Molecular Therapy
Nucleic Acids
Review

The impact of ncRNAs on type 2 diabetes: A comprehensive review covering molecular mechanisms to clinical applications

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Type 2 diabetes (T2D) is a complex metabolic disorder with rising global prevalence. This review examines the diverse roles of non-coding RNAs (ncRNAs) in T2D, focusing on their involvement in key biological processes such as insulin signaling, glucose metabolism, oxidative stress, and inflammation. We explore how ncRNAs interact with known T2D risk genes and contribute to epigenetic regulation associated with disease progression. Particular attention is given to the emerging potential of ncRNAs as biomarkers for early diagnosis and as targets for personalized therapeutic strategies. We also discuss current advances in modulating ncRNA expression, including findings from experimental models and clinical trials published between 1998 and 2025. Finally, the review considers how lifestyle factors and common comorbidities influence ncRNA expression, highlighting their wider implications in the context of T2D. Overall, the findings underscore the growing importance of ncRNAs in understanding, diagnosing, and treating T2D.

INTRODUCTION

Since Berson and Yalow's research into the poor response of diabetics to insulin in the 1960s, insulin resistance has been explored, identified, and recognized as a major contributing factor to type 2 diabetes (T2D).[1] T2D is a complex disease characterized by increased blood glucose concentrations due to resistance, and insufficient production of insulin, caused by an interaction of genetics (inherited), epigenetics, lifestyle (diet, exercise), and environmental factors (obesity, lifestyle, stress, smoking, and age).[2–6] This is a major disorder affecting millions of individuals around the world and is associated with multiple complications, including cardiovascular diseases such as diabetic nephropathy (DN), neuropathy, retinopathy, and kidney disease.[7–9]

The traditional view of diabetes has focused on perturbations in protein-coding genes that directly impact insulin production and glucose metabolism. However, it has been found that non-coding RNAs (ncRNAs), once dismissed as the " junk DNA" of the genome introduced by Susumu Ohno in 1972, are now emerging as crucial players in regulating gene expression, cellular processes, and the development of T2D.[10]

NcRNAs are molecules that are not capable of encoding proteins (housekeeping and regulatory ncRNAs) but perform a diverse range of regulatory actions within the cell. Although many ncRNAs are relatively short, some, like long non-coding RNAs (lncRNAs), can reach several kilobases in length.[11] They can regulate gene activity at several levels, including gene transcription, which preferentially transcribes a subset of genes based on the transcription factors present in each cell type, and epigenetic modifications, which include histone modifications and methylation of DNA. It is increasingly evident that ncRNAs play a critical role in various epigenetic modification mechanisms. These molecules regulate cytosine methylation, where a methyl group (one carbon bonded to three hydrogen atoms) is specifically attached to cytosine in a CpG dinucleotide, resulting in the formation of 5-methylcytosine. Additionally, ncRNAs are involved in histone modifications that are associated with gene expression regulation in complex organisms, among other unrelated functions.[12–15]

By understanding the impact of ncRNAs in T2D, researchers aim to uncover new insights into the disease's underlying mechanisms and identify promising therapeutic targets. This review specifically aims to summarize the roles of ncRNAs in T2D pathophysiology, including insulin signaling, glucose metabolism, and inflammation, to evaluate their potential as diagnostic biomarkers and therapeutic agents, and finally, to discuss factors influencing ncRNA expression, such as lifestyle and comorbidities. Through this focused synthesis, we aim to clarify the clinical relevance of ncRNAs and their translational potential in T2D management.

CLASSIFICATION AND TYPES OF ncRNAs

The transcription of RNA originates from approximately 90% of the genome. However, only 1% to 2% of the transcribed genome is responsible for encoding traditional protein-coding RNAs, leaving

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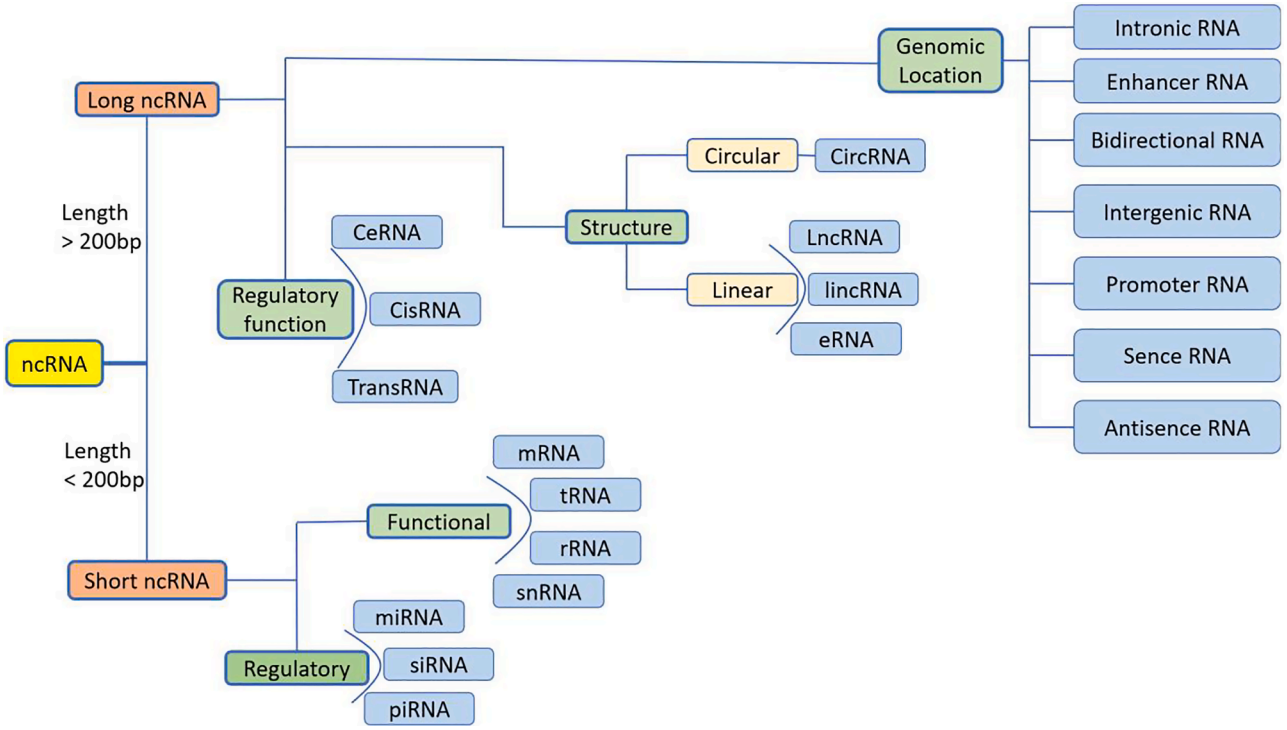

Figure 1. LncRNAs and small ncRNAs are the two categories into which ncRNAs are divided based on length

Short ncRNAs are divided into functional: (snRNA) small nuclear RNA, (rRNA) ribosomal RNA, (tRNA) transfer RNA, (mRNA) messenger RNA, and regulatory: (piRNA) piwi RNA, (siRNA) small interfering RNA, and (miRNA) micro-RNA. Long ncRNAs can also be divided into three groups based on their structure, function, and genomic location. They are separated structurally into circular and linear RNAs: (CircRNA) circular RNA, (eRNA) enhancer-derived RNA, (lincRNA) long intergenic noncoding RNA, (LncRNA) and long non-coding RNAs and based on their regulatory function (ceRNA) competing endogenous RNA, (transRNA) *trans*-acting RNA, and (cisRNA) *cis*-acting RNA.

the remaining 98%–99% of RNAs historically considered non-coding.[16] ncRNAs can be distinguished into housekeeping and regulatory types, which are also classified based on their length into short ncRNAs (such as small interfering RNAs [siRNAs], microRNAs [miRNAs], and piwi-interacting RNAs [piRNAs]) and long ncRNAs (e.g., lncRNAs and circRNAs).[17,18] Notably, recent studies have shown that some lncRNAs and circRNAs can encode functional micropeptides, suggesting that the boundary between coding and ncRNAs may be more dynamic than previously thought (Figure 1).[19]

miRNA

First described in 1993,[20] miRNAs are small ncRNAs typically composed of 19–23 nucleotides with a hairpin conformation. They bind to the 3′ untranslated region of specific messenger RNAs (mRNAs) to control gene expression during the post-transcriptional phase.[21] This regulation of mRNA targets by miRNAs typically leads to transcript destabilization and translational repression, influencing a wide array of cellular processes, including metabolism, cell development, proliferation, differentiation, and apoptosis. When miRNAs have perfect complementarity with their target, they can lead to mRNA cleavage (Figure 2).[22] A variety of miRNAs have been reported in humans, and they are expressed in most cells; however, a small amount of miRNA known as circulating miRNA has been detected in the extracellular environment. These molecules can be found in various fluids in the body including saliva, follicular fluid, tears, and urine.[23,24] The movement, rigidity, and protection of circulating miRNA are controlled by exosomes and microvesicles produced by various biofluid cell types.[25]

