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The role of microRNAs in diabetes

MicroRNAs are very short RNA molecules, 21–22 nucleotides in length, that are not translated into proteins. Their discovery dates back to 1993, when Victor Ambros and Gary Ruvkun identified lin-4 in the nematode Caenorhabditis elegans, a finding that marked the beginning of a new era in biology: small RNAs can influence cellular development and physiology by regulating gene expression. More than two decades later, this work has been recognized with the Nobel Prize in Physiology or Medicine, highlighting the importance of miRNAs in regulating virtually all biological processes and disease areas studied to date.

Although all the cells in our body share the same genes, when and which of these genes are translated into proteins (the structural and functional building blocks of the cell) must be strictly regulated so that each cell can perform its specific function. Only about 2% of our genome encodes proteins, meaning that a large fraction of the remaining genome is **non-coding**, contains regulatory sequences, and generates RNAs that are not translated into proteins but play essential roles in gene regulation. Among them, miRNAs act by precisely regulating the production of specific proteins through modulation of their messenger RNAs (mRNA) ***(Figure 1)***. What makes miRNAs particularly important is that they can simultaneously regulate the expression of multiple genes by binding to multiple mRNAs. This is achieved through partial base complementarity with target mRNAs. This binding promotes degradation of the target mRNA or reduces the rate at which it is translated into proteins, **leading to gene silencing** (1). More than 2000 different miRNAs have been identified in mammalian cells, and they are estimated to regulate the expression of more than 70% of our genes, thereby contributing to defining cellular identity, maintaining normal tissue function, and enabling appropriate responses to developmental and environmental signals.

Interest in miRNAs in the field of diabetes arose from the discovery, more than twenty years ago, that a specific miRNA, miR-375, can regulate insulin secretion (2). MiR-375 is an abundant miRNA in pancreatic β cells of the islets of Langerhans, the only cells in our body responsible for producing insulin in response to increased glucose levels after a meal. This finding was quickly followed by pioneering studies demonstrating that miRNAs are essential for endocrine development and the formation of hormone-producing cells. Since then, the field has grown exponentially: currently, dozens of studies each year investigate how miRNAs influence β-cell biology, nutrient sensing, islet stress responses, autoimmunity, and the potential use of circulating miRNAs as **biomarkers**. All of this has shaped our current view of miRNAs as central components of regulatory networks that maintain β-cell identity and function and that become altered during diabetes (3).

miRNAs IN β-CELL FUNCTION

The initial study from Stoffel's laboratory identified myotrophin (MTPN) as one of the first validated target mRNAs mediating part of the effects of miR-375 on exocytosis[2]. Shortly thereafter, it was shown that miR-375 is essential for endocrine pancreas development in zebrafish and influences insulin gene expression as well as its exocytosis. These findings established 2 key concepts: (i) miRNAs can directly regulate core components of stimulus–secretion coupling, and (ii) a single miRNA can influence multiple aspects of β-cell function, from gene expression to the secretory machinery. The subsequent generation of mice with loss of function of miR-375 provided one of the clearest demonstrations that a single miRNA can regulate glucose homeostasis in vivo: these animals developed diabetes due to impaired proliferation and reduced β-cell mass, and miR-375 proved necessary for compensatory β-cell expansion in the context of obesity (4).

FIGURE 1.

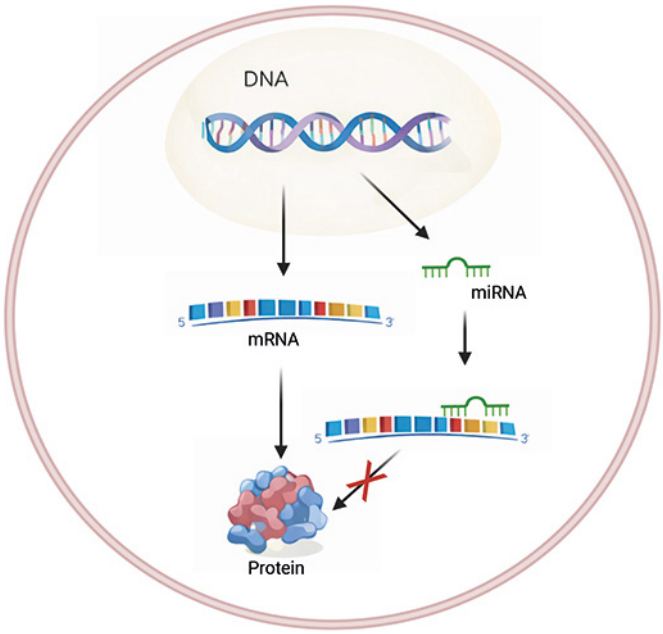

FIGURE 1. Regulation of protein production mediated by microRNAs. DNA is transcribed into messenger RNA (mRNA), which can be translated into protein. DNA also gives rise to microRNAs (miRNAs), which are transcribed and processed to generate mature single-stranded molecules that bind to target mRNAs. miRNA binding inhibits mRNA translation and/or induces degradation of the target mRNA, leading to reduced protein production.

