# Application of microRNAs in diabetes mellitus

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## Abstract

MicroRNAs (miRNAs) are small molecules negatively regulating gene expression by diminishing their target mRNAs. Emerging studies have shown that miRNAs play diverse roles in diabetes mellitus. Type 1 diabetes (T1D) and T2D are two major types of diabetes. T1D is characterized by a reduction in insulin release from the pancreatic β-cells, while T2D is caused by islet β-cell dysfunction in response to insulin resistance. This review describes the miRNAs that control insulin release and production by regulating cellular membrane electrical excitability (ATP:ADP ratio), insulin granule exocytosis, insulin synthesis in β-cells, and β-cell fate and islet mass formation. This review also examines miRNAs involved the insulin resistance of liver, fat, and skeletal muscle, which change insulin sensitivity pathways (insulin receptors, glucose transporter type 4, and protein kinase B pathways). This review discusses the potential application of miRNAs in diabetes, including the use of gene therapy and therapeutic compounds to recover miRNA function in diabetes, as well as the role of miRNAs as potential biomarkers for T1D and T2D.

**Key Words**
- diabetes
- insulin resistance
- microRNA
- T1D
- T2D

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## Introduction

Diabetes mellitus (DM) affects 347 million people worldwide. The World Health Organization predicts that diabetes-related deaths could double between 2005 and 2030. The research conducted by American Diabetes Association estimated that the national economic burden of diagnosed diabetes in the USA in 2012 was $245 billion, including $176 billion in direct medical costs and $69 billion in reduced productivity, a 41% increase from the estimates in 2009 (American Diabetes Association 2013). DM is a complex disease characterized by high blood glucose levels. There are two major forms of diabetes. Type 1 diabetes (T1D) results from a lack of insulin production in pancreatic β-cells. T2D is due to resistance to insulin, resulting in ineffective use of insulin in the body. Long-term hyperglycemia in both T1D and T2D may lead to macrovascular (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) (Fowler 2008). Though conventional treatments for diabetes are effective, recent advances in molecular biology have provided a better understanding of diabetes and the potential to develop molecular theranostics for the disease.

MicroRNAs (miRNAs) play a crucial role in the regulation of protein-encoding genes. They are single-stranded non-coding RNA molecules of approximately 22 nucleotides in length, which function as regulators of gene expression by binding to the 3′ UTR region of mRNAs and destabilizing them or inhibiting their translation (Bartel 2004). A number of studies show that miRNAs play

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an important role in the etiology and pathogenesis of DM and its complications. Though miRNAs and their roles in diabetes remain largely unknown, results from a number of studies indicate that miRNAs may serve as potential biomarkers for the diagnosis and prognosis of diabetes. In this review, we summarize recent findings about the roles of miRNAs in diabetes, as well as their target genes and proteins. Moreover, we also discuss the potential application of miRNAs in diabetes.

## Roles of miRNAs in diabetes

### miRNAs and insulin release

Insulin release is initiated by electrical excitation of the β-cell membrane. Following a meal, glucose in circulation leads to an increased glucose uptake into β-cells through glucose transporters (called GLUTs). Glucose is metabolized in β-cells, which causes the production of ATP and an increase in the ATP:ADP ratio, resulting in the closure of ATP-sensitive potassium channels ($K_{ATP}$ channels) in the cell membrane and subsequent depolarization of the membrane. The depolarization of cell membranes opens the voltage-gated calcium channel, leading to calcium influx, and the accumulation of calcium triggers the fusion of secretory vesicles to the plasma membrane to release insulin (Layden *et al*. 2010, Rorsman & Braun 2013). Insulin acts on the cells of peripheral tissues, mainly in fat, skeletal muscle, and liver, by binding the insulin receptors in cell membrane and, in turn, activates glucose uptake and metabolization. Insulin plays a crucial role in glucose homeostasis. The reduced production and incomplete utilization of insulin are the major mechanisms resulting in T1D and T2D. miRNAs are involved in β-cell membrane electrical excitation (initiated by an increase in ATP:ADP ratio), insulin synthesis, exocytosis processes (docking, fusion, and exocytosis of insulin granules), and β-cell fate and pancreatic mass formation (Fig. 1).