Islet-expressed microRNAs have emerged as critical regulators of pancreatic β-cell activities, including insulin release, cell proliferation, and apoptosis. Changes in the expression of specific microRNAs can either support insulin secretion as an adaptive response or contribute to β-cell dysfunction and hyperglycemia. Recent findings highlight their involvement in complex regulatory networks and suggest their potential use as biomarkers and therapeutic targets in diabetes management.[26]

siRNA

siRNA is a double-stranded RNA (dsRNA) molecule that can turn on gene silencing through an RNA interference (RNAi) process, by targeting complementary mRNA sequences, preventing their translation into proteins.[27,28] The mechanism of RNAi was uncovered by Fire et al. in 1998.[29] They discovered that the silencing effectors in a small, transparent worm known as *Caenorhabditis elegans* (measuring around 1 mm) were double-stranded RNAs. They

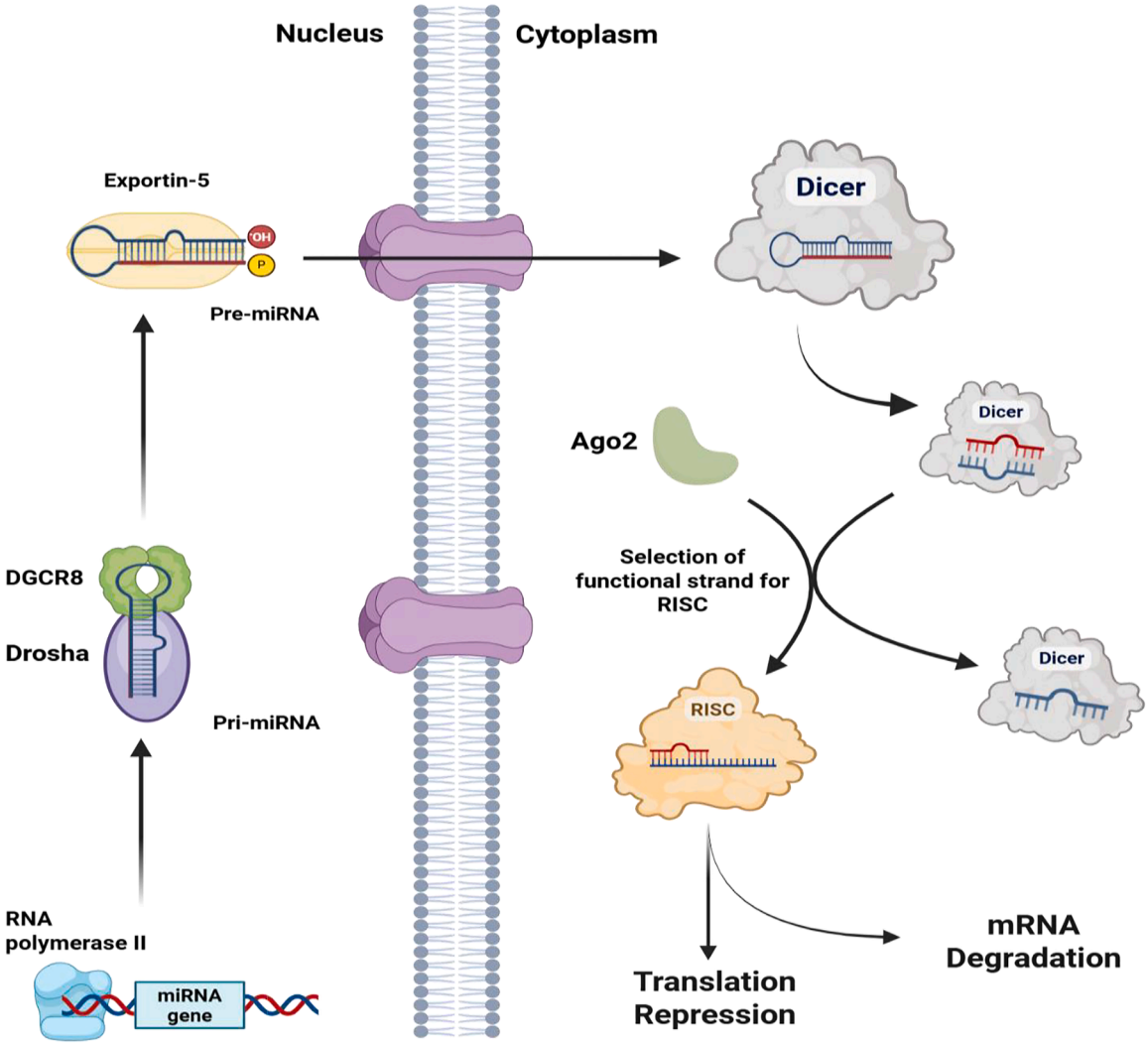

Figure 2. Schematic representation of the canonical miRNA pathway showing nuclear and cytoplasmic processing steps

miRNA genes are transcribed by RNA polymerase II into pri-miRNAs, which are processed by Drosha-DGCR8 into pre-miRNAs and exported to the cytoplasm via Exportin-5. Dicer processes pre-miRNAs into duplexes, from which the guide strand is loaded into the RISC complex with Ago2 to mediate translation repression or mRNA degradation. Created in https://BioRender.com.

treated this non-parasitic worm by using an RNA sequence that could interfere with muscular functions, with either single-stranded RNA (ssRNA) or double-stranded RNA (dsRNA), and they found that ssRNAs were less effective than dsRNA in silencing the same mRNA. Endogenous siRNAs (endo-siRNAs) have been demonstrated to form dsRNA structures from extended hairpin conformations or base-pairing of both sense and antisense transcripts obtained by bidirectional transcription or from complementary transcripts originating from separate loci.[30,31]

piRNA

Piwi-interacting RNAs (piRNAs) are a family of approximately 21–34 nt long RNA molecules that express uridine at the 5′ end and 2′ O-methylation at the 3′ terminal.[32] Discovered two decades ago in Drosophila melanogaster testis (fruit fly),[33] derived from ssRNA precursors, and they are essential for gene regulation, antiviral defense, and transposon repression, by guiding PIWI complex to particular mRNA targets via a complementarity sequence between the targeted RNA and piRNAs.[32] Depending on the complementarity of the piRNA and the mRNA, the PIWI proteins can act as a piRNA-directed RNase to directly cut transposon mRNAs, thereby inhibiting translation of the transposon (Figure 3).[34,35] According to relevant research, piRNAs may be classified into two different subclusters. The first one is the pachytene piRNA cluster, which is particularly abundant during meiosis and is expressed until the haploid spermatid stage. The second type of piRNA cluster is the

