y., Fan, C., Li, X., Li, G., Li, Y., Xiong, W., & Zeng, Z. (2018). Circular RNAs (circRNAs) in cancer. Cancer Letters, 425, 134–142. https://doi.org/10.1016/j.canlet.2018.03.035

Zogg, H., Singh, R., & Ro, S. (2022). Current Advances in RNA Therapeutics for Human Diseases. International Journal of Molecular Sciences, 23(5). https://doi.org/10.3390/ijms23052736