Beyond miR-375, global disruption of miRNA production revealed that these molecules are essential not only for **endocrine development** but also for maintaining the **identity** and function of mature β cells (3). Mechanistically, loss of miRNAs in β cells dysregulated networks that include both repressors and activators of insulin gene expression, highlighting a key concept in the field: miRNAs act cooperatively, and their biological effects reflect the combined balance of many miRNAs rather than the action of a single dominant regulator ***(Figure 2)***. A particularly influential conceptual advance was the demonstration that miRNAs help maintain β-cell identity by repressing "disallowed" genes—genes widely expressed in other tissues but that must remain repressed in mature β cells to preserve proper stimulus–secretion coupling. Repression of Slc16a1 (MCT-1, monocarboxylate transporter 1) by the miR-29 family is a classic example that helped establish this paradigm (3).

miRNAs IN TYPE 2 DIABETES (T2DM)

A central theme that has emerged over 2 decades of research is that miRNA expression in islets is highly dynamic and strongly influenced by nutrient availability, metabolic stress, and »

FIGURE 2.

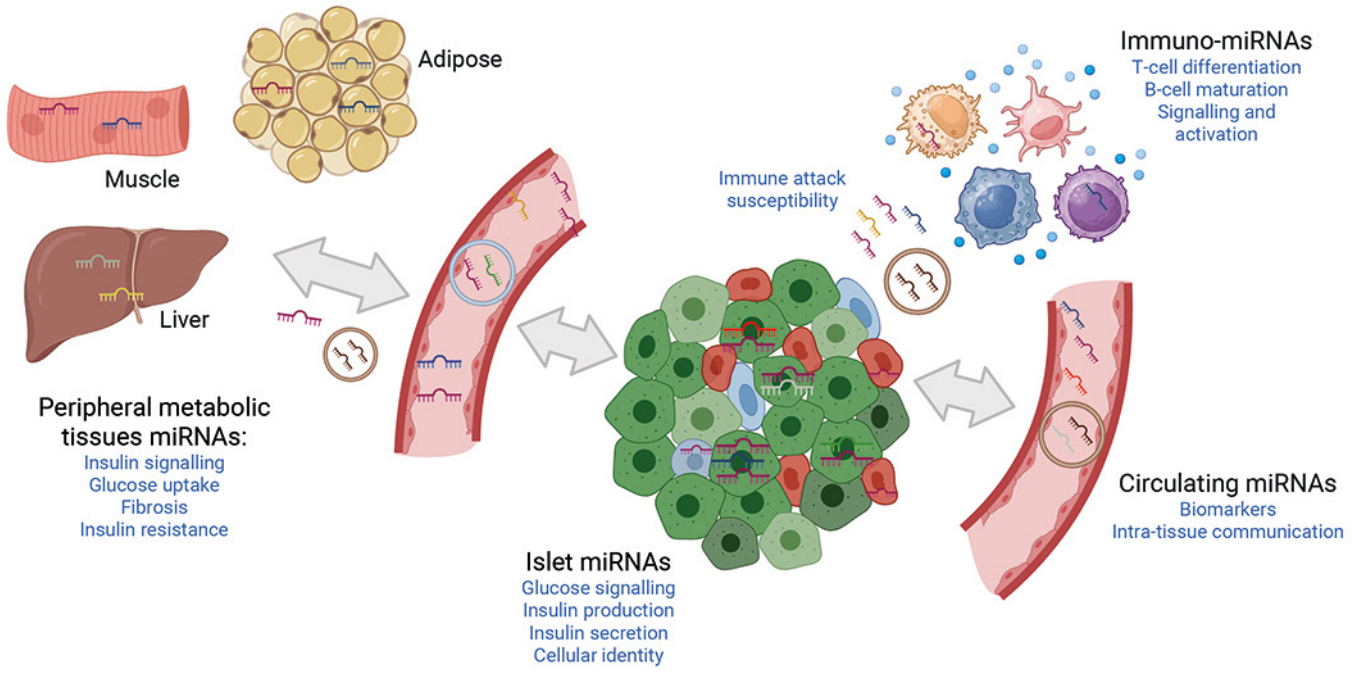

FIGURE 2. MicroRNA-mediated communication between metabolic tissues, the immune system, and pancreatic islets in diabetes. miRNAs regulate key processes in peripheral metabolic tissues (muscle, liver, and adipose tissue), pancreatic islets, and the immune system, influencing insulin signaling, glucose metabolism, immune activation, and β-cell identity and function. Circulating miRNAs, both free and vesicle-encapsulated, enable inter-tissue communication and may act as biomarkers, while immune cell–derived miRNAs can also directly affect islet function. Dysregulation of these miRNA networks contributes to β-cell dysfunction and the development of diabetes.