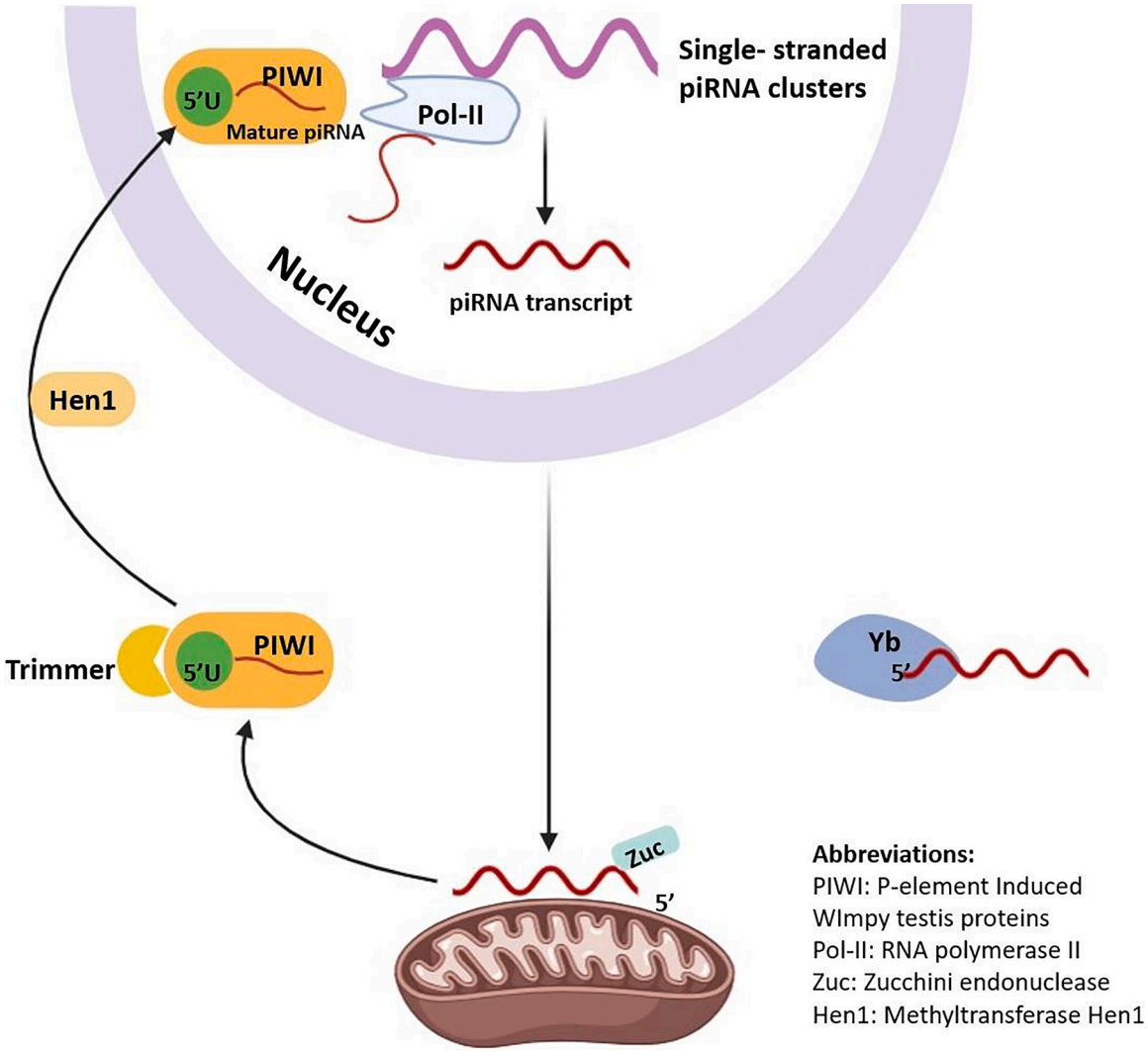

Figure 3. Primary biogenesis of piRNAs is the term used to describe this process

First, RNA polymerase II transcribes single-stranded piRNA clusters to initiate piRNA synthesis. Yb bodies then transport the resulting piRNA transcripts to the outer mitochondrial membrane. Second, the Zucchini (zuc) endonuclease and related components located on the mitochondria then cleave it, producing a precursor piRNA (pre-piRNA) with the 5′ end uridine as the first nucleotide. Following its binding to PIWI proteins, pre-piRNA is further trimmed at the 3′ end by the exonuclease Trimmer, resulting in its maturation length. Following this, completely mature piRNA is produced when methyltransferase Hen1 methylates mature piRNAs. Created in https://BioRender.com.

pre-pachytene piRNA cluster, which occurs particularly in premeiotic germ cells.[36,37]

LncRNAs

LncRNAs are a different class of non-coding regulatory RNAs. LncRNAs represent approximately 80% of total ncRNAs with lengths over 200 nt, which are not translated into proteins and are considered to have a significant role or operate as a crucial component in various biological processes.[38] They control interacting protein-coding genes in a variety of ways, complementing DNA bases to form stable triple-helix complexes that restrict the expression of target genes.[39] LncRNA can also be involved in repairing damaged DNA; the host cell can relentlessly produce diverse DNA damage types, such as bulky adducts, double-stranded breaks, single-stranded breaks, base alkylation, and base mismatches.[40] For instance, lncRNA DDSR1 was found as a regulator of DNA repair by homologous recombination through its interaction with BRCA1 and hnRNPUL1 (an RNA-binding protein implicated in DNA end resection).[41] Furthermore, the stability of p53 and the regulation of the p53-dependent DNA damage response have been linked to DINO, a conserved DNA-damage-inducible lncRNA, which is also necessary for cell-cycle arrest, gene expression, and apoptosis in response to DNA damage.[42] LncRNAs can regulate multiple components of cellular homeostasis, including cancer cells' proliferation,

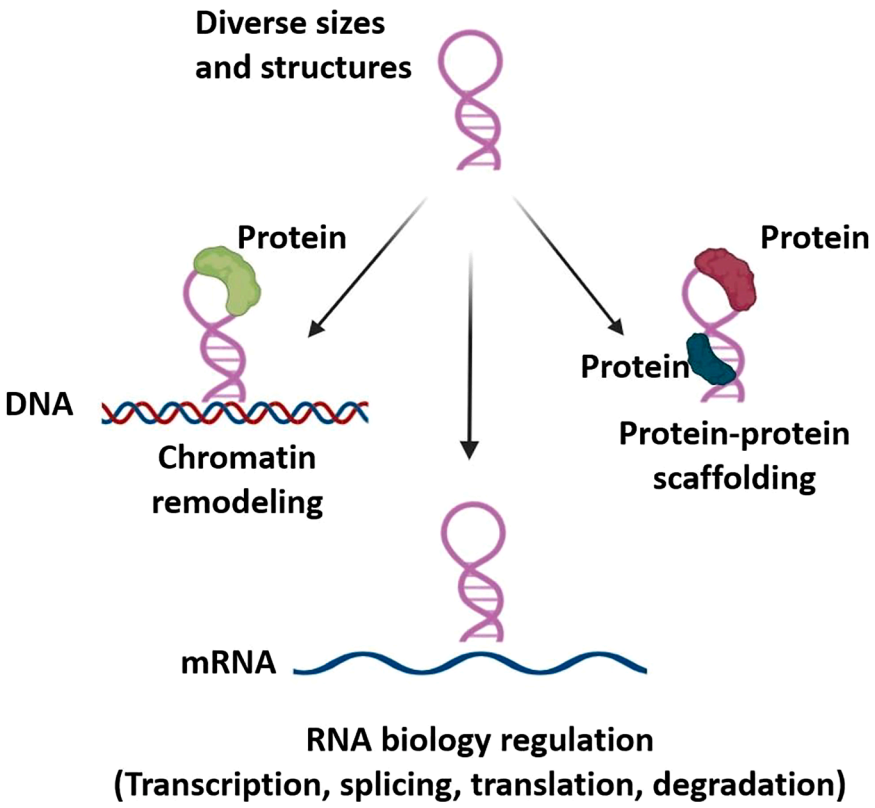

Figure 4. An overview of the potential roles of long non-coding RNAs (lncRNAs), including their impact on chromatin and DNA modification, their role as scaffolds in promoting protein-protein interactions, and their influence on RNA function
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metastasis, invasion, and angiogenesis.[43] For instance, as an oncogene, HOTAIR is frequently overexpressed in various types of cancer, including lung cancer, melanoma, esophageal cancer, stomach cancer, and breast cancer.[44–46] Furthermore, HOTAIR may promote autophagy by upregulating ATG3 and ATG7, thereby facilitating the growth of hepatocellular carcinoma. The upregulation of HOTAIR can silence miR-454-3p, leading to a decrease in the signaling cascade targeting ATG12. This also reduces autophagy in a chondrosarcoma cell line.[47,48] LncRNAs actively interact with miRNAs, functioning as miRNA molecular sponges or decoys to modulate their cytoplasmic levels by binding specific miRNAs and sequestering them from their target mRNAs. As a result of direct targeting of miRNAs, lncRNAs can be destabilized and act as competitors to common mRNA targets (Figure 4).[49]

CircRNAs

Circular RNAs, or "circRNAs," were originally discovered in pathogens and proposed to be in the RNA of viruses as a viroid in 1976 that contains "single-stranded and covalently closed circRNA molecules."[50] For decades, they appeared to be the result of splice failures.[51–55] At the beginning of 2010 and with the development of technologies for deep RNA sequencing (RNA-seq) and innovative bioinformatics tools, circRNAs have been identified along with their corresponding activities.[56,57] CircRNAs are composed of closed-loop structures because of back-spliced exons, where an upstream 3′ splice site is attacked by a 5′ splice donor. This results in a 3′–5′ phosphodiester bond that forms a circRNA molecule in the nucleus. While many circRNAs are transferred into the cytoplasm, where they can bind with miRNAs or proteins to perform diverse tasks, some circRNAs that retain intronic sequences are predominantly retained in the nucleus. In the cytoplasm, circRNAs can also be sorted into multivesicular endosomes (MVEs) alongside a variety of other nucleic acids, lipids, and proteins. After exosomes are released from dividing cells into bodily fluid, circRNAs circulate and start to perform their biological functions (Figure 5).[58]

ncRNAs AND T2D PATHOGENESIS

Regulation of insulin signaling and glucose metabolism by ncRNAs

The regulation of insulin signaling and glucose metabolism is a vital mechanism that maintains blood glucose homeostasis. Insulin is a peptide hormone synthesized by β cells in the islet of Langerhans. It can bind to particular receptors on target cells and trigger a metabolic response that regulates the uptake of glucose, storage, and utilization in cells.[59] NcRNAs have been identified as important regulators in this network. Among them, microRNAs are involved in post-transcriptional regulation of gene expression and have been identified to target important insulin signaling pathway components.[59] Several miRNAs have been found as significant regulators of insulin sensitivity, glucose absorption, and metabolism in numerous tissues, including the liver (such as let-7b, miR-7, miR-15b, miR-19a, miR-27a, miR-29, miR-30c, miR-33, miR-34a, miR-122, miR-128-1, miR-143, miR-144, miR-148, miR-186, miR-223, miR-378, miR-451-1, miR-466b, and miR-802), muscle (let-7, miR-27a, and miR-128-1), and adipose tissue (miR-99b, miR-103, miR-107, and miR-155).[60–62]

siRNAs have also proven to be essential in identifying the specific functions of insulin receptor substrates (IRS) and Akt isoforms in human skeletal muscle, casting light on their specialized glucose and lipid metabolism activities. For example, IRS-1 and Akt2 are necessary for myoblast development and glucose metabolism, whereas IRS-2 and Akt1 are vital in lipid metabolism. This highlights the complex interaction between several insulin signaling networks and metabolic outcomes. siRNA-based gene silencing has revealed genes such as Insr, Akt1, Akt2, and Pten as essential components of the insulin signaling system, offering vital insights into the control of glucose and lipid metabolism.[63] Furthermore, the inhibition of