**miRNAs alter ATP:ADP ratio in insulin secretion** Uncoupling protein 2 (UCP2) in pancreatic β-cells reduces ATP levels, causes a decrease in ATP:ADP ratio, and

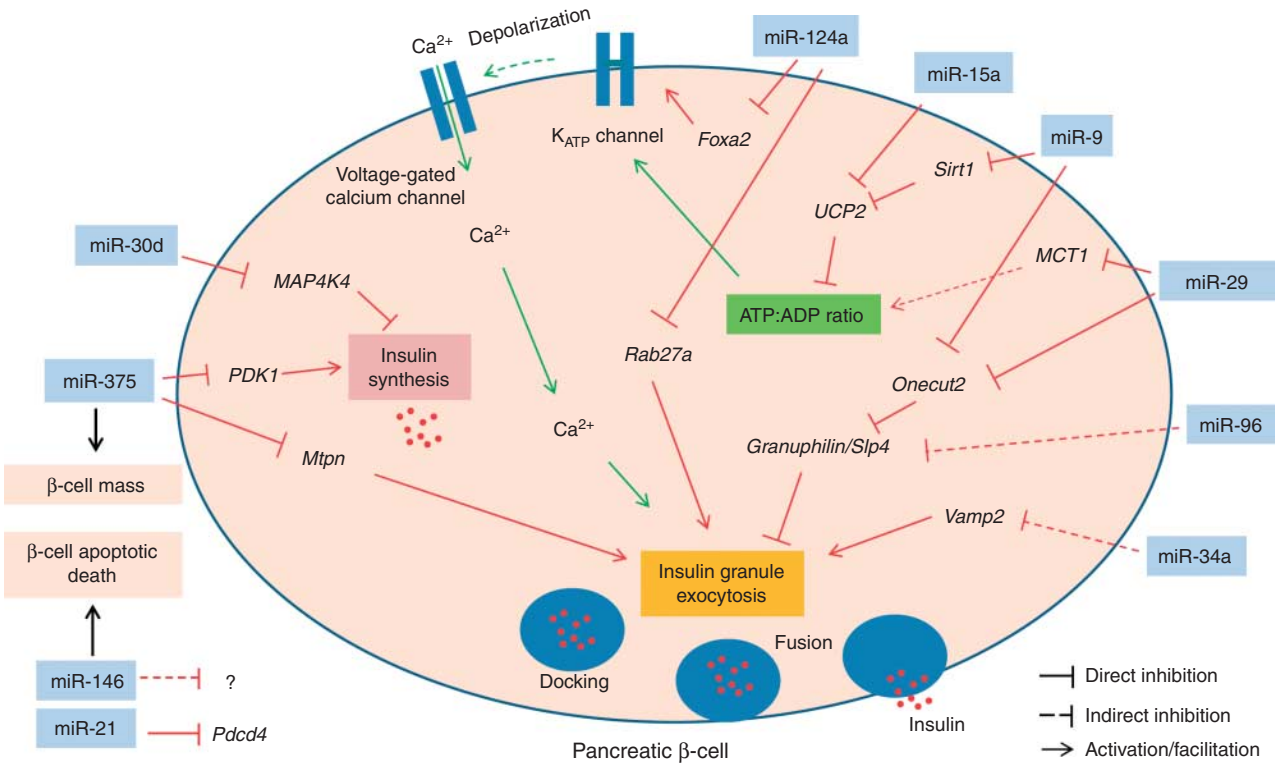


**Figure 1**
miRNAs involved in insulin release in pancreatic β-cells and β-cell fate. Foxa2, forkhead box A2; $K_{ATP}$ channel, ATP-sensitive potassium channel; MAP4K4, MAPKKKK4; MCT1, monocarboxylate transporter 1; Mtpn, myotrophin; Onecut2, one cut homeobox 2; Pdcd4, programmed cell death 4; PDK1, phosphoinositide-dependent protein kinase 1; Rab27a, member RAS oncogene family; Sirt1, sirtuin (silent mating type information regulation 2 homolog) 1; Vamp2, vesicle-associated membrane protein 2; UCP2, uncoupling protein 2.



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subsequently decreases glucose-stimulated insulin secretion (Bordone *et al*. 2006). *UCP2* is a direct target of miR-15a in β-cells. Prolonged stimulation of MIN6 cells with glucose downregulates miR-15a, resulting in an increase in *UCP2* and a reduction in insulin secretion (Sun *et al*. 2011). miR-9 diminishes *SIRT1* in β-cells and reduces the glucose-stimulated insulin secretion (Ramachandran *et al*. 2011), probably through enhanced expression of UCP2 (Bordone *et al*. 2006, Ramachandran *et al*. 2011, Sun *et al*. 2011). miR-29a and miR-29b also negatively control insulin release by reducing monocarboxylate transporter 1 (*MCT1* (*SLC16A1*)), which acts as a substrate for mitochondrial oxidation to increase the cytosolic ATP:ADP ratio and triggers insulin release in β-cells (Pullen *et al*. 2011). miR-124a targets *FOXA2*, regulating the $K_{ATP}$ channel subunits, Kir6.2 and Sur-1, and pancreatic development (Baroukh *et al*. 2007).

