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Role of MicroRNAs in Diabetes

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Abstract

Diabetes is one of the most common chronic diseases in the world. Multiple and complex factors including various genetic and physiological changes can lead to Type 1 and Type 2 diabetes. However, the major mechanisms underlying the pathogenesis of diabetes remain obscure. With the recent discovery of MicroRNAs (miRNAs), these small ribonucleotides have been implicated as new players in the pathogenesis of diabetes and diabetes-associated complications. MiRNAs have been shown to regulate insulin production, insulin secretion, and insulin action. This review summarizes the recent progress in the cutting-edge research of miRNAs involved diabetes and diabetes related complications.

Keywords

diabetes; miRNA; diabetic complications; insulin; pancreas

Introduction

Diabetes is a serious chronic disease worldwide and is caused by defects in insulin production, insulin secretion, and insulin signaling [1,2]. There are two types of diabetes: Type 1 diabetes (T1D) is due to self-destruction of the insulin producing beta cells in the pancreas, and Type 2 diabetes (T2D) is caused by defects in insulin action and insulin production [1]. In both types of diabetes, the patients develop serious secondary complications associated with diabetes, such as microvascular complications [3,4], oxidative stress and endothelial dysfunction (ED) [5], neonatal complications [6], foot complications related to peripheral neuropathy (PN) and peripheral vascular disease (PVD) [7], cardiovascular disease and kidney failure [8].

The recent breakthrough discovery of a family of endogenous small RNAs termed microRNAs (miRNAs) [9,10] has shed light on their roles in control of glucose homeostasis [11,12]. MiRNAs are a novel class of non-coding RNAs that are widely expressed in plants and animals to regulate gene expression post-transcriptionally by cleavage or translational repression of their specific target mRNAs [13]. The expression of miRNAs is often tissue-specific or developmental-specific, and thus miRNAs play an important role in repression of gene expression at specific stages in various biological processes.

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Recent data suggest that miRNAs play a direct role in insulin secretion [14], pancreatic islet development [15], beta cell differentiation [16], and indirectly control glucose and lipid metabolism [17] and are involved in secondary complications associated with diabetes [18, 19]. It is therefore not surprising that a conditional knockout of Dicer 1, the sole Dicer enzyme responsible for the biogenesis of miRNAs in humans and mice, led to gross defects in all pancreatic lineages in mice [20]. In this mini-review, we will discuss the potential roles of miRNAs in insulin production and secretion from pancreatic beta cells, their role in insulin signaling in insulin sensitive tissues such as muscle, fat and liver, and provide insights into their function in diabetic complications. The miRNAs of interest and their specific roles in glucose homeostasis are summarized in Table 1 and will be discussed in more detail in this review.

MiRNAs and Production and Secretion of Insulin from Pancreatic Beta Cells

The implication that miRNAs can regulate insulin secretion came with the cloning of miR-375, which is one of the abundant miRNAs in pancreatic islets and beta cells [14]. MiR-375 has been shown to regulate glucose-stimulated insulin secretion in a negative manner, since overexpression of miR-375 inhibits insulin secretion. Consistent with this, inhibition of endogenous miR-375 function using antagomiRs enhances insulin secretion [14]. One of the target genes of miR-375 was identified as Myotrophin (Mtpn), which has been shown to control the release of the neurotransmitter catecholamine. Similar to overexpression of miR-375, knockdown of Mtpn by siRNA also results in decreased insulin secretion [14]. Furthermore, it has been shown that miR-375 can directly bind to the 3'UTR of Mtpn and overexpression of miR-375 causes down regulation of Mtpn, suggesting the idea that Mtpn is a direct target of miR-375 [14].

Myotrophin (Mtpn) has been shown to interact with the actin-capping protein CapZ, which inhibits the assembly of F-actin. It is possible that myotrophin leads to changes in the actin network and thereby affects granule docking and fusion [11,21]. Interestingly, miR-375-regulated insulin secretion appears to be calcium-independent, since miR-375 does not cause changes in intracellular calcium levels [14]. Mice with homozygous deletion of miR-375 appear to have hyperglycemia due to decreased total pancreatic beta cell mass and insulin levels [17]. This suggests that in addition to regulating insulin secretion, miR-375 may also play an important role in pancreatic beta-cell development.