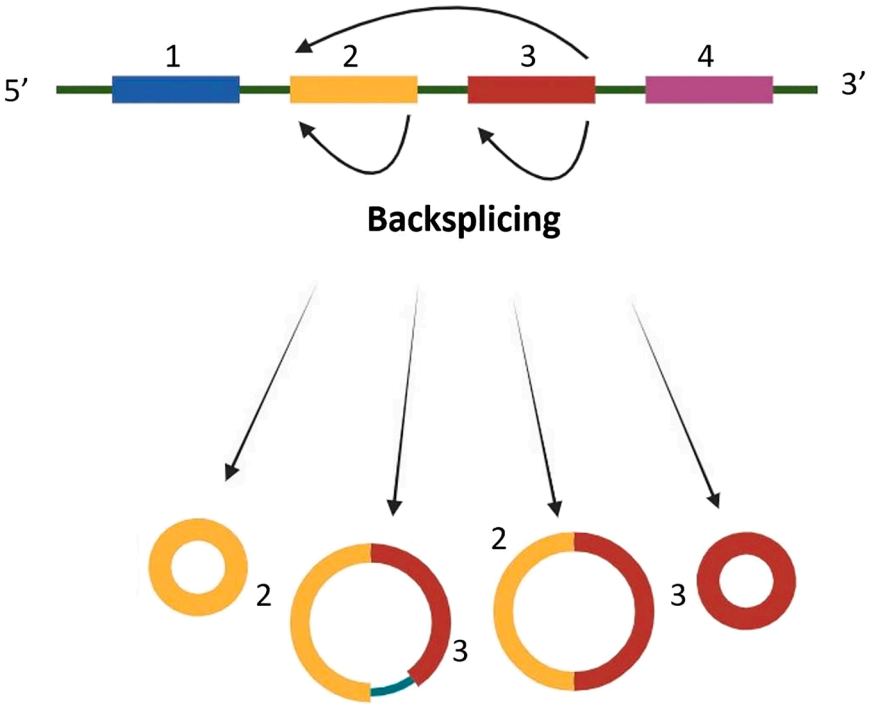

Figure 5. CircRNA is created by backsplicing
The backsplicing location of a transcript can produce distinct types of circular RNAs. Created in https://BioRender.com.

PTEN, PTP1B, JNK1, and p70S6K through siRNA has shown promise in protecting against insulin resistance caused by palmitate, highlighting their potential as therapeutic targets for boosting insulin action in T2D.[64]

Recent studies also suggest a potential involvement of PIWI-interacting RNAs in the glucose metabolism regulation of insulin signaling. Notably, piRNAs have been linked to the regulation of β-cell activities, insulin production, and the development of pancreatic β cells. Additionally, computational predictions of potential piRNA targets have highlighted their high concentration in genes implicated in the secretion, action of insulin, and carbohydrate metabolism.[65] Whereas the precise mechanisms of action and specific targets of piRNAs in the context of glucose metabolism and insulin signaling require further experimental validation, the emerging evidence indicates a potential role for piRNAs in the molecular events driving β-cell phenotype acquisition and dysfunction in diabetes conditions.[66]

LncRNAs have similarly been recognized as key players in the regulation of insulin signaling and glucose metabolism, regulating multiple biological functions related to metabolic disorders, including diabetes, nonalcoholic fatty liver disease (NAFLD), and obesity.[67–69] Notably, lncRNAs such as H19, MEG3, and MALAT1 have been shown to interact with crucial molecules of the insulin signaling pathway, thereby affecting lipid and glucose metabolism.[70] The dysregulation of lncRNAs, including MEG3, H19, MALAT1, and GAS5, has been linked to the pathogenesis of insulin resistance and metabolic disorders by modulating insulin signaling and glucose/lipid metabolism.[70] Furthermore, studies have shed light on the importance of lncRNAs, such as Blnc1, in hepatic insulin resistance, where their dysregulation has been linked to abnormal glucose and lipid metabolism.[71]

circRNAs have lately received a lot of interest for their roles in insulin signaling and glucose metabolism. Notably, these molecules have been linked to the regulation of several molecular processes involved in glucose homeostasis and the pathogenesis of metabolic diseases.[72] For instance, circCIRBP, one of the numerous circRNAs in human pancreatic islets, has exhibited a relation with the insulin secretory index, suggesting its possible role in regulating insulin secretion.[73] Furthermore, CDR1as was the earliest circRNA to be investigated in pancreatic β cells; it comes from the antisense transcript of the cerebellar-degeneration-related protein 1 gene and has more than 70 miR-7 binding spots.[56,74] According to studies, miR-7 is an antagonist of β-cell glucose-stimulated insulin secretion (GSIS), and its overexpression in transgenic mouse islets causes insulin-deficient diabetes.[75] Therefore, by upregulating the expression of miR-7 target genes, overexpression of CDR1as increases insulin production in islet cells.[56]

Inflammation, oxidative stress, and ncRNAs in T2D

Inflammation plays a crucial role in the pathogenesis of T2D, and emerging evidence suggests that ncRNAs are intricately involved in the regulation of inflammatory processes associated with the disease.[76] For instance, a Study on male Wistar rats has demonstrated that the dysregulation of miR-146, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), IL-1β, and nuclear factor κB (NF-κB) results from a diminution of the expression levels of TRAF6 and IRAK1 in the islets of the diabetic group compared to the control.[77] Another study on the cell culture of the mouse pancreatic β-cell line MIN6 cells shows that the expression of miR-25 and miR-92b is upregulated by palmitate and pro-inflammatory cytokines, causing a repression of insulin synthesis and accelerated β-cell death.[78] Similarly, another study shows that miR-153 expression is upregulated in IL-1β-treated β cells and produces insulin secretion defects.[79] Regarding lncRNAs, a study on 62 participants shows increased levels of lncRNAs such as HOTAIR, MEG3, LET, MALAT1, MIAT, and proinflammatory markers (TNF-α, IL-6, MCP1, and IL-1β) in patients with T2D compared to control subjects.[76] As for circRNA, a study on 43 individuals with T2D and 45 healthy subjects shows that circANKRD36 expression was upregulated in peripheral

blood leukocytes and associated with chronic inflammation in T2D.[80] In addition, the downregulation of circPIP5K1A was found to worsen insulin resistance and lipid metabolic disorders while reducing inflammation by targeting miR-552-3p, which regulates ENO1 expression.[81]