**miRNAs control insulin granule exocytosis** miR-9 miRNA exerts a negative regulatory effect on insulin release by cleaving the target transcription factor, *ONECUT2* (a *Granuphilin* gene repressor), and increasing the level of *Granuphilin* (*SLP4*) (a Rab3/27 effector), which facilitates exocytosis processing by mobilizing insulin granules from the readily releasable pool to the cell membrane (Plaisance *et al*. 2006). Interestingly, studies of miRNA expression profiles shows that the increase in miR-29a/b/c in the islets of prediabetic NOD mice is also associated with impaired glucose-induced insulin secretion by diminishing the expression of *Onecut2* (Roggli *et al*. 2012). miR-96 is also negatively associated with *Granuphilin*, independently from *ONECUT2*, and negatively regulates insulin exocytosis (Huang *et al*. 2009). miR-375 is abundantly expressed in the islet cells and the overexpression of miR-375 suppresses glucose-stimulated insulin release by reducing myotrophin (*Mtpn*), a regulator of the actin network in membrane docking and fusion for insulin exocytosis (Poy *et al*. 2004). miR-124a directly targets *RAB27A*, downregulates *NOC2*, and upregulates *SNAP25*, *RAB3A*, and *Synapsin1a*, facilitating insulin exocytosis (Lovis *et al*. 2008*a*, Merrins & Stuenkel 2008). miR-34a is upregulated in *db/db* mice, in which miR-34a is associated with the decreased expression of vesicle-associated membrane protein 2 (*Vamp2*), a key player in docking and fusion of insulin granules in β-cell membranes (Lovis *et al*. 2008*b*).

**miRNAs control insulin synthesis** miR-375 targets 3′-phosphoinositide-dependent protein kinase-1 (*PDK1*) and decreases glucose-induced insulin gene expression and protein synthesis (Hashimoto *et al*. 2006, El Ouaamari *et al*. 2008). miR-30d induces insulin expression in β-cells via targeting MAP4K4, the negative regulator of the insulin transcription factor, MAFA (Zhao *et al*. 2012).

**miRNAs control pancreatic cell fate and pancreas formation** miR-375 is essential for the formation of insulin-secreting pancreatic islets (Kloosterman *et al*. 2007) and maintains the normal pancreatic α- and β-cell mass (Poy *et al*. 2009). It has been reported that increased expression of miR-21, miR-34a, and miR-146a has been induced by interleukin 1β (IL1β) and tumor necrosis factor α (TNFα) in *db/db* mice (Lovis *et al*. 2008*b*, Roggli *et al*. 2010). miR-21 targets *PDCD4* and induces cell death through the Bax family of apoptotic proteins (Lu *et al*. 2008, Ruan *et al*. 2011). miR-146 contributes to the enhancement of free-acid-induced β-cell apoptosis (Lovis *et al*. 2008*b*).

## miRNAs and insulin resistance

Insulin secreted from β-cells has numerous actions on the peripheral tissues that maintain glucose homeostasis during the uptake of food. In the skeletal muscle, insulin increases glucose transport, permitting glucose entry, and glycogen synthesis. In the liver, insulin promotes glycogen synthesis and inhibits gluconeogenesis. In the adipose tissue, insulin suppresses lipolysis and promotes lipogenesis (Rottiers & Naar 2012, Samuel & Shulman 2012). Insulin resistance indicates that the peripheral tissues fail to respond to the normal level of insulin, and manifests as an elevated glucose level with decreased insulin-mediated glucose uptake in the skeletal muscle and adipose tissue, and as an impaired suppression of glucose output in the liver (Peppa *et al*. 2010). Herrera *et al*. (2009, 2010) profiled a cluster of miRNAs in insulin target tissues in Goto-Kakizaki (GK) rats, a spontaneous rat model of T2D, and found upregulation of miR-222 and miR-27a in adipose tissue; upregulation of miR-125a, miR-195, and miR-103 in liver; and downregulation of miR-10b in muscle.