It has been recently suggested that the effects of miR-375 on Mtpn expression and insulin secretion may be via the transcription factor nuclear factor-kappaB (NF-kappaB) [11]. Activation of NF-kappaB is associated with improved glucose-stimulated insulin secretion [22], while inactivation of NF-kappaB results in decreased insulin secretion from beta cells [11]. Myotrophin has been shown to function as a transcriptional activator of NF-kappaB in cardiomyocytes, suggesting the idea that regulation of myotrophin levels by miR-375 may lead to changes in NF-kappaB activity [23]. Furthermore, it has been suggested that in addition to Mtpn, miR-375 may also play a role in regulating the expression of the ubiquitin specific protease 1 (Usp1), Janus Kinase 2 (Jak2), a non-receptor tyrosine kinase involved in cytokine signaling, and adiponectin receptor 2 (Adipor2) [11,24]. Considering the prediction that each miRNA can regulate more than 200 different transcripts, it is not surprising that miRNA-375 has several other targets besides Mtpn.

In addition to miR-375, several other miRNAs, including miR-124a and let-7b have been predicted to bind to the 3' UTR of Mtpn using a computational prediction approach called PicTar [24]. MiR-375 followed by miR-124 and let-7b are the most abundant miRNAs in the mouse insulinoma cell line MIN6 [25]. While let-7b appears to be in general ubiquitously expressed in most mouse tissues [26], miR-375 and miR-124a seem to have a more tissue- or

cell-specific expression. Consistent with the idea that the same target can be regulated by multiple miRNAs, miR-375, miR-124 and let-7b appear to regulate Mtpn expression in a coordinated manner [24].

MiR-124a, which was originally found to be highly expressed in brain and neurons, is also abundant in the pancreatic beta cells [25,27,28]. In a recent study, the levels of miR-124a have been shown to be low at E14.5 in the developing pancreas and significantly increased at gestational age E18.5 [16]. This indicates that miR-124a may be important in regulation of pancreatic beta cell development. One of the established target genes for miR-124a is FoxA2 (forkhead box protein A2, also known as HNF3 beta), a transcription factor important for beta-cell differentiation, pancreatic development, glucose metabolism and insulin secretion [16, 29–32]. Overexpression and silencing of miR-124a in MIN6 beta cells causes changes in FoxA2 levels and of its downstream target genes Pdx-1 (pancreatic and duodenal homeobox 1), Kir6.2 (inwardly-rectifying potassium channel), and Sur-1 (sulfonylurea receptor) [16]. FoxA2 plays an important role in endocrine pancreas development and has been shown to regulate the expression of the beta-cell specific transcription factor Pdx-1 and the two subunits of the K_{ATP} channel, Kir6.2 and Sur1. Overexpression or downregulation of miR-124a had not affect insulin secretion, although it caused changes in intracellular free calcium levels [16].

However, a recent study suggests that overexpression of miR-124a in the pancreatic beta cell line MIN6 increases insulin secretion under basal conditions, but decreases insulin secretion mediated by high concentrations of glucose [33]. The effect of miR-124a on insulin secretion seems to be mediated via increased levels of SNAP25, Rab3A and Synapsin-1A and decreased levels of Rab27A and Noc2 [33]. Only Rab27A appears to be a direct target for miR-124a and the effect of miR-124a on the expression of the other genes involved in insulin secretion seems to be indirect via changes in their mRNA levels [33].

It is tempting to speculate that a common set of miRNAs may play a positive or negative role in control of glucose metabolism in both neuronal tissues and pancreatic beta cells. Indeed, miR-9, another miRNA that has been previously considered to be brain-specific [26], is expressed in both brain and pancreatic beta cells. Overexpression of miR-9 causes a decrease in glucose-stimulated insulin exocytosis via targeting the transcription factor Onecut2 [34]. Onecut2 represses the expression of Granuphilin/Slp4, by directly binding to its promoter. Granuphilin is a Rab GTPase effector, that is associated with the secretory granules and negatively regulates insulin release [34]. These data suggest that miR-9 inhibits insulin secretion by repressing the expression of Onecut2 transcription factor and thereby increasing the levels of Granuphilin, which downregulates insulin secretion. Another microRNA that has been shown to modulate Granuphilin levels is miR-96 [33]. MiR-96 has been shown to downregulate insulin secretion via upregulation of Granuphilin mRNA and protein levels. In addition, miR-96 also decreases Noc2 expression, a Rab effector protein involved in secretion [33].

Several miRNAs have been shown to be differentially expressed in the insulin producing pancreatic beta cells [14,20,25,35]. A recent report suggests that miR-7 is the most abundant miRNA in rat and human pancreatic islets compared to acinar cells, while miR-375 appears to be more abundant in intra-islets [35]. Although, several miRNAs including miR-375 and miR-124a have been implicated in regulation of insulin secretion and pancreatic beta-cell development, the exact role for most of the miRNAs identified from pancreatic islets remains to be determined.