Oxidative stress (OS) plays a crucial role in the development and progression of vascular complications related to T2D.[82] It is characterized by high levels of reactive oxygen species (ROS) such as hydrogen peroxide (H2O2), superoxide anion (O2−), and hydroxyl radicals (OH·), along with weakened antioxidant defenses including enzymes like superoxide dismutase (SOD). In diabetes, overproduction of ROS is associated with a decrease in destruction or increase in the production of antioxidants, such as catalase (CAT), SOD, and glutathione peroxidase (GSH-Px), causing tissue susceptibility to OS and the subsequent development of diabetic complications.[82] In addition, non-enzymatic protein glycation, glucose oxidation, and enhanced lipid peroxidation in diabetes cause cellular damage, insulin resistance, and the onset of diabetic comorbidities, emphasizing the significance of ROS in T2D pathogenesis.[83] As the primary source of OS in diabetes, mitochondria contribute to the formation of ROS, increasing oxidative damage and promoting endothelial dysfunction in diabetic patients' blood vessels.[83] Several ncRNAs have been shown to regulate OS responses in T2D. For instance, the miR-23a/27a/24-2 cluster is known to upregulate c-Jun N-terminal kinases (JNKs), which activate caspase-dependent and caspase-independent apoptosis in HEK293 cells, leading to elevated ROS levels.[84,85] Furthermore, a study on db/db mice revealed that miR-27a targets nuclear factor erythroid-2-related factor 2 (NRF2), interfering with ROS homeostasis in diabetic nephropathy, while omentin 1 upregulates NRF2 and lowers OS by restricting miR-27a and improving kidney function in T2D.[86] On the other hand, lncRNAs are also increasingly recognized as risk factors for oxidative stress in diabetes. Dysregulation of several lncRNAs, such as MALAT1, MEG3, GAS5, SNHG16, and CASC2, has been implicated in the regulation of OS responses in DN, where their dysregulation has been linked to the modulation of pathways involved in OS.[87] Additionally, a study on HK-2 cells found that the expression of GAS5 was decreased in HG-treated HK-2 cells, whereas its overexpression decreases malondialdehyde (MDA) and ROS levels, which improves SOD levels.[88] In addition, recent research has also highlighted the regulatory roles of circRNAs in response to OS in T2D. Several studies have reported the dysregulation of specific circRNAs, such as circ_0000712 and circRNA-0077930, to OS processes and their impact on T2D-associated complications.[89,90]

NcRNAs in diabetic wound healing

Wound healing is a complex and well-coordinated process that plays a crucial role in repairing tissue after an injury. In healthy individuals, this process moves smoothly through several overlapping stages, with immune cells, skin cells, and the extracellular matrix (ECM) working together in harmony.[91] However, in people with T2D, this healing process is often delayed or disrupted. Factors such as long-lasting inflammation, limited blood vessel growth, and issues with tissue remodeling can all contribute to slower or impaired healing in diabetic patients.[91,92]

The lncH19 has been identified as a key regulator of wound healing.[93] In animal models, lncH19 expression rapidly increases after injury, peaking around day 3, and its absence leads to delayed tissue repair.[93] In human studies, higher levels of lncH19 were observed in wounded skin from individuals without diabetes compared to their normal, unwounded skin. However, in patients with T2D and obesity, lncH19 expression in injured tissues was markedly reduced, suggesting that decreased lncH19 may contribute to impaired wound healing in diabetic conditions.[93]

Beyond lncH19, lncRNAs are emerging as important players in diabetic wound healing. Some lncRNAs that show tissue- and disease-specific patterns and can even be detected in blood or wound tissues, such as URIDS, ANRIL, MT1P3, GAS5, and ENST00000411554, also display altered expression in the blood or skin of patients with diabetic foot ulcers (DFUs).[94] Specifically, lncURIDS is markedly increased in the serum and skin tissues of DFU patients and may contribute to delayed wound healing.[95] LncGAS5 is overexpressed in the skin of DFU patients, predominantly within M1 macrophages during the early inflammatory phase.[96] Additionally, lncRNA ENST00000411554 is notably downregulated in the skin of DFU patients compared to non-DFU tissues.[97]

In individuals with T2DM, miR-20b-5p is significantly elevated in circulating exosomes.[98] This miRNA impairs angiogenesis by targeting the Wnt9b/β-catenin signaling pathway, ultimately contributing to delayed wound healing. Experimental models have shown that inhibiting miR-20b-5p can enhance vascularization and accelerate tissue repair.[98]

Recent findings have identified miRNA-365-2-5p as an important factor in the regulation of wound healing.[99] Researchers have developed a new peptide, CyRL-QN15, which combines minimal sequence length with strong wound-healing properties. Treatment with CyRL-QN15 in mouse models significantly enhanced wound closure by suppressing miRNA-365-2-5p activity. As a result, there was an increased expression of SIRT1 and FOXO1 proteins, alongside a reduction in STAT2 levels. These molecular changes contributed to improved keratinocyte proliferation and migration, while simultaneously dampening the inflammatory response at the wound site.[99] These results may represent a promising future target for improving wound healing outcomes in diabetic patients, a hypothesis that warrants further investigation in T2D-specific contexts.

Interaction of ncRNAs with known T2D risk genes

ncRNAs have been found to interact with known T2D risk genes, exerting regulatory influences on their expression and activity. Multiple studies have confirmed the interaction of multiple ncRNAs with T2D-associated genes. For instance, microRNAs including miR-124a, miR-375, miR-9, and miR-34a have been found to target and modulate the expression of T2D risk genes such as FOXO1,

FOXA2, STAT3, PTEN, TCF7L2, and PPARG, consequently affecting insulin secretion and glucose homeostasis.[100–102] Similarly, lncRNAs like MEG3, MALAT1, and H19 have been implicated in the regulation of T2D-associated genes, contributing to the dysregulation of insulin signaling and glucose metabolism.[103–105] In addition, MBTPS1 and HECTD4 have been identified among the target genes for lncRNAs ENST00000565382 and ENST00000364558, respectively, with their involvement in the lysosomal and phagocytic signaling pathways that lead to an increased risk of T2D.[106] On the other hand, circRNAs also contribute to T2D pathogenesis by regulating gene expression. For instance, circHIPK3 has been shown to regulate pancreatic beta cell function and insulin secretion by sponging multiple miRNAs, thereby affecting T2D-associated genes such as Slc2a2, Akt1, and Mtpn.[107] Moreover, circRNAs such as circANKRD36 and circRNA_103827 have been found to modulate T2D risk genes involved in insulin signaling and glucose metabolism.[80,107] In addition, PIWI-interacting RNAs have emerged as potential regulators in T2D. Relevant research has indicated their potential interaction with T2D risk genes such as Piwil2 and Piwil4, shedding light on their putative involvement in T2D pathogenesis.[66] For instance, piRNAs are broadly expressed in somatic cells of the heart,[108] liver,[109] kidney,[110] pancreatic islet,[66] and nervous system,[111] where they are implicated in the regulation of genes related to insulin secretion and glucose metabolism.[66] siRNAs have also contributed to understanding the genetic landscape of T2D. A study performed in 2009 utilized a high-throughput RNA interference (RNAi) screening approach to identify genes associated with T2D. A whole-genome RNA interference screen highlighted the significance of Spry2 in insulin transcription and the unfolded protein response, offering information on its possible relevance in T2D.[112] Furthermore, the use of siRNA screens, combined with network-based algorithms, has enabled the identification of genes with putative roles in insulin signaling and resistance, offering a promising avenue for unraveling the complexities of T2D.[113,114]

Epigenetic modifications mediated by ncRNAs in T2D

Epigenetic modifications, including DNA methylation, histone modifications, and RNA-mediated processes, play a pivotal role in the onset and progression of T2D.[115] DNA methylation, which happens naturally during DNA replication, is a covalent bonding of a methyl group (CH3) to the 5′ position of the cytosine residue in the dinucleotide 5′-cytosine-phosphodiester bond-guanine-3’ (5′-CpG-3′) to create 5-methylcytosine (5mC).[116] Studies have shown that miRNA dysregulation, such as that of miR-148b, may be linked to the regulation of DNA methylation through its targeting of DNMT1, a key enzyme involved in DNA methylation.[117] Furthermore, miR-30a and let-7a-3 have been reported to be elevated at five CpG sites associated with DNA methylation in the promoters of differentially expressed miRNAs in T2D patients compared to control subjects.[118] LncRNAs have been implicated in regulating gene expression at the transcriptional, post-transcriptional, and epigenetic levels.[76] A study identified some lncRNAs, including those associated with the mitochondrial ATP-synthase-coupling factor 6 (ATP5J) enzyme, and highlighted the potential role of lncRNAs in T2D diagnosis and treatment management.[119,120] Another study revealed that the expression of the lncRNAs, SALRNA1, and THRIL was decreased in patients with T2D and negatively correlated with inflammation and hyperglycemia.[76] Similarly, THRIL regulates TNF-α expression by epigenetic mechanisms, whereas TNF-α reduces THRIL expression via a negative feedback loop.[121]

ncRNAs AS BIOMARKERS FOR T2D

Identification of ncRNA biomarkers for T2D diagnosis

ncRNAs have emerged as crucial regulators in the pathogenesis of T2D and are increasingly recognized as potential biomarkers for T2D development and clinical management.[122] Among these, microRNAs have shown particular promise as diagnostic tools and therapeutic targets for T2D.[123] Their stability in extracellular environments and detectability in bodily fluids make them ideal biomarkers for capturing physiological changes associated with T2D.[117] Notably, the islets of diabetic mice and humans exhibited elevated levels of miR-223. However, miR-223 deficiency dramatically suppresses β-cell proliferation and insulin secretion, whereas its overexpression inhibits forkhead box O1 and SRY-box 6 signaling, thereby promoting β-cell proliferation and function.[124] Additionally, MiR-130a plays a crucial role in endothelial progenitor cell activity by modulating the expression of GAX and HOXA5 (anti-angiogenic homeobox genes), and it is associated with T2D.[125] It is also implicated in the proliferation of vascular smooth muscle cells in hypertension, liver steatosis, and hepatic insulin sensitivity.[126,127] Also, miR103/107 are crucial in modulating insulin signaling in the liver and adipose tissues by targeting caveolin-1 (a critical regulator of the insulin receptor). Inactivation of these miRNAs in adipocytes is associated with insulin receptor stability, increased insulin signaling, reduced adipocyte size, and increased insulin-stimulated glucose uptake.[128] Importantly, miR-483-5p has been independently identified in a large prospective cohort as a serum biomarker that predicts future onset of insulin-resistance-related-T2D and cardiovascular disease.[129] Elevated miR-483-5p levels were associated with incident diabetes and cardiovascular events after adjusting for age and sex, with partial mediation by obesity and insulin resistance for diabetes risk, but an independent association with cardiovascular disease risk. Furthermore, miR-483-5p levels correlated with metabolic parameters such as BMI, fasting insulin, HDL cholesterol, and triglycerides, underscoring its relevance in metabolic regulation.[129]