» disease. Studies in mouse models of **obesity and T2DM**, during pregnancy, and in human donor islets have repeatedly described changes in miRNA profiles, implicating them in β-cell compensation, apoptosis, and loss of identity. Importantly, a more limited set of mechanistic studies has provided direct insights into how miRNAs link nutrient and stress signaling to β-cell dysfunction. One example is the selective overexpression of members of the miR-200 family in islets from individuals with T2DM and in the db/db mouse model. Forced expression of miR-200 in β cells promotes diabetes by repressing stress-resistance and anti-apoptotic networks (5). Another relevant example is the dysregulation of miRNAs located in the imprinted genomic region DLK1–MEG3 due to alterations in DNA methylation in human T2DM (6) Other mechanistic examples include miRNAs involved in compensatory proliferation, insulin transcription, exocytosis, oxidative stress, and endoplasmic reticulum homeostasis, illustrating how miRNAs converge on multiple β-cell vulnerabilities relevant to T2DM (7).

Although much of the early literature on miRNAs in diabetes focused on pancreatic islets and insulin secretion, it is now clear that miRNAs also play an important role in regulating **glucose homeostasis** in peripheral tissues that determine insulin sensitivity, such as the liver, skeletal muscle, adipose tissue, and vasculature (8) ***(Figure 2)***. In these organs, miRNAs fine-tune key pathways of insulin action—such as insulin receptor signaling (PI3K–AKT), glucose uptake and utilization, lipid storage and mobilization, mitochondrial function, and inflammatory stress responses. Dysregulation of these miRNA programs in obesity and T2DM can directly contribute to insulin resistance by shifting the balance of metabolic and inflammatory networks and by altering inter-organ communication. This communication between organs may be mediated not only by classical hormones and cytokines but also by miRNAs themselves. Many miRNAs are released into circulation, either bound to proteins or packaged in extracellular vesicles (EVs), which protect them from degradation. This has driven 2 parallel lines of research in T2DM: on one hand, the use of cir- »

THE DISCOVERY OF microRNAs WAS RECOGNIZED WITH THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE IN 2024

culating miRNAs as minimally invasive biomarkers reflecting metabolic stress, tissue dysfunction, or disease progression; and on the other, the possibility that EV-associated miRNAs actively contribute to metabolic crosstalk between organs. In this context, adipose tissue, liver, muscle, and immune cells have been proposed as sources of circulating miRNAs that correlate with insulin resistance and inflammation, while emerging studies suggest that stressed islets may also release miRNAs that influence peripheral metabolism ***(Figure 2)***. For example, secretion of miR-29 family members by islets in response to elevated fatty acids has been linked to liver targeting and impaired insulin signaling, suggesting that β-cell stress responses may, in certain contexts, actively contribute to systemic insulin resistance (9).

miRNAs IN TYPE 1 DIABETES (T1DM)

The involvement of miRNAs in the pathogenesis of **T1DM** primarily revolves around two axes: modulation of β-cell susceptibility to immune-mediated destruction and the contribution of immune cell–derived miRNAs to autoimmunity. miRNA expression in islets is altered in T1DM both in murine models and in humans, and in response to conditions that mimic T1DM, such as cytokine exposure (10).

The role of immune cell–derived miRNAs in islet autoimmunity has been another major area of progress, with several **"immuno-miRNAs"** specifically expressed or enriched in lymphocytes ***(Figure 2)***. For example, activated T lymphocytes release exosomes containing miR-142-3p, miR-142-5p, and miR-155, which can be taken up by β cells, triggering apoptosis through chemokine signaling and promoting further immune infiltration. Functional studies demonstrated that miR-142-3p impairs the induction and stability of regulatory T cells (Treg), while its inhibition restores their function and reduces autoimmunity in pancreatic islets[11]. These findings highlight the existence of a bidirectional communication channel: immune cells not only respond to signals derived from islets but also actively reprogram β cells through EV-mediated miRNA transfer. These studies underscore the relevance of immune-derived miRNAs in immune homeostasis and highlight their potential as therapeutic targets for immune modulation.