MiRNAs and Insulin Action

MiRNAs are not only involved in insulin production and secretion, but also control insulin signaling in target tissues of insulin action. Studies on miRNA expression in skeletal muscles of Goto-Kakizaki (GK) rats, a non-obese model of type 2 diabetes, identified two miR-29 family members including miR-29a and miR-29b, but not miR-29c to be upregulated in these diabetic animals compared to control animals [36]. Further analysis using Northern blots revealed that members of the miR-29 family were up regulated in all three insulin-responsive tissues, such as muscle, fat, and liver of diabetic rats. Overexpression of miR-29a/b/c in 3T3-L1 adipocytes, a murine insulin-responsive fat cell line, inhibited insulin-stimulated glucose uptake. High levels of miR-29 led to insulin resistance mimicking the insulin resistance in cells incubated with high glucose and high insulin [36]. MiR-29a and miR-29b levels were upregulated in the presence of high glucose (hyperglycemia) and high insulin (hyperinsulinemia) in 3T3-L1 adipocytes [36]. Two candidate genes Insig1 (insulin-induced gene 1), an ER membrane protein that is involved in control of cholesterol biosynthesis and Cav2 (caveolin 2) have been validated as targets of miR-29a/b/c using luciferase reporter assays and by Western blotting. Overexpression of miR-29 caused a decrease in the levels of Insig1 and Cav2 proteins [36].

MiR-143 has been shown to be up-regulated during adipocyte differentiation [37]. Reduction of miR-143 by transfecting 2'-*O*-methoxyethyl phosphorothioate-modified antisense RNA oligonucleotides inhibited the expression of adipocyte-specific genes (insulin-sensitive glucose transporter GLUT4, hormone sensitive lipase HSL, fatty acid-binding protein aP2 and peroxisome proliferator-activated receptor PPAR-2), and the accumulation of triglycerides [37]. Interestingly, knockdown of miR-143 led to upregulation of one of the predicted targets, the mitogen-activated protein kinase ERK5/BMK1/MAPK7 suggesting that miR-143 may act through the target gene ERK5. In addition to miR-143, other miRNAs important for regulation of human and mouse adipocyte differentiation have been identified using various screens [37,38]. In *Drosophila*, miR-14 was found to regulate adipocyte droplet size and triacylglycerol levels [39] and miR-278 appears to control insulin sensitivity in adipose tissue [40]. However, miR-14 and miR-278 have been found so far only in insects and there are no known homologues of these miRNAs in mammals. Taken together, these findings suggest that miRNAs play important roles in fat metabolism in both flies and humans.

Insulin receptor substrate (IRS) proteins are important components of the insulin signaling pathway. There are at least three IRS proteins in humans and mice, including IRS1 and IRS2, which are widely expressed, and IRS-4, which is limited to the thymus, brain, kidney and beta cells [41]. IRS3 is only present in mice and is largely restricted to adipose tissue fulfilling a similar function to IRS1. IRS1 knockout mice are small and insulin resistant, whereas IRS2 deficient mice are infertile and develop diabetes, but have a normal size [42,43]. Both IRS1 and IRS2 are tissue specific with no redundancy in most cases. In adipocytes, both IRS1 and IRS2 are expressed and have synergistic effects. Although IRS2 is central to the development of type 2 diabetes and its associated complications, only IRS1 has recently been identified to be a target of miRNAs, specifically miR-145 [44]. Overexpression of miR-145 in human colon cancer cells caused a decrease in IRS-1 protein levels without affecting IRS-1 mRNA levels. IRS-1 appears to be a direct target of miR-145, since the IRS-1 3'-UTR contains binding sites for miR-145 and binding of miR-145 to these sites was confirmed by Luciferase reporter assays [44]. Furthermore, overexpression of miR-145 in colon cancer cells led to growth arrest, similar to the treatment with IRS-1 siRNA [44].

MiRNAs and Diabetic Complications

MiRNAs appear to play a role also in the establishment of diabetes complications. Data from our laboratories and others indicate that diabetic complications are often associated with changes in the levels of certain miRNAs in various tissues, including brain, heart, liver and kidney.