Several meta-analyses were carried out, providing different lists of miRNAs as potential biomarkers for T2D patients. The first one was from 1993 to 2015 and suggested that in T2D patients, 40 miRNAs were significantly dysregulated, including miR-34a, miR-29a, miR-103, miR-375, miR-132, miR-107, miR-144, and miR142-3p as potential circulating biomarkers and two as potential tissue biomarkers, miR-223 and miR-199a-3p.[130] Another case-control meta-analysis on a total of 494 miRNAs revealed that in T2D, six miRNAs were selected as potential circulating biomarkers of T2D (miR-223, miR-148b, miR-19a, miR-130a, miR-27b, and miR-26b), and miR-21 and miR-146a as specific tissue biomarkers were

extremely particular to the cornea and heart.[131] The differences in identified miRNAs between the two studies could be attributed to variations in sample types, patient populations, analytical methods, or study periods.

LncRNAs have garnered significant attention due to their potential as biomarkers for T2D, such as H19, MEG3, MALAT1, and its associated complications.[122] A systematic review and meta-analysis conducted by Su et al. in 2023 established the value of lncRNAs as diagnostic biomarkers for T2D, including TUG1, HOTAIR, MALAT1, MEG3, and PVT1, along with their consequences, such as DN and DR (diabetic retinopathy).[132] Another study on 127 Chinese T2D patients with 130 controls defined the expression profiles of lncRNAs by the microarray analysis and obtained 68 differently expressed lncRNAs, including ENST00000588707.1 and TCONS_00004187, which may be involved in glycolipid metabolism through regulation of the GCKR gene and serve as potential markers for the diagnosis of T2D.[133] Additionally, according to an Egyptian study, cell-free lncRNAs (LY86-AS1, GAS5, and HCG27_201) have the potential to be useful diagnostic and predictive biomarkers for diabetes mellitus (DM). Among these, HCG27_201 gene expression performed the best, with a sensitivity of 91% and specificity of 64%, suggesting that it may be a useful diagnostic biomarker for pre-diabetes.[134] In Saudi Arabia, lncRNA profiling identified lnc-LEP-2:7 and lnc-LEP-2:6 as promising biomarkers for T2D. These lncRNAs, with area under the curve (AUC) values of 0.940 and 0.958, respectively, may mediate interactions with the LEP promoter region, facilitating RNA polymerase II recruitment and initiating gene transcription.[135]

circRNAs, due to their covalently closed-loop structures and exceptional stability, are also emerging as valuable biomarker candidates in T2D. For instance, downregulated hsa_circ_0056891 and hsa_circ_0063425 may contribute to the pathophysiology of T2D and may be implicated in the PI3K/Akt signaling pathway. These two circRNAs are important circulating biomarkers for T2D early identification.[136] In addition, hsa_circ_CCNB1 showed a positive correlation with glucose (GLU), IL-6, TNF-α, and glycosylated hemoglobin (GHb), whereas circ_0009024 showed a negative correlation with these attributes, which may provide potential biomarkers for the diagnosis of T2D.[137]

Challenges and limitations in using ncRNAs as biomarkers

Using ncRNAs as biomarkers presents several challenges and limitations that need to be considered: (1) tissue-specific expression: many ncRNAs have tissue-specific expression patterns, making it difficult to develop and confirm consistent biomarkers across tissues and cell types. This variation in expression patterns might limit the general use of ncRNA biomarkers.[138] (2) Stability and standardization: the stability of ncRNAs in clinical samples, such as blood, constitutes a problem because these molecules are prone to degradation. Furthermore, established techniques for sample collection, processing, and analysis are essential for ensuring the accuracy and consistency of ncRNA biomarker assessments.[139] (3) Biological variability and heterogeneity: identifying consistent ncRNA biomarkers is difficult due to individual biological variability and disease heterogeneity. Factors like age, gender, genetic background, and environmental variables can all contribute to change, necessitating the use of large and diverse populations for biomarker validation.[138]

THERAPEUTIC POTENTIAL OF TARGETING ncRNAs

ncRNAs as therapeutic targets for T2D

Pharmacological treatment remains the most effective approach to delaying the progression of T2D.[140] The anti-diabetic medications can target adipose and muscle tissue to lower insulin resistance, function in the liver to prevent glucose production, or stimulate the pancreas to secrete insulin.[141] However, while these medications can help reduce the consequences of diabetes, they cannot prevent the disease's development. The demand for novel diabetic medications remains serious. ncRNAs have emerged as potential therapeutic targets for T2D and related complications. They play a significant role in the pathogenesis and development of T2D, offering promise as both diagnostic and therapeutic tools.

miRNA therapies might be used to either restore downregulated miRNAs (by miRNA mimics) or prevent the upregulation and subsequent activity of a specific miRNA/s (via anti-microRNAs [anti-miRs] or miRNA inhibitors).[142,143] miRNA mimics are intended to replicate the actions of endogenous miRNAs. An miRNA mimic typically consists of a double-stranded RNA molecule where the guide strand matches the mature endogenous miRNA sequence, while the passenger strand is modified to avoid its incorporation into the RNA-induced silencing complex (RISC). This design ensures that only the intended mature miRNA sequence is active in silencing target genes.[144] Meanwhile, miRNA inhibitors inhibit the action of miRNAs by binding to the mature miRNA through partial or full reverse complementarity, thereby preventing the miRNA from suppressing its target mRNA translation.[142] A 2017 study found that the development of various types of DM is correlated with changes in miRNA levels.[145] Additionally, increasing evidence suggests that interventions targeting the levels of these ncRNAs can restore insulin secretion and/or activity, potentially preventing or treating the disease.[145] For instance, miR-223 plays a crucial role in maintaining β-cell mass and regulating metabolic stress. It has also been implicated in obesity and cardiovascular disease, both of which are associated with T2D.[146,147] Furthermore, a study revealed that miR-223 was related to positive responses to T2D therapy, indicating that miR-223 has potential diagnostic significance for T2D.[148] In the same context, an islet enriched with miR-375 has various roles in β cells, including insulin production, secretion, regeneration, and proliferation. Thus, miR-375 is likely the most promising pharmaceutical target for diabetes therapy.[149] Another study employed epidemiological and bioinformatics tools to investigate the association between circRNA, miRNA, and lncRNA with T2D and reported that hsa-miR-3690, hsa-miR-607, hsa-miR-29a-5p, lncRNA MEG3, TUG1, and hsa_circ_0071106 have been correlated with the risk of T2D. The same study found that a mixture of hsa-miR-607, lncRNA TUG1, and hsa_circ_0071106 had a better

diagnostic value than a single measure, making it an efficient diagnostic approach for T2D diagnosis.[150]

Considering the potential therapeutic advantages of siRNAs (for example, lncRNA levels can be inhibited using RNA interference technology)[151] and antisense oligonucleotides (ASOs), including locked nucleic acid (LNA) GapmeRs (a class of ASOs that induce enzyme-mediated degradation of target RNAs via RNase H),[152,153] in treating diseases in humans, it is important to note that siRNAs are often less efficient at knocking down nuclear-localized lncRNAs compared to ASOs.[154] The efficacy of these pharmacological techniques may be obstructed by the long sequences and complex secondary structures of lncRNAs. Additionally, silencers can be unstable, prone to nuclease degradation, and have limited target affinity. However, chemical modifications (e.g., LNA, 2′-O-methyl) have been developed to enhance nuclease resistance, improve binding affinity, and reduce off-target effects.[155] Researchers assessed the main biological processes and signaling pathways and discovered 104 lncRNAs, 27 of which were upregulated and 77 of which were downregulated, that are therapeutic targets for liraglutide in the treatment of T2D. Their lncRNA sequencing findings provide a solid foundation for comprehending, from an epigenetic perspective, the mechanism behind the effect of liraglutide treatment on diabetes.[156]

