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REVIEW

Role of microRNAs (miRNAs) in the pathophysiology of diabetes mellitus

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ABSTRACT

Diabetes mellitus is becoming the critical problem among the entire world and it is difficult to understand the molecular mechanism representing the concept of diabetic pathology. Recently the knowledge of the involvement of genetics in type 2 diabetes mellitus (T2DM) susceptibility has sketched a great concentration towards the transcriptional activity of β cells within the pancreas. This disease becomes the leading cause of death, so it is necessary to study the molecular pathogenesis, phenotypes, and characteristics to design the therapeutic parameters. Here in this review role of miRNA is being illustrated as it plays a crucial role in the pathogenesis, progression, and fate of beta cells of pancreas regulating the insulin secretion. Here in this review, we try to include the effects and pathophysiology of various miRNA in diabetes mellitus and on the various sites of the human body.

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Diabetes mellitus is a heterogeneous metabolic disorder in which the β cells of pancreas dysfunctions resulting into the improper secretion of insulin which ultimately leads to the irregular blood sugar level along with the disturbance in the carbohydrate, fat, and protein metabolism.[1, 2] Based on the etiology and clinical presentation, diabetes is common of four major types which are type I diabetes, type II diabetes, gestational and other specific diabetes. Among the several types of diabetes; type II diabetes mellitus has higher dominance in the developing countries which leads to the disturbance of insulin level affecting the concentration of the blood glucose level. Type II diabetes mellitus is followed by the resistance of insulin of muscular tissues, liver tissues, adipose tissue and is then also affects the function of β cells of the pancreas which secretes the insulin.[3] Diabetes is the most common endocrine disorder and by the year of 2025, it is estimated that around 300 million people will suffer from this disease.[4-6] The cause of diabetes can be a genetic or due to the various inappropriate life factors such as cigarette smoking, physical inactivity, sedentary lifestyle and regular alcohol consumption. Among the two types of diabetes mellitus; type II occurs especially due to the genetic, behavioral risk factors combined with environmental factors.[7, 8] GLP-1 agonist and DPP-IV are the two therapeutic approaches of diabetes mellitus resulting into the balancing of blood sugar level in fasting as well as in

postprandial condition and shows the therapeutic effect on the proper functioning of β cells of pancreas.[9-11]

MicroRNA is the family of small endogenous non-coding single stranded RNA molecule in eukaryotes having 17-25 nucleotides which were first described in nematode *Caenorhabditis elegans* in 1993. MicroRNAs are important regulatory molecules in many biological processes.[12-14] miRNA plays a significant role in the regulatory mechanisms operating in various organisms including the developmental timing and host pathogen interaction, and it also has a major role in cell differentiation, tumorigenesis, apoptosis and proliferation which ultimately results in the modulation of the pathology and physiology of various disease like cardiovascular disease, cancer, diabetes by interfering in the development and function of β cells thus misbalancing the concentration of insulin and various other diseases. It is found that miRNA functions by RNA silencing and regulating post transcriptionally which represents the changes in the mi RNA processing and stability to the gene expression by binding to the specific sites in the 3′ untranslated region of their target miRNAs.[15-17]

miRNA shows participation in the β cell biology, insulin resistance, type I and type II diabetes mellitus and its various complication in whole anatomy and physiology of the human being. Alteration in the miRNA may

TABLE I.—*Role of various miRNA in the pathophysiology of diabetes mellitus.*[22-46]

Name	Target sites	Expression	Pathophysiology	Role in diabetes	Species
miR-15a [22, 23]	Skeletal muscle	Down	Involved in cell cycle regulation, regulates gene expression in metabolism	Promotes insulin biosynthesis by inhibiting endogenous UCP-2 (uncoupling protein-2) expression in mouse β cells	Human
miR-9 [24-26]	Endothelial cells	Down	Pancreatic islets differentiation and development	Responsible for insulin secretion by encoding respective genes, Onecut 2; also inhibits the expression of granuphilin which is a negative regulator of insulin exocytosis	Human
miR-29a [27-29]	White adipose tissue	Up	Interaction with multiple transcription factors such as PPARs and adipocyte enriched to regulate many aspects of lipid and glucose metabolism	Increased expression of this miRNAs could be involved in the initial cellular response of adipocytes to hyperglycemia	Rat, human
miR-124a [30-33]	Pancreas	Down	Vital for pancreatic β cell development modulates exocytosis system by directly targeting Foxa 2	Found in an increased amount in diabetic patient and directly target to GTPase Rab 27a to negatively regulate insulin secretion	Human
miR-96 [34]	Serum	Up	Negatively associated with granuphilin but not interferes with Onecut2	Negatively regulates insulin exocytosis	Human
miR-375 [35-37]	Serum	Up	β cell proliferation and is responsible for maintaining the normal pancreatic β cell mass	By targeting the number of growth inhibiting genes and is required for β cell proliferation of islets of pancreatic cells	Human and mouse pancreatic β cells
miR-34a [38]	Serum	Up	β cell survival/apoptosis	β cell survival/apoptosis of MIN-6 cells and hPSCs differentiated IPCs	Mouse and human
miR-21 [39, 40]	Serum	Up	β cell differentiation	β cell differentiation of pancreatic progenitor cells and may be involved in vascular diabetic complication also mediates renal fibrosis	Human
miR-146a fibronectin-targeting miRNA [41, 42]	Endothelial cells	Down	β cell differentiation	β cell differentiation of hPSCs differentiated IPCs also decreases fibronectin in diabetes in the retinas, kidneys, and hearts	Human
miR-222 [27, 43]	Adipose tissue	Up	Directly inhibits to P27KIP1 and P57KIP2	It mediates vascular damage in HG and advanced glycation end-product in diabetic mice	Rats
miR-27a [44-46]	Adipose tissue	Up	Targets the epidermal growth factor in which promotes tumorigenesis in several breast cancers	Patients diagnosed with metabolic syndrome and T2DM have increased level of miR-27a	Rat