The first miRNA that was shown to change its levels in diabetic hearts was miR-133. The changes of miR-133 levels in heart were associated with two types of consequences: (1) a long QT syndrome (LQTS) [18], and (2) cardiac hypertrophy [45]. QT is a measure of the time between the start of the Q wave (representing depolarization of the interventricular septum) and the end of the T wave (representing repolarization or recovery of the ventricles) in the heart's electrical cycle. LQTS is a life-threatening disorder that affects the heart's electrical system and may lead to fainting, cardiac arrest and possibly sudden death [46]. Human ether-a-go-go-related gene (HERG) was identified as a LQTS gene encoding a cardiac potassium channel responsible for rapid delayed rectifier K^+ current (IKr) [47]. Interestingly, the down regulation of HERG in diabetic hearts is mainly at the post-transcriptional level. In diabetic hearts, the HERG protein was reduced by about 60% while the mRNA levels remained essentially unaltered [18,48]. MiR-133 has been demonstrated to repress HERG expression and miR-133 expression levels itself appears to be regulated by the serum response factor SRF [18].

A recent report indicates a remarkable overexpression of miR-133 in diabetic rabbit hearts [18] and db/db mouse hearts (Tang et al., unpublished data). The up-regulation of miR-133 in diabetic rabbit hearts was induced by the serum response factor (SRF), which was robustly activated in the diabetic heart [18]. Delivery of exogenous miR-133 into the rabbit myocytes and cell lines led to post-transcriptional repression of ERG, down-regulating ERG protein level without altering its transcript level and caused substantial depression of I(Kr), an effect abrogated by the miR-133 antisense inhibitor (antagomiR). Functional inhibition or gene silencing of SRF down regulated miR-133 expression and increased I(Kr) density. Repression of ERG by miR-133 is likely reflected by the differential changes of ERG protein and transcript, and thereby depresses I(Kr), which contributes to repolarization, slowing QT prolongation and the associated arrhythmias, in diabetic hearts.

In addition to its role in the induction of LQTS by repressing ERG, miR-133 also controls cardiac hypertrophy [45]. Cardiac hypertrophy is characterized by thickening of the heart muscle (myocardium) that causes a decrease in size of the heart chamber, including the left and right ventricles. A common cause of cardiac hypertrophy is high blood pressure (hypertension) and heart valve stenosis, typical symptoms of long-term complications due to diabetes. Interestingly, the function of miR-133 in cardiac hypertrophy seems to be the opposite of its function in LQTS. While over-expression of miR-133 induces LQTS, downregulation of miR-133 levels lead to cardiac hypertrophy. In vitro over-expression of miR-133 or miR-1 (both miRNAs come from the same transcriptional unit) inhibits cardiac hypertrophy. In contrast, suppression of miR-133 by antagomiRs induces a more pronounced hypertrophy than that with conventional hypertrophy inducers [45]. Blocking of miR-133 function *in vivo* using an antagomiR causes marked and sustained cardiac hypertrophy. In this case, miR-133 has been shown to target a set of different genes: RhoA, a GDP-GTP exchange protein that regulates cardiac hypertrophy, Cdc42, a signal transduction kinase implicated in hypertrophy, and Nelf-A/WHSC2, a nuclear factor involved in cardiogenesis [45]. The significance of miR-133 dual functions with opposite roles in the control of LQTS and cardiac hypertrophy remains to be determined. The fact that diabetic hearts express higher levels of miR-133 suggests that miR-133 induced LQTS may play a more influential role in diabetic complications. Interestingly, miR-1, another muscle-specific miRNA that shares the same

transcriptional unit with miR-133, is expressed in the heart to a lesser extent. MiR-1 was shown to regulate cardiac arrhythmogenic potential through targeting KCNJ2, encoding the K^+ channel subunit Kir2.1 and GJA1, encoding connexin 43 [49]. It remains to be established whether the expression of miR-1 is similarly altered as miR-133 in diabetic hearts.

Diabetic nephropathy (DN), also known as Kimmelstiel-Wilson syndrome and intercapillary glomerulonephritis, is a progressive kidney disease that causes kidney failure in patients with longstanding diabetes mellitus. Of many genes that are involved in diabetic DN, one gene, Smad-interacting protein 1 (SIP1), has recently been identified to be a target of miR-192, a miRNA highly expressed in the kidney [19]. It is suggested that TGF-β (transforming growth factor beta), SIP1, δEF1 (δ-crystallin enhancer binding protein), Col1a2 (collagen type I alpha 2) and miR-192 constitute a regulatory loop that is important in the control of kidney function. TGF-β upregulates miR192 levels, which then causes downregulation of SIP1 through translational repression. TGF-β also down regulates the transcription factor δEF1, through unknown mechanisms. Consequently, down regulation of SIP1 and δEF1 collectively enhances the expression of Col1a2 by de-repressing the E-box elements located on the Col1a2 promoter. Up-regulation of TGF-β or miR-192 was observed in glomeruli isolated from streptozotocin-induced diabetic mice as well as diabetic db/db mice compared to corresponding nondiabetic controls. These findings suggest a role for miR-192 in kidney and DN development [19].

