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Role of micro RNA involved in Diabetes Mellitus

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Abstract

Micro RNAs (miRNAs), a class of endogenous small non-coding RNAs in eukaryotes that regulate cellular transcriptome at the post-transcriptional level has been recognized. More than 2000 miRNAs have been identified in the human genomes that have orchestrated a variety of biological and pathological processes. Disruption of miRNA levels correlates with many diseases, including diabetes mellitus, a complex multi-factorial metabolic disorder affecting large number of people worldwide. MiRNAs are involved in the pathogenesis of diabetes mellitus by affecting pancreatic β-cell functions, insulin resistance, or both. The altered miRNAs are involved in the core processes associated with diabetes such as carbohydrate and lipid metabolisms, insulin signaling pathway and the adipocytokine signaling pathway. This dysregulated miRNAs in different tissues during development of diabetes provides molecular insights to diagnostic and/or therapeutic utilities in diabetes mellitus. In this review, the investigations of the regulatory roles of important miRNAs in pancreas has been discussed that can be used to treat diabetes mellitus.

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1. Introduction

The recent breakthrough discovery of a family of endogenous small RNAs ~22 nucleotide long single-stranded and non-coding is called microRNAs (miRNAs), has been a focus of attention for researchers has shed light on their roles in control of glucose homeostasis[1]. 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. 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[2]. Recently, micro RNAs (miRNAs) have emerged as central post-transcriptional regulators of gene expression. They regulate many key biological processes, including cell growth, death, development and differentiation. Loss- or gain-of-function of specific miRNAs appears to be a key event in the genesis of many diverse diseases.

Diabetes is a serious chronic disease worldwide and is caused by defects in insulin production, insulin secretion and insulin signaling. The World Health Organization (WHO) reported that, as of 2000, there were 171 million cases of diabetes worldwide and this number will rise to 366 million, or 4% of the population, in 2030 [3].There are mainly two types of diabetes: Type 1 diabetes (T1D) is due to self-destruction of the insulin producing beta cells in the pancreas and Type2 diabetes (T2D) caused by defects in insulin action and

insulin production. In all this types of diabetes, the patients develop serious secondary complications associated with diabetes, such as micro vascular complications, oxidative stress and endothelial dysfunction (ED), neonatal complications, foot complications related to peripheral neuropathy (PN) and peripheral vascular disease (PVD), cardiovascular disease and kidney failure.

Recent data suggest that miRNAs play a direct role in insulin secretion pancreatic islet development, beta cell differentiation, indirectly control glucose, lipid metabolism and secondary complications associated with diabetes. An increasing number of miRNAs have been found involved in diabetes mellitus pathogenesis [4]. Dysregulation of miRNA can lead to profound impairment of glucose metabolism [5]. MiRNA expression profiles of various tissues (e.g., pancreas, adipose tissue, and liver) from T2D patients or hyperglycemia animal models have been established in recent years and make it easier to uncover novel miRNA regulators in diabetes. In this review, 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 have been discussed which can be used to treat diabetes mellitus.

2. Research Method

The literature search was performed using the Pubmed databases on articles published till October 2016. All the well-designed original studies published in English that covered the types of miRNAs on different tissues in diabetes. The literature was also enhanced by articles obtained as cross references from the bibliography of the selected articles. The aim of this article is to review and highlight the the potential roles of miRNAs in insulin production and secretion from pancreatic beta cells, their role in insulin signaling in insulin sensitive tissues to treat diabetes.

3. Results and Analysis

3.1. Role of miRNA involved in diabetes [6, 7, 8, 9,10, 11]

miRNA	**Target**	**Effect on diabetes**
miR-375	Pancreas	Helps in pancreatic development, regulates insulin secretion in beta cells and increases their death by lipoapoptosis by regulating viability and proliferation. It is up regulated in beta cells of T2D patients. Its deletion causes severe insulin-deficient diabetes in obese mice.
miR-29(a/b/c)	Adipose	Induced by high glucose and high insulin.Over expression leads to insulin resistance.
miR-143	Adipose	Participates in adipocyte differentiation and isinduced in adipogenesis and down regulated in obesity.
miR-9	Pancreas and cardiac muscle	Expressed in pancreatic development. Impairs insulin secretion in beta cells and upregulated in cardiomyocytes of streptozotocin (STZ) induced diabetic mice.
miR-124a	Pancreas	Up regulated by glucose. Regulates the insulin exocytosis pathway, causing exaggerated insulin release when no glucose is available but reduced glucose-induced insulin secretion.
miR-195	Pancreas and liver	Expressed in pancreatic development and up regulated in liver of diabetic rats.
miR-192	Kidney	Induced by transforming growth factor-b and highly expressed in glomeruli of STZ-induced diabetic mice.
miR-222	Adipose	Up regulated in response to high glucose in adipose tissue of diabetic rats.
miR-126	Pancreas and skeletal muscle	Expressed in pancreatic development.Up regulated in skeletal muscle of GK rats and in livers of obese mice compared with STZ mice.
miR-133a	Cardiac and skeletal muscle	Over expressed in rabbit diabetic heart, where it induces prolongation of QT interval. Down regulated in cardiac hypertrophy in mouse and human hearts and in hearts of STZ induced diabetic mice. Also reduced in human skeletal muscle in T2D. High fasting glucose associates with lower expression of this miRNA.
miR-296	Pancreas	Expressed in beta cell islets and up regulated by glucose.
miR-96	Pancreas	Negatively regulates insulin exocytosis through up regulation of granuphilin.
miR-34a	Pancreas and liver	Increases in beta cells in response to palmitate,making them