**miRNAs and hepatic insulin resistance** miRNAs regulate insulin resistance in liver and hepatocytes and this is well documented by many studies. Upregulation of miR-143 in the livers of diabetic rats (Jordan *et al*. 2011) and obese mice (Takanabe *et al*. 2008) has been observed. Further study has shown that miR-143 downregulates *Orp8*, and in turn impairs the ability of insulin to induce the activation of PKB (Akt) signaling, a central signaling node of insulin action to induce glucose metabolism (Jordan *et al*. 2011).



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miR-802 is upregulated in the livers of obese mice and obese human subjects, the increase in miR-802 silences *HNF1B*, resulting in a diminished ability of insulin to activate PKB signaling (Kornfeld *et al*. 2013).

Hepatic *Sirt1* deficiency in mice has been demonstrated to impair mTORC2/AKT signaling and results in hyperglycemia and insulin resistance (Wang *et al*. 2011). The upregulation of miR-181a in diabetic liver and hepatocytes decreases *Sirt1*, inactivating insulin signaling and glucose metabolism (Zhou *et al*. 2012). miR-96 and miR-126 directly target the insulin receptor substrate 1 (*IRS1*) 3′ UTR. The reduction in IRS1 is involved in insulin resistance under conditions of mitochondrial dysfunction in hepatocytes (Ryu *et al*. 2011, Jeong *et al*. 2013).

Protein tyrosine phosphatase 1B (*PTP1B*), a target of miR-122, inhibits hepatic insulin signaling by dephosphorylating tyrosine residues in the insulin receptor (IR) and IRS. A high-fat diet induces the phosphorylation of JUNK1 in mice, and decreases the expression of miR-122, resulting in an increase in hepatic insulin resistance (Yang *et al*. 2012). Another study has shown that the reduction in miR-200a/b/c in the livers of *db/db* mice is associated with the inactivation of the AKT/GSK signaling pathway. A decrease in *Fog2*, a direct target of miR-200a/b/c, impairs the AKT/GSK-mediated glycogenesis in liver, resulting in hepatic insulin resistance (Dou *et al*. 2013).

**miRNAs and insulin resistance of adipose tissue** miR-103 and miR-107 are well studied in adipocytes. Upregulation of miR-103/-107 was demonstrated in obese mice. Overexpression of miR-103/-107 in either liver or fat impaired the insulin sensitivity, and silencing of miR-103/107 in adipocytes enhanced insulin signaling, decreased adipocyte size, and enhanced insulin-stimulated glucose uptake via upregulating *Caveolin-1*, a critical regulator for stabilizing the insulin receptor (Trajkovski *et al*. 2011). miR-221 is positively associated with BMI, and is upregulated in human pre-adipocytes. A study showed that miR-221 could downregulate adiponectin receptor 1 (*ADIPOR1*)-mediated actions of insulin, possibly via peroxisome proliferator-activated receptor (*PPAR*) signaling (Meerson *et al*. 2013). An increase in miR-93 in the adipocytes of polycystic ovary syndrome patients diminished the *GLUT4* expression by directly binding the 3′ UTR, indicating the mechanism of insulin resistance in diabetes patients (Chen *et al*. 2013).

In addition, studies have shown that many miRNAs were highly associated with insulin resistance in adipose tissue though the directly targeted gene was not identified. Upregulation of miR-29 in adipose tissue of GK rats and 3T3-L1 adipocytes led to repression of insulin-stimulated glucose uptake, through inhibition of AKT activation. However, AKT is not the direct target of miR-29 (He *et al*. 2007). Downregulation of miR-21 was found in insulin-resistant adipocytes but overexpressing miR-21 significantly increased insulin-induced phosphorylation of AKT and GSK3β and the translocation of GLUT4 in insulin-resistant adipocytes (Ling *et al*. 2012). The target gene of miR-21 was not identified, but was possibly a component of the PTEN–AKT pathway. miR-320 was upregulated in insulin-resistant adipocytes and anti-miR-320 oligonucleotides activated AKT signaling, possibly by targeting the p85 subunit of PI3K, and increased the protein expression of GLUT4, sequentially enhancing insulin-stimulated glucose uptake (Ling *et al*. 2009).