act as an early marker for the changes in the diabetes homeostasis and can be for the therapeutic targets of diabetes.[18, 19] miRNA involved in the pathogenesis of diabetes mellitus by interfering in the β cell membrane electrical excitation (initiated by an increase in the ratio of ATP and ADP), insulin synthesis, the fate of β cell, pancreatic mass formation and exocytosis processes which include docking, fusion, and exocytosis of insulin granules. Disturbance in the regulation of miRNA is responsible for the impairment of the glucose metabolism (Table I).[20, 21]

Human pancreatic cells and miRNA

A specific subset of miRNA plays a crucial role in the regulation and functioning of alpha and beta cells of pancreas among which β cells are responsible for the secretion of insulin managing the diabetic influences. For example, miR-24, miR-26, and miR-148 contribute to the characterization and management of pancreatic β cells.[22] miRNAs are involved in the development, apoptosis, cell proliferation and in the neuronal cell fate and is altered in several disorders like diabetes, autoimmune diseases, cardiovascular and exhibit diversity in the metabolic control for the proper functioning of different cells, tissues, organs of the human body. Some miRNA machinery genes such as such as Drosha, *DGCR8*, *Dicer1*, *XPO5*, *TRBP*, and *AGO2* are responsible for the formation of protein processing the various miRNAs affecting to the physiology of several organs and their system.[23, 24] *Dicer* is required for maintaining the adult pancreas and dysregulation of *Dicer1* in β cells results into the impaired islets architecture, decreased insulin secretion, exhibit glucose tolerance, and development of diabetes.[25, 26] miR-375 mediates the β-cells proliferation which is observed in obesity and pregnancy as well this miR-375 also suggested as the keen player in the network on interacting with transcription factor that is responsible for the pancreatic development and maintenance of their β cells of islets of Langerhans.[27, 28] Tattikota *et al.* have recently illustrated that Ago2 participates in the insulin secretion and β cells compensatory expansion and also found that its level is increased during insulin resistance which is necessary for β-cells compensatory expansion occurs during insulin resistant state.[29, 30] Pancreatic regeneration possibly by targeting the Ngn3 by the influence of miR-195, miR-16, miR-15a and miR-15b has been suggested by Joglekar *et al*. in 2007 (Figure 1).[31]

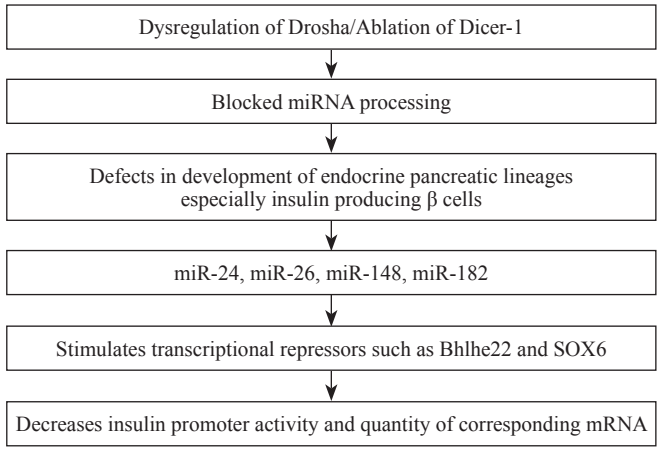

Figure 1.—Pathogenesis of miRNA in diabetes mellitus.

Some miRNA is found in human islets in large concentration like miR-375, miR-7-5p, miR-148a-3p, miR-26a-5p, and miR-127-3p.[32-34] Pancreas agenesis occurs due to the total inactivation of miRNA maturation which represents the necessity of miRNA for early phase development.[34]

Discussion

Although a distinct number of articles or studies are available describing the effect of microRNA in diabetes mellitus; their up regulation, down regulation in various physiological parameters. In this review article, we try to provide a relation between the various miRNA and their role in diabetes. Also, it expresses the biological function of microRNA and pathophysiology of miRNA in diabetes mellitus. miRNA involves in the cell differentiation, cell proliferation, apoptosis and neuronal cell death which results in some diseased conditions including diabetes, *e.g*. miR-375 involves in the cell proliferation. miR-15a interferes with the metabolism to regulate gene expression.[35, 36] Discussed regarding some miRNA machinery gene responsible for the formation of several miRNA affecting the glucose metabolism.[37, 38] miR-222 and miR-27a shows its effect on adipose tissue by up-regulation in rat species.[39-41] In this review, we accumulate the different parameters related to the effect of miRNA on various tissues of distinct species like human and rats.

From this review, it can be concluding that miRNA exhibits the potential contribution in the pathogenesis and thus in the treatment of Diabetes Mellitus also. But there is a need to give keen concentration for the therapeutic parameters for the healthy survival of diabetic patients by minimizing their various side effects.

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