		more susceptible to death by apoptosis and inhibiting nutrient-induced insulin secretion. Up regulated in the livers of STZ-induced diabetic mice. Found in the blood stream and can differentiate between non-diabetic and early T2D patients.
miR-146b	Pancreas	Contributes to increased apoptosis of beta cells. Expression induced by cytokines and sodium palmitate.
miR-657	Liver	Regulates insulin-like growth factor 2 receptor and variants in its regulation.
miR-30d	Adipose	Up regulated in presence of high glucose. Up regulates insulin gene transcription.
miR-320	Cardiac and vascular endothelium	Up regulated in GK rats with impaired angiogenesis.
miR-103	Pancreas and liver	Over expression accelerates adipogenesis.Reduced in response to TNF-alpha. Down regulated in obesity. Up regulated in liver of diabetic rats.
miR-107	Pancreas and adipose	Over expression accelerates adipogenesis.Reduced in response to TNF-alpha. Up regulated in beta cells in presence of high glucose.
miR-1	Cardiac and skeletal muscle	Regulates cardiac potential.Up regulated by high glucose in cardio myocytes, where it accelerates apoptosis. High levels found in ventricle ofdiabetic patients. Impaired insulin response in skeletal muscle of T2D patients. Significantly down regulated in the heart of STZ-induced diabetic mice.
miR-223	Heart	Up regulated in the insulin-resistant heart, where it increases glucose uptake through increase of Glut4.
miR-125(a/b)	Liver and vascular tissue	Up regulated in liver of hyperglycemic rats.Increase of this mi RNA results in a pro-inflammatory diabetic phenotype in vascular smooth muscle cells.
miR-27(a/b)	Adipose	Impairs human adipocyte differentiation and targets peroxisome proliferators'–activated receptor g. Up regulated in adipose tissue of diabetic rats.
miR-216a,miR217	Kidney	Highly expressed in kidney and up regulated by transforming growth factor-b.
miR-122	Liver	Suppression in liver results in reduced fatty acid accumulation. Down regulated in liver of STZ induced diabetic mice.
miR-320	Adipose and vascular endothelium	Highly up regulated in insulin-resistant adipocytes. Targets p85, leading to increased insulin resistance in adipocytes. Up regulated in myocardial icrovascular cells in GK rats, where it impairs angiogenesis.
miR-21	Pancreas and liver	Up regulated by nuclear factor and fatty acids in liver. Induced by interleukin-1b and TNF-a in Pancreatic islets. Expression increased in rats on high-fat diet and in liver of T2D patients. Over expression reduces maximal glucose induced insulin release in beta-cells
miR-206	Cardiac and skeletal muscle	Up regulated in skeletal muscle of diabetic and Pre-diabetic patients. Up regulated by high glucose in cardiomyocytes. Accelerates cardiomyocyte apoptosis.
miR-93	Vascular endothelium	Down regulated by high glucose through down regulation of its host gene MCM7.
miR-30a	Adipose	Down regulated in T2D individuals, independent of obesity.
miR-181d	Liver	Most effective mi RNA at reducing intracellular lipid content of hepatocytes.

3.2. MiRNAs – its role in production and secretion of insulin from pancreatic beta cells [12, 13, 14]

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. It has been shown to regulate glucose-stimulated insulin secretion in a negative manner as over expression inhibits insulin secretion. Consistent with this,

inhibition of endogenous miR-375 enhances insulin secretion. Interestingly, miR-375-regulated insulin secretion appears to be calcium-independent as it does not cause changes in intracellular calcium levels. 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 over expression of miR-375, knockdown of Mtpn by siRNA also results in decreased insulin secretion. Furthermore, it has been shown that miR-375 can directly bind to the 3'UTR of Mtpn and over expression of miR-375 causes down regulation of Mtpn, suggesting the idea that Mtpn is a direct target of miR-375. 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. Mice with homozygous deletion of miR-375 appear to have hyperglycemia due to decreased total pancreatic beta cell mass and insulin levels. 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 insulins secretion may be via the transcription factor nuclear factor-kappaB. Activation of NF-kappaB is associated with improved glucose-stimulated insulin secretion6, while inactivation of NF-kappaB results in decreased insulin secretion from beta cells. 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. 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). Considering the prediction that each miRNA can regulate more than 200 different transcripts, it is not surprising that miRNA-375has several other targets besides Mtpn. Other than miR-375 other miRNAs are involved in pancreatic function, especially insulin secretion (e.g., *miR*-184, *-33*, *-187*, *-29a*, and *-30a*). Although *miR-29* has a role in regulating β-cell proliferation along with its negatively regulation of insulin secretion by directly targeting *Stx-1a*, a t-SNARE protein involved in insulin exocytosi]. *MiR-124a* is increased in type 2 diabetic human pancreatic islets and negatively regulates insulin secretion by directly targeting the GTPase and *Foxa2* contribute to β-cell dysfunction in T2DM.

4. Conclusion

From the above information we can conclude that miRNA can be used as therapeutic control for diabetes. Pancreatic islet cells, secretion of insulin, production of adequate amount of insulin are under the control of miRNA. Diabetes or chronic hyperglycemia leads to changes in miRNA expression profiles in many tissues, such as muscle, liver, pancreas, heart and kidney. The role of miRNAs in diabetes are rather complex and changes in miRNA levels can lead to diabetes at early stages can be a cause of longstanding diabetes at late stages. MiRNAs present a new class of biomarkers for various diseases, such as cancer and will also be useful as biomarkers for both type 1 and type 2 diabetes. Furthermore, recent progress in the development and use of miRNA or antagonistic miRs to target miRNAs *in vivo* may provide novel therapeutic tools for the treatment of diabetes.

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