**miRNAs and insulin resistance of skeletal muscle** Let-7 suppressed the multiple components of the insulin–PI3K–mTOR pathway, via targeting insulin-like growth factor 1 receptor (*IGF1R*), insulin receptor (*INSR*), and *IRS2* to mediate insulin resistance in skeletal muscle (Zhu *et al*. 2011). Frost & Olson (2011) demonstrated that knockdown of *let-7* improved insulin sensitivity in liver and muscle, resulting in increased lean and muscle mass, but not increased fat mass, and prevented ectopic fat deposition in the liver. The upregulation of miR-223 was found in insulin-resistant heart muscle of T2D patients, while overexpression of miR-223 was positively associated with GLUT4, but not PI3K signaling or MAPK activity in cardiomyocytes (Lu *et al*. 2010). The upregulation of miR-494 induced by TNFα desensitizes C2C12 muscle cells to the effects of insulin by inhibiting the pathway downstream of Akt, which was associated with the regulation of *STXBP5* (an inhibitor of glucose transport) and *SLC2A4* (the gene encoding GLUT4) expression (Lee *et al*. 2013). Katta *et al*. (2013) demonstrated that miR-1 and miR-133 were associated with insulin resistance in insulin-resistant obese Zucker rats. Recently, several studies involving miRNA microarray analysis have been conducted using the GK diabetic model. Huang *et al*. (2009) showed at least a twofold decrease in miR-23a/b, miR-24, miR-126, miR-130a, miR-424, and miR-450 and at least a twofold increase in miR-307 and let-7f in the skeletal muscle of GK rats vs Wistar rats. Herrera *et al*. (2010) found a significant decrease in miR-10b in the skeletal muscle of GK rats compared with Wistar Kyoto rats and Brown Norway rats. He *et al*. (2007) found an increase in miR-29a/b/c in the skeletal muscle of GK rats compared with normal Wistar rats. However, the



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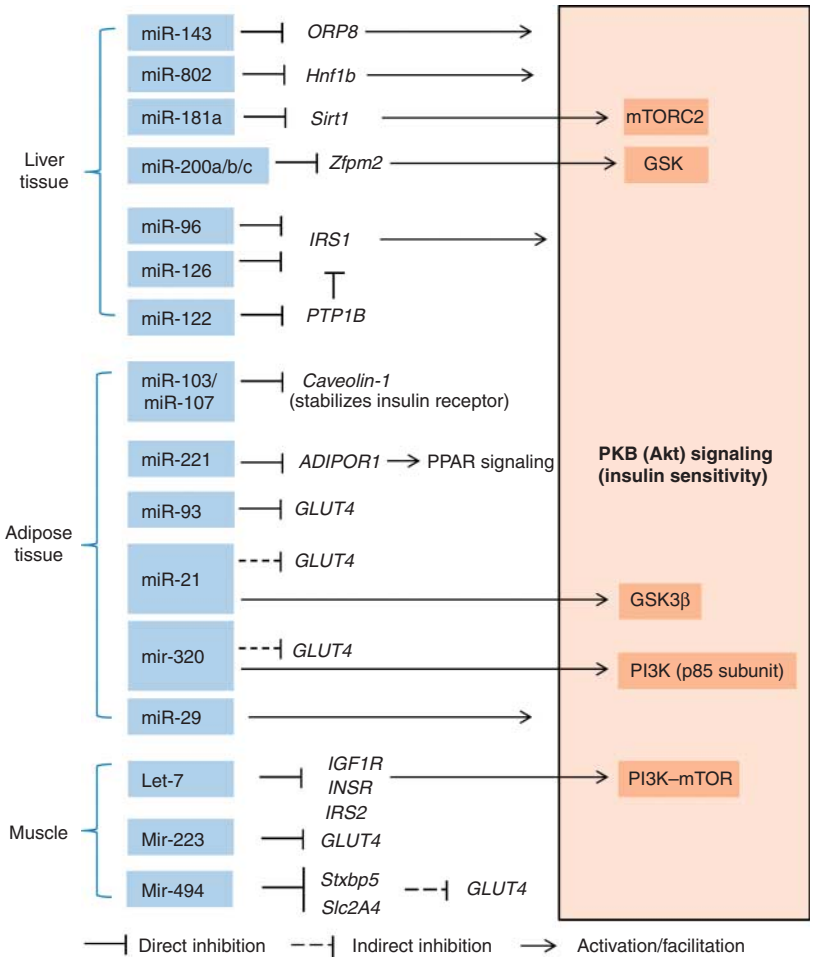