In addition, as in T2DM, circulating miRNAs have been explored as biomarkers of T1DM onset and β-cell replacement therapies, with EV-associated miRNAs playing central connecting roles[10]. Sebastiani et al. were the first to link the expression of a miRNA (miR-326) in peripheral blood lymphocytes with autoantibodies in T1DM, associating miRNA levels with disease. In a recent large-scale effort, Hardikar et al. constructed a dynamic risk index derived from circulating miRNA profiles in the international **PREDICT T1DM** study, which included 5,983 samples from seven countries and four continents. By prioritizing miRNAs with strong biological relevance to the endocrine pancreas, they identified a refined panel of 50 miRNAs consistently altered in T1DM (12).

Notably, because miR-375 is abundant and relatively enriched in β cells, it has also become a leading candidate in efforts to identify circulating biomarkers of β-cell loss in diabetes and in the context of islet transplantation. Other miRNAs, such as miR-216a-5p, miR-148a-3p, and miR-29b-3p, were also found to be elevated in circulation in preclinical transplant models and in patients undergoing total pancreatectomy with islet autotransplantation (TPIAT), where they correlated negatively with graft function[13]. However, this type of study remains limited and often constrained by small sample sizes and limited reproducibility.

PROGRESS, PERSISTENT CHALLENGES AND TRANSLATIONAL HORIZON

Despite the abundance of descriptive studies, important open questions remain. We are still far from fully understanding the mechanisms driving changes in miRNAs in response to nutrients and disease, or the extent to which specific miRNA programs causally contribute to diabetes progression rather than reflecting secondary stress responses. The genomic regions that activate miRNAs may be located far from the mature miRNA sequence, complicating the identification of their promoters or linking their expression to metabolic signals or genetic variation. miRNA levels are also modulated by their processing and degradation rates, but these steps have been scarcely studied in β cells. Finally, even when a miRNA is present, its activity may be modified by other cellular molecules: some proteins affect the binding affinity of miRNAs to their targets, and other RNAs can act as "sponges" that reduce their effect. These additional layers of control are well recognized in other tissues but remain poorly characterized in islets and other metabolic cells.

An emerging question is whether we have focused too narrowly on the "stan-

» dard" forms of miRNAs. Many miRNAs exist as slightly different sequence variants, known as **isomiRs**, which arise during miRNA biogenesis or through subsequent modifications. These variants may differ at their ends and therefore regulate distinct sets of genes. Recent studies suggest that isomiRs constitute a substantial fraction of miRNAs present in islets, raising the possibility that relevant regulatory information is lost when analyses treat all variants as a single miRNA.

The stability of miRNAs in blood and their sensitivity to pathological changes have generated strong interest in circulating miRNAs as non-invasive biomarkers of diabetes risk, progression, and treatment response. However, biomarker studies have often been limited by small cohort sizes, population heterogeneity, and methodological variability, resulting in modest overlap between proposed profiles. Larger and multi-cohort studies are promising, but they also highlight a practical challenge: robust prediction may require panels of multiple miRNAs, which may pose challenges in cost, standardization, and clinical implementation.

From a therapeutic perspective, miRNAs offer an attractive concept: by modifying a single miRNA, it is possible to modulate an entire gene network relevant to β-cell survival, identity, or insulin secretion. This is fundamentally different from targeting insulin resistance in peripheral tissues, as β cells represent a limited and vulnerable cell population whose dysfunction ultimately determines disease progression. However, this is also the main challenge, as the simultaneous alteration of multiple genes increases the risk of unintended effects, and targeted delivery to β cells remains a major barrier. Systemically administered oligonucleotide inhibitors or mimetics tend to accumulate in liver and kidney rather than in islets, limiting their potency and specificity. Viral-based strategies can achieve high expression but raise concerns regarding tissue specificity, reversibility, and immunogenicity. Emerging strategies, including ligand-conjugated oligonucleotides (e.g., exploiting GLP-1R-mediated uptake), nanoparticle delivery systems, and local manipulation in transplantation contexts, may improve feasibility but remain in early stages. Determining whether these strategies can be efficiently and safely delivered to human β cells in vivo remains a key translational question. D

CONCLUSION

In conclusion, miRNAs have emerged as central regulators of diabetes biology, integrating gene networks that control β-cell development, identity, and stress responses, while also playing roles in immune regulation, peripheral insulin sensitivity, and inter-organ communication. Although significant progress has been made, key challenges remain in defining causal interactions between miRNAs and their target genes, understanding how metabolic signals regulate miRNA programs, and translating this knowledge into robust biomarkers or safe and tissue-specific therapies. Addressing these gaps will be essential to fully realize the potential of miRNAs in the diagnosis and treatment of both T1DM and T2DM.

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