MiRNAs and Endocrine Pancreas Development

A recent report on conditional deletion of Dicer in pancreatic progenitor cells using the Pdx-1-Cre expression construct indicates that Dicer is required for the development of β δ exocrine and duct cells [20]. The same group identified also 107 different miRNAs in the developing mouse pancreas at gestational stage E14.5. At embryonic day E9.5 the developing pancreas expresses the transcription factors FoxA2, Hes1 (hairy and enhancer of split 1) and Pdx-1, which are crucial for early pancreas development. FoxA2 (HNF3 beta) and its target genes Pdx-1, Kir6.2 and Sur1 have recently been shown to be regulated by miR-124a [16]. Neurogenin 3 (NGN3), a transcription factor essential for pancreatic endocrine differentiation is also regulated by several miRNAs, including miR-15a, miR-15b, miR-16 and miR-195 [50]. Furthermore, miRNA-216 and miR-217 have been shown to be specifically enriched in pancreatic tissue [51] and are thus predicted to be important for pancreas development.

In addition to its role in insulin secretion, miR-375 has been recently reported to play a role in pancreatic islet development in zebrafish [15]. Knockdown of miR-375 using morpholino oligonucleotides caused defects in the morphology of the pancreatic islets, which became dispersed after 36 hours post fertilization. Moreover, in situ hybridization studies suggest that miR-375 is expressed in the endocrine progenitor cells in E14.5 pancreas and co-localizes with Pdx-1. These data suggest that miR-375 has dual functions: mediating insulin secretion and pancreatic islet development. However, the specific target genes of miR-375 involved in pancreatic islet development remain still to be identified.

Conclusions and Perspectives

It is predicted that over 30% of human genes are regulated by miRNAs [52–55]. Although, the majority of human miRNAs have been identified using various screens, the major challenge currently is to define the function of miRNAs in various tissues by identifying and validating their targets. The functional analysis of individual miRNAs is complicated by the fact that miRNAs have normally a large number of target genes and each gene can also be regulated by several different miRNAs [55]. Furthermore, recent data suggest that miRNAs can also stimulate the translation of mRNAs [56] or bind to the promoter regions of genes and activate transcription [57]. Moreover, there is also evidence that miRNAs can regulate the levels of

other miRNAs [58] and the abundance of specific miRNAs may be regulated by various stimuli [59–61]. Most of the loss of function studies on miRNAs to date have used the conditional Dicer knock-out mice [20,62–64]. However, since miRNAs can have both positive and negative roles in gene expression, it is important to carry out loss of function studies with individual miRNAs. In fact, several tools have been developed to overexpress miRNAs in specific tissues [65] or to block the function of individual miRNAs *in vivo* using miRNA sponge or target mimicry techniques [66,67], which will help to reveal the tissue-specific roles of individual miRNAs.

Emerging evidence suggests that miRNAs play an important in insulin production, secretion and action. Diabetes or chronic hyperglycemia leads to changes in miRNA expression profiles in many tissues, such as muscle, liver, pancreas, heart and kidney. The roles of miRNAs in diabetes are rather complex: changes in miRNA levels can lead to diabetes at early stages or be a consequence of longstanding diabetes at late stages. miRNAs present a new class of biomarkers for various diseases, such as cancer and miRNAs will also be useful as biomarkers for both type 1 and type 2 diabetes. Furthermore, recent progress in the development and use of miRNA antagomiRs to target miRNAs *in vivo* may provide novel therapeutic tools for the treatment of diabetes and its complications in future.

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Table 1

MiRNAs and their target genes with roles in glucose homeostasis

miRNA	Target Tissue	Function	Target Genes	References
miR-375	pancreas	insulin secretion, pancreatic islet development	Mtpn, Usp1, Jak2, Adipor2	[14], [11], [24]
miR-124a	pancreas	pancreatic islet development	FoxA2, Rab27A	[16], [33]
MiR-9	pancreas	insulin secretion	Onecut2	[34]
miR-29a, b	muscle, adipose, liver	glucose transport	Insig1, Cav2	[36]
miR-143	adipose tissue	adipocyte differentiation	ERK5/BMK1/MAPK7	[37]
miR-145	colon	cell proliferation	IRS1	[44]
miR-133	heart	a long QT syndrome, cardiac hypertrophy	HERG, RhoA, Cdc42, Nelf-A/WHSC2	[18], [45]
miR-1	heart	heart development and physiology	KCNJ2, GJA1	[49]
miR-192	kidney	kidney and diabetic nephropathy development	SIP1	[19]