**Figure 2**
miRNAs involved in insulin sensitivity and insulin resistance. ADIPOR1, adiponectin receptor 1; *Zfpm2*, *zinc* finger protein friend of GATA family member 2; GLUT4, glucose transporter type 4; GSK, glycogen synthase kinase; Hnf1b, hepatocyte nuclear factor 1β; IGF1R, insulin-like growth factor 1 receptor; INSR, insulin receptor; IRS1, insulin receptor substrate 1; IRS2, insulin receptor substrate 2; mTOR, mammalian target of rapamycin; mTORC2, mTOR complex 2; ORP8, oxysterol-binding protein-related proteins; PI3K, phosphoinositide 3-kinase; PKB, protein kinase B; PPAR, peroxisome proliferator-activated receptor; PTP1B, protein-tyrosine phosphatase 1B; Slc2A4, solute carrier family 2 member 4; Sirt1, sirtuin (silent mating type information regulation 2 homolog) 1; Stxbp5, syntaxin-binding protein 5.

molecular mechanism of these miRNAs in insulin resistance requires further investigation.

Taken together, miRNAs regulate insulin sensitivity and resistance mainly by targeting the components of the insulin/PKB signaling pathway and GLUT4-mediated glucose uptake and metabolism (Fig. 2).

## Potential application of miRNAs in diabetes

### Therapeutic targets for improving insulin release and insulin sensitivity

Altered expression of miRNAs in diabetes causes malfunction of insulin release and insulin resistance. Restoration of expression of miRNAs to normal levels may have therapeutic potential for maintaining sufficient insulin secretion and insulin sensitivity. Several approaches have been developed to restore miRNAs to normal levels. Anti-miRNA oligonucleotides (AMOs) are one of the most common strategies in miRNA gene therapy, in which AMOs directly and specifically bind to miRNA sequences to prevent binding of miRNA to the target. The other oligonucleotide-based techniques include miRNA mimics, which comprise the same nucleotide sequences as the endogenous miRNA. The regulation of miRNA with viral-based and reagent-based transfection has been successfully used in animal experiments, showing the therapeutic potential for diabetes.



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**Anti-miRNA oligonucleotides** AMOs have been shown to possess therapeutic potential in targeting miRNAs-related human diseases (Weiler *et al*. 2006). AMOs are chemically modified oligonucleotide analogs, allowing small RNA to cross the physical barrier and improving the efficiency of therapeutics, e.g. 2′-fluoro and 2′-*O*-methyl conjugations and 2′-4′-methylene bridges, linking with a locked nucleic acid (LNA; Weiler *et al*. 2006, Czech *et al*. 2011). Though AMO is not clinically used for diabetes, some studies have demonstrated that the antisense oligonucleotides exert effects on miRNA-mediated diabetes as described below.

El Ouaamari *et al*. (2008) showed that application of 2′-*O*-methyl-miR-375 antisense oligonucleotides increased expression of its target gene *PDK1* and reverted insulin release back to normalcy in INS-1E cells. Trajkovski *et al*. (2011) showed that the inhibition of miR-103 and miR-107 by 2′-*O*-methyl-miR-103 and -107 antisense oligonucleotides improves glucose homeostasis and insulin sensitivity in *ob/ob* mice. Roggli *et al*. (2010) found that blocking the miR-21, miR-34a, or miR-146a function with antisense molecules could prevent the reduction in glucose-induced insulin secretion in MIN6 β-cells under ILβ treatment, but Lovis *et al*. (2008*b*) showed that blocking the miR-34a or miR-146 activity using oligonucleotides partially protected palmitate-treated MIN6B1 β-cell lines from apoptosis but was insufficient to restore normal insulin secretion.

Inhibition of miR-320 using anti-miR-320 oligonucleotides restored the insulin sensitivity in insulin-resistant 3T3-L1 adipocytes, evidenced by activation of insulin – PI3K signaling pathways and insulin-stimulated glucose uptake (Ling *et al*. 2009). Treatment with antisense oligonucleotides (2′-*O*-methyl-miR-181a) increases SIRT1 protein levels and activity, and improves insulin sensitivity in HepG2 hepatocytes (Zhou *et al*. 2012).

The inhibition of miR-29 with LNA antisense-based anti-miR29 increased insulin-induced AKT signaling, but barely augmented insulin-dependent glucose uptake (He *et al*. 2007). The discrepancy with AMO treatment indicated the involvement of numerous other target molecules of the insulin-signaling pathway (He *et al*. 2007). LNA antisense-based anti-let-7 improved the impaired glucose tolerance, at least in liver and muscle, of mice (Frost & Olson 2011).