Strategies for modulating ncRNA expression

As previously mentioned, RNA-based therapies have emerged as a potential approach in the field of T2D regulation. These therapeutics encompass a variety of forms, each with its unique mechanism of action. First, antisense oligonucleotides (ASOs) and siRNAs are compounds designed to attach precisely to RNA molecules, inhibiting translation or promoting RNA degradation, thereby decreasing the synthesis of disease-related proteins.[157,158] Second, ASO antimiRs are used to silence specific miRNAs, counteracting the overexpression of miRNAs related to T2D, while short hairpin RNAs (shRNAs) can be used to mimic endogenous miRNA activity within cells.[142,159] Third, miRNA mimics are used to restore the function of underexpressed miRNAs, whereas miRNA sponges act as competitive inhibitors, sequestering and neutralizing overactive miRNAs to prevent them from binding their natural mRNA targets.[144,160] While these RNA-based tools have significant therapeutic promise, one of the primary challenges is delivering them effectively and selectively to the target tissues. Nanocarriers such as lipid nanoparticles and exosomes have been studied to improve delivery efficiency while reducing degradation and off-target effects.[161,162] For example, lipid-based nanoparticles showed potential in delivering adiponectin mRNA to the liver, pancreas, and adipose tissue in diabetic animals, significantly improving insulin sensitivity and reducing inflammation.[161] Similarly, engineered exosomes provide a biocompatible and low-immunogenicity option for RNA delivery, capable of crossing biological barriers and facilitating targeted delivery to specific tissues.[163] Their endogenous origin minimizes the risk of immune activation, and their surface can be changed to increase organ selectivity, such as the pancreas or skeletal muscle. As a result, exosomes are gaining traction as delivery systems for small RNAs, lncRNAs, and circRNAs in metabolic disorders, including T2D.[163,164]

Clinical trials and experimental studies using ncRNA-based therapies

Currently, 19 RNA-based medicines have been approved by regulatory agencies such as the US Food and Drug Administration (FDA), with many more in the pipeline entering phase II or III clinical development (Table 1). It is interesting that while miRNA-based treatments are gaining popularity due to their combined benefits of being naturally occurring and capable of targeting many genes within a pathway, no lncRNA-based therapies have yet made it to the clinical stages.

CROSSTALK BETWEEN ncRNAs AND OTHER FACTORS IN T2D

Influence of lifestyle factors on ncRNA expression

At the moment, preventing or controlling T2D is mostly dependent on developing healthy lifestyle practices, such as consuming a balanced diet and exercising.[165] It is well known that diet and exercise can both somewhat improve T2D, a lipotoxicity-related disease associated with an unhealthy lifestyle.[166] The expression of ncRNAs can be strongly influenced by lifestyle variables, including diet and environmental exposures, which may likely contribute to the emergence of T2D. For instance, it was shown that following aerobic activity, the IR-causing gene miR-143 was downregulated.[167] Subsequently, it was shown that in adipocytes receiving insulin treatment, the lncRNA lncASIR (a downstream regulator of the insulin signaling system) stimulates the transcription of genes involved in the insulin pathway.[168] Furthermore, when comparing the diabetic group with physical activity to the control subjects, swimming caused a significant reduction in the expression of inflammatory cytokines, NF-κB, and miR-146a, along with a notable increase in the levels of TRAF6 and IRAK1.[77] Another study identified 25 miRNAs associated with both exercise and T2D. Among these, four miRNAs exhibited different expression patterns in T2D compared to physical exercise (PE): miR-15a (UCP-2), miR-96 (CACNA1E), miR-192 (GCR), and miR-532 (ASK1/BAK1 genes). These miRNAs may represent important molecular pathways regulated by PE in T2D.[169] Additionally, the field of nutrimiromics investigates how diet influences changes in gene expression *in vitro* and/or *in vivo*, which may have an impact on the susceptibility of developing T2D.[170] For instance, polyphenols influence the expression of miR-103, let-7, miR-29, miR-27, and miR-122, while a high-fat diet (HFD), calorie restriction, and polyunsaturated fatty acids affect the expression of miR-21.[171] Furthermore, exosomal miRNAs regulate genes in human tissues and influence their passage through the digestive system via milk. Milk-derived miR-21 stimulates mTORC1, which is critically involved in insulin synthesis, secretion, and β-cell homeostasis. However, sustained activation of mTORC1 can lead to weight gain and increased body fat, thereby increasing the risk of diabetes.[172]

Table 1. RNA therapeutics approved by the US Food and Drug Administration (FDA)

Therapeutic	Year	Status/warnings or clinical trials	Administration	Intended organ	Disease	Target gene and pathway
Fomivirsen (Vitravene)	1998	withdrawn in 2002 and 2006	IVT	eye	CMV	CMV IE-2 mRNA
Pegaptanib sodium (Macugen)	2004	no longer authorized/ warning for endophthalmitis, elevated intraocular pressure, and allergic reactions	IVT	eye	AMD	vascular endothelial growth factor (VEGF) mRNA
Mipomersen (Kynamro)	2013	stopped in 2019	subcutaneous	liver	hereditary hypercholesterolemia homozygous	apolipoprotein B mRNA
Defibrotide sodium (Defitelio)	2016	available/warnings for bleeding and hypersensitivity reactions	IVT	endothelial cells (ECs)	VOD and renal or pulmonary dysfunction	increase tissue plasminogen activator (t-PA) and thrombomodulin expression and decrease von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1) expression
Eteplirsen (Exondys 51)	2016	available/warning for hypersensitive response/ side effects: rash, pyrexia, flushing, urticaria, bronchospasm, dyspnea, and cough	IVT	muscle	DMD	dystrophin (DMD) pre-mRNA splicing (exon 51 skipping)
Nusinersen (Spinraza)	2016	available/clinical trial scheduled in November 2023 and another until July 2027	intrathecal	central nervous system	SMA	survival of motor neuron 2 (SMN2) pre-mRNA splicing (exon 7 inclusion)
Inotersen (Tegsedi, AKCEA-TTR-LRx)	2018	available/warnings of stroke and cervicocephalic arterial dissection, immunological, inflammatory effects, liver damage, hypersensitivity responses, and reduced blood vitamin A levels	subcutaneous	liver	hereditary transthyretin amyloidosis	transthyretin (TTR) mRNA
Patisiran (Onpattro)	2019	available	IVT	liver	hereditary transthyretin amyloidosis	transthyretin (TTR) mRNA
Golodirsen (Vyondys 53, SRP-4053)	2019	available/clinical trial scheduled for October 2025	IVT	muscle	DMD	DMD pre-mRNA splicing (exon 53 skipping)
Givosiran (Givlaari)	2019	available	subcutaneous	liver	acute hepatic porphyria	delta aminolevulinic acid synthase 1 (ALAS1) mRNA
Viltolarsen (Viltepso, NS-065, NCNP-01)	2020	available	IVT	muscle	DMD	DMD pre-mRNA splicing (exon 53 skipping)
Lumasiran (Oxlumo, ALN-GO1)	2020	available	subcutaneous	liver	PH1	hydroxyacid oxidase 1 (HAO1) mRNA
Inclisiran (Leqvio)	2021	available/side effects reactions at the injection site, joint stiffness,	subcutaneous	liver (site of PCSK9 protein synthesis)	HeFH and clinical ASCVD	inhibits PCSK9 mRNA to reduce PCSK9 protein, boosting LDL receptor recycling and LDL-C clearance.