**Virus-based miRNA regulation** miRNA expression can also be manipulated by introducing the expression plasmid into cells through virus-based transfection and reagent-based transfection (Trajkovski *et al*. 2011). Mice that received injections of adenovirus expressing miR-107 displayed an increase in both random and fasting blood-glucose levels, impaired glucose tolerance after an i.p. glucose injection, and decreased insulin sensitivity (Trajkovski *et al*. 2011). Overexpression of miR-181a using adenovirus-based transfection in C57/BL6 mice by tail vein injection impaired hepatic insulin signaling and attenuated glucose homeostasis, while downregulation of miR-181a with i.p. injection of LNA antisense oligonucleotides improved glucose homeostasis in mice with diet-induced obesity (Zhou *et al*. 2012). Recently, non-viral-based miRNA regulation has been successfully developed to treat diabetic complications and other diseases, such as diabetic nephropathy, lung fibrosis, and cardiac fibrosis (Xiao *et al*. 2012, Chen *et al*. 2014, Zhang *et al*. 2014). These studies showed that miRNA regulation by virus-based and reagent-based transfection may be applicable to T1D and T2D though the potential risks of the therapy need to be further investigated.

**Therapeutic chemical compounds** miRNA inhibits the expression of the target gene and in turn affects the downstream signaling. A decrease in miR-122 led to hepatic insulin resistance, while licorice flavonoids had been shown to reduce obesity-induced insulin resistance (Yang *et al*. 2012). Joven *et al*. (2012) showed that plant-derived polyphenols could regulate the expression of miRNA paralogs, miR-103/-107 and miR-122, and prevent diet-induced fatty liver disease in hyperlipidemic mice. Moreover, Parra *et al*. (2010) showed that adipose miRNAs (miR-103/-107, miR-122, and miR-123) were sensitive to dietary conjugated linoleic acid treatment in mice. Although the mechanisms involved are unclear, the discovery and development of therapeutic drugs to disturb miRNAs implicated in pathogenesis of diabetes might be an alternative approach.

## miRNAs as potential biomarkers of DM

miRNAs are potential biomarkers for many diseases, e.g. acute myocardial infarction (AMI) and hepatocellular carcinoma (HCC). Wang *et al*. (2010) showed that circulating miR-208a was found in individuals with AMI with 90.9% sensitivity and 100% specificity. Li *et al*. (2010) demonstrated that three serum miRNAs (miR-25, miR-375, and let-7) could be used as biomarkers that distinguished hepatitis B virus-positive HCC from the controls with 97.9% sensitivity and 99.1% specificity, while miR-375 alone predicted HCC with 96% specificity and 100% sensitivity. However, the diagnostic potential



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of miRNAs in diabetes is largely unexplored. Several studies have shown that circulating miRNAs can serve as potential biomarkers for diabetes (Guay & Regazzi 2013).

**Potential miRNA biomarkers in T1D** Circulating miR-375 levels have been shown to be a biomarker of β-cell death, and were significantly increased at 2 weeks before onset of diabetes in NOD mice, a model of autoimmune diabetes (Erener *et al*. 2013). Elevated expression of miR-326 was found in peripheral blood lymphocytes of T1D patients with ongoing islet autoimmunity (Sebastiani *et al*. 2011). Clinically, Nielsen *et al*. (2012) showed the upregulation of twelve serum miRNAs (miR-152, miR-30a-5p, miR-181a, miR-24, miR-148a, miR-210, miR-27a, miR-29a, miR-26a, miR-27b, miR-25, and miR-200a) in T1D patients; particularly they found that miR-25 was negatively associated with β-cell function. SalasPerez *et al*. (2013) detected downregulation of miR-21a and miR-93 in peripheral blood mononuclear cells from T1D patients.

**Potential miRNA biomarkers in T2D** A serum miRNA analysis of T2D patients shows that seven miRNAs (miR-9, miR-29a, miR-30d, miR-34a, miR-124a, miR-146a, and miR-375) were significantly elevated compared with individuals with normal glucose tolerance (NGT) and five miRNAs in the above list (miR-9, miR-29a, miR-34a, miR-146a, and miR-375) were significantly upregulated compared with levels in individuals with prediabetes, although miRNA expression was not significantly different between NGT and pre-diabetes (Kong *et al*. 2011). Zampetaki *et al*. (2010) found lower levels of plasma miRNAs (miR-20b, miR-21, miR-24, miR-15a, miR-126, miR-191, miR-197, miR-223, miR-320, and miR-486) in T2D patients, but a modest increase in miR-28-3p. Importantly, a decrease in miR-15a, miR-29b, miR-126, and miR-223 and an increase in miR-28-3p levels in plasma indicated the manifestation of disease, indicating their value for predicting T2D. Karolina *et al*. (2011) identified miR-144, miR-146a, miR-150, and miR-182 in the blood of T2D patients as the signature miRNAs for predicting of T2D. In addition, Pescador *et al*. (2013) showed that three serum miRNAs (miR-138, miR-376a, and miR-15b) are potential biomarkers for distinguishing obese patients from obese-T2D and T2D patients; meanwhile, the combination of miR-503 and miR-138 can distinguish diabetic from obese-diabetic patients. Furthermore, Zhao *et al*. (2011) found that three serum miRNAs (miR-132, miR-29a, and miR-222) can predict gestational DM with 66.7% sensitivity and 63.3% specificity (area under the curve = 0.642).

So far no commercial products are available for diabetes diagnosis. The potential clinical use of miRNAs as diabetic biomarkers still needs further investigation.

## Discussion and prospects

miRNAs play multiple roles in the maintenance of glucose homeostasis in the human body by regulating β-cell development and differentiation, insulin secretion, and insulin actions on the insulin target tissues, liver, adipose tissue, muscle, etc. Upregulation and downregulation of miRNAs are strongly associated with T1D and T2D. miRNAs directly target genes involved in β-cell survival and insulin exocytosis, and insulin resistance is the central mechanism of miRNAs-mediated T1D and T2D (Fernandez-Valverde *et al*. 2011, Guay *et al*. 2011, Rottiers & Naar 2012, Samuel & Shulman 2012, Williams & Mitchell 2012). Manipulation of miRNAs and insulin signaling may have therapeutic potential. AMOs for miRNAs (anti-miR-181a, anti-miR-320, etc.) have demonstrated the sufficient ability to restore miRNA to normal levels and revert the abnormalities of insulin signaling. Nevertheless, resistance of tissues to the uptake of AMOs is a major obstacle for developing AMO strategy for the clinical use (Xiao *et al*. 2012). Virus-based gene delivery (adenovirus vectors, lentivirus vectors, etc.) is the most widely used gene delivery approach with high transfection rate; however, toxicity, host immune response, and potential mutagenesis limit the clinical benefits (Mah *et al*. 2002, Jia & Zhou 2005). Advances in science have led to the development of nonviral vectors-mediated gene therapies to overcome the shortcomings, e.g. the sleeping beauty transposon system (Aronovich *et al*. 2011) and the ultrasound microbubble-mediated gene delivery system (Lan *et al*. 2003, Chen *et al*. 2011, Zhong *et al*. 2013). Transposon-based miR-29b overexpression via mouse tail vein injection resulted in higher levels of transfection and long-term expression of miR-29b in the lungs of mice, without obvious pathological changes (Xiao *et al*. 2012). Ultrasound microbubble-mediated miR-21 small hairpin RNA transfer caused a twofold increase in miR-21 expression in diabetic kidney, which attenuated renal fibrosis and inflammation in *db/db* mice (Zhong *et al*. 2013). However, these gene delivery approaches remain at the preclinical stage and are far from the clinical use. The development of safe, highly efficient, tissue-specific miRNA gene therapy is still a big challenge. Interestingly, some chemical compounds, e.g. licorice flavonoids and linoleic acid, regulated miRNAs and attenuated the pathogenesis of diabetes (Parra *et al*. 2010, Yang *et al*. 2012). The development of chemical



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compounds to regulate miRNAs implicated in diabetes could be another potential strategy to manipulate diabetes.

Though miRNAs and their roles in diabetes remain under-explored, some studies have demonstrated that miRNAs may act as potential biomarkers for diagnosis and prognosis of diabetes. The sensitivity and specificity of miRNAs in the identification of pancreatic β-cell fate, insulin secretion, and insulin action have not satisfied the clinical need so far in pilot studies. As each miRNA may have numerous targets, and is involved in complex processes of physiology and pathology, we believe that a cluster of miRNAs, instead of a single miRNA, could be used as diabetes biomarker with better sensitivity and specificity that meet the clinical requirements.

Though the understanding of the involvement of miRNAs in diabetes is in its infancy, advances in investigating the role of miRNA in diabetes may potentially provide a powerful tool to predict, diagnose, treat, and prognose diabetes in the future.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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