(*Continued on next page*)

Table 1. *Continued*

Therapeutic	Year	Status/warnings or clinical trials	Administration	Intended organ	Disease	Target gene and pathway
		urinary tract infections, diarrhea, bronchitis, limb pain, and shortness of breath				
Casimersen (Amondys 45)	2021	available/warnings for renal damage, and kidney function	IVT	muscle	DMD	DMD pre-mRNA (exon 45 binding)
Vutrisiran (Amvuttra)	2022	approved by the FDA/adverse reactions include arthralgia, dyspnea, and decreased serum vitamin A levels	subcutaneous	liver (site of transthyretin protein synthesis)	polyneuropathy of hereditary transthyretin-mediated amyloidosis	targets mutant and wild-type transthyretin (TTR) mRNA, reducing TTR protein production
Nedosiran (Rivfloza)	2023	approved by the FDA/adverse reactions include mild injection site reactions such as erythema, pain, bruising, and rash	subcutaneous	liver (site of oxalate production)	PH1	inhibiting LDHA mRNA in the liver and reducing oxalate production
Tofersen (Qalsody)	2023	approved by the FDA/adverse reactions include pain, fatigue, arthralgia, CSF, white blood cell increases, and myalgia	administered intrathecally via lumbar puncture	CNS	ALS associated with SOD1 mutation	antisense oligonucleotide that binds to SOD1 mRNA, leading to its degradation and reduced synthesis of SOD1 protein
Olezarsen (Tryngolza)	2024	approved by the FDA/warnings include hypersensitivity reactions	subcutaneous	liver (site of apoC-III production)	FCS	inhibits production of apoC-III protein by targeting its mRNA, enhancing triglyceride clearance
Fitusiran (Qfitlia)	28 March 2025	approved by the FDA/ side effects include viral and bacterial infections such as nasopharyngitis, respiratory tract infections, thrombotic events, gallbladder disease, and liver toxicity	subcutaneous	liver (antithrombin production site)	hemophilia A and B	targets antithrombin (AT) mRNA to reduce AT levels, enhancing thrombin generation and improving blood clotting

IVI, intravenous; CMV, immunocompromised individuals' retinitis caused by the cytomegalovirus; AMD, age-related macular degeneration; VOD, severe hepatic veno-occlusive disease; DMD, Duchenne muscular dystrophy; SMA, spinal muscular atrophy; PH1, primary hyperoxaluria type 1; HeFH, hypercholesterolemia; ASCVD, atherosclerotic cardiovascular disease; CNS, central nervous system (brain and spinal cord); CSF, cerebrospinal fluid; ALS, amyotrophic lateral sclerosis; LDHA, lactate dehydrogenase A; FCS, familial chylomicronemia syndrome.

ncRNA is also known to play an important role in the pathogenesis of diabetes-related physical activity. A study investigated the therapeutic potential of aerobic exercise to improve cognitive function in T2D mice and explored the roles of miR-382-3p and MALAT1 in T2D-related cognitive impairment. In this study, aerobic exercise was shown to increase MALAT1 levels in serum exosomes, which in turn suppressed miR-382-3p, boosted BDNF expression, prevented hippocampal cell death, and improved cognitive dysfunction in T2D mice.[173] In contrast, another study showed that exercise reduced MALAT1 and induced miR-320a levels in obese children and adolescents, and these changes in the MALAT1/miR-320a axis were associated with improvements in endothelial function markers. Thus, training-induced improvements in vascular function may be associated with regulation of the MALAT1/miR-320a axis.[174]

Role of ncRNAs in T2D comorbidities

Diabetic cardiomyopathy (DCM) is a common and serious consequence of diabetes characterized by cardiac fibrosis, myocardial dysfunction, and microvascular abnormalities. It can manifest even in the early stages of diabetes and the absence of traditional cardiovascular risk factors such as coronary artery disease and hypertension.[175]

Recent studies at the preclinical level have identified several different microRNAs involved in the pathophysiology of DCM. Using an *in vitro*/*in vivo* approach, it was shown that in DCM there was a downregulation of miR-1 and an upregulation of miR-146a, miR-34a, miR-125b, miR-19b, miR-155, miR-210 and miR-221, and miR-27a.[176] One of the most highly represented miRNAs, miR-21, has been implicated in multiple disease processes, notably diabetes and cardiovascular disease (CVD). As a result, miR-21 expression was elevated in the infarcted region in a number of models of ischemic heart disease and was associated with hypertrophy, myocardial fibrosis, and cardiac cell survival.[177] Furthermore, miR-21 antagonists have major therapeutic prospects for the future therapy of diabetic disease, including cardiomyopathy-related complications.[177] Another key miRNA, miR-133, regulates several pathological and physiological processes in the heart, including cardiac hypertrophy, and is highly expressed in cardiac tissue. Furthermore, miR-133a has been shown to target serum and glucocorticoid-regulated kinase 1 (SGK-1) and insulin growth factor 1 (IGF-1), both of which might have an impact on the heart hypertrophy process.[178] Recent findings suggest that the miR-133 family is a potent inhibitor of cardiac fibrosis and hypertrophy, even under mechanical stress such as pressure overload.[179] Overexpression of miR-133a inhibits cardiomyocyte hypertrophy, while its suppression exacerbates it, highlighting its critical role in cardiac homeostasis.[179]

LncRNAs have also been implicated in the molecular mechanisms underlying DCM. Elevated levels of MIAT have been detected in heart tissues and serum of DCM patients and are accompanied by increased levels of inflammatory cytokines, including IL-1β, IL-17, TNF-α, and IL-6.[180] Moreover, lentiviral-based MIAT knockdown in diabetic rats reduced fibrotic markers (collagen I and III) and inflammatory cytokines in the heart tissue (left ventricle), prevented apoptosis, improved cardiac ejection fraction, and ameliorated DCM.[180] Simultaneously, in human heart tissue, it was shown that lncRNA CRNDE was elevated and negatively associated with indicators of cardiac fibrosis, such as COL1A1.[181] *In vitro*, the overexpression of Crnde in cardiac fibroblasts decreased the expression of myofibroblast markers (Acta2, Col3a1, and Col1a1) caused by TGF-β1.[181] LncRNA Crnde was discovered to suppress the expression of important myofibroblast marker genes such as Acta2 and to prevent SMAD family member 3 (Smad3) from binding to the Smad binding element.[181] Interestingly, in the early myocardial infarction patients, the levels of the mitochondrial lncRNA LIPCAR expression were downregulated but increased later. In individuals with T2D, LIPCAR expression inversely correlates with diastolic function and is associated with chronic heart failure, suggesting its utility as a prognostic marker.[182]

CircRNAs have been shown to have a significant role in the progression of several diseases, such as cardiovascular disease, cancer, and T2D.[183] In DCM, there is an upregulation of CDR1as, which, by preventing mammalian sterile 20-like kinase 1 (MST1) from being ubiquitinated, stimulates the Hippo signaling system and may cause apoptosis in cardiomyopathy.[184] In addition, a study found that circ_0071269 was associated with DCM and provided further insight into the many biological processes regulated by this circRNA. It specifically targeted miR-145 and controlled the proliferation and pyroptosis of H9c2 cells by upregulating Gasdermin A (GSDMA).[185] Another circRNA, circ_0071269, was found to regulate the proliferation and pyroptosis of H9c2 cells by targeting miR-145 and upregulating GSDMA, thus contributing to DCM pathogenesis.[183] Additionally, circRNA mm9_circ_008009, designated as DICAR (diabetes-induced circulation-associated circRNA), has been found downregulated in both DCM and treated mouse cardiomyocytes.[186] Its human homolog, hsa_circ_0131202, interacts with valosin-containing protein (VCP) to prevent degradation of Med12, thereby suppressing pyroptosis. Notably, the synthetic DICAR junction sequence has demonstrated potential to rescue cardiomyocytes from pyroptotic death, suggesting its therapeutic promise in diabetes-associated cardiac dysfunction.[186]

FUTURE DIRECTIONS AND CHALLENGES

While the investigation of ncRNAs in T2D is promising, many challenges need to be overcome before their full potential can be exploited. One major challenge is the accurate and reproducible determination of ncRNA expression levels. The size and structural complexity of ncRNAs make their detection and quantification technically challenging, requiring the development of innovative experimental and computational techniques.[139]

Determining the functional relevance of specific ncRNAs in the pathogenesis of diabetes is still a challenge. Numerous ncRNAs have been identified as dysregulated in diabetes, but their specific roles and mechanisms of action remain to be clarified. Further research is needed to understand the functional interplay between

ncRNAs, protein-coding genes, and cellular pathways relevant to T2D and improve the analytical precision and accuracy by combining cutting-edge technologies such as nanotechnology with more established techniques.[187]

Additionally, the transformation of laboratory discoveries into clinical applications remains a significant challenge. The development of ncRNA-based diagnostics and therapeutics requires a high level of validation and optimization, as well as approval and addressing safety concerns. To realize the clinical potential of ncRNA-based therapies, future research should focus on moving from preclinical findings to well-designed clinical trials. These studies should evaluate how safe, effective, and deliverable these treatments are in humans, using standardized protocols and clear outcome measures.

CONCLUSION

NcRNAs have emerged as key regulators in the development and progression of T2D, offering new perspectives on its diagnosis and treatment. This review highlights their roles in insulin signaling, glucose metabolism, inflammation, and epigenetic modulation and emphasizes their potential as biomarkers and therapeutic targets. Notably, we identified 19 RNA-based therapeutic medicines, including the most recent one reported on March 28, 2025, underscoring the ongoing and growing clinical interest in targeting ncRNAs. As research advances, these molecules could help develop more precise and personalized approaches to managing T2D.

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AUTHOR CONTRIBUTIONS

I.M.A., collected, interpreted data, and prepared manuscript; H.S., revised and validated the manuscript for the final submission; B.F., edited and reviewed the manuscript for the final submission; B.A., edited and reviewed the manuscript for the final submission; E.K., conceptualized, designed the study, revised, and validated the manuscript for the final submission.

DECLARATION OF INTERESTS

The authors declare no conflicts of interest.

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