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miRNA in type 2 diabetes

ABSTRACT

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia, i.e. elevated blood sugar levels, which stems from a defect in production or action of insulin secreted by pancreatic beta cells. Type 2 diabetes, which involves reduced sensitivity of tissues to insulin, is the most common form of diabetes. Over the years knowledge concerning the etiology of both type 1 and type 2 diabetes was extended, which enabled implementation of new methods of treatment and prevention. Unfortunately, a monogenic factor conditioning the emergence of this disease still has not been isolated, hence scientists more often focus on regulators of expression of various metabolic proteins, e.g. miRNA, which are one of the more important factors regulating expression. First reports concerning the role of miRNA in metabolism in animal organisms come from observations of miR-14 mutants in fruit flies (*Drosophila melanogaster*). miRNA are single-stranded RNA molecules with a length of approx. 19–150 nucleotides.

A single miRNA molecule can excite expression of several genes, inhibit it, or excite some and inhibit others. MicroRNA regulates the process of insulin secretion, cellular differentiation of beta cells in pancreatic islets and additionally influence glucose and lipid metabolism. All these issues are potential subjects of further research. Expansion of knowledge concerning microRNA and its role in disease processes is a target for devising new therapeutic strategy, and therefore utilization in production of drugs. Most research is currently in its initial phase, but even preliminary results are highly promising. (Clin Diabet 2016; 5, 3: 95–99)

Key words: diabetes, microRNA, treatment, molecular biology

Introduction

"Diabetes mellitus is a chronic disease, belonging to the group of metabolic diseases. It is characterized by hyperglycemia resulting from a defect in insulin secretion and/or action" [1].

Type 2 diabetes constitutes approximately 90% of all cases of diabetes [2]. It is primarily caused by reduced sensitivity of tissues to insulin coupled with disorders of the secretion function of pancreatic β cells. As a progressive disease, it develops latently and its initial symptoms are usually not apparent; diagnosis by a diabetologist may occur even after several years of hyperglycemia [3]. Development of type 2 diabetes is mostly affected by environmental factors; however, genetic factors are also not without significance [4]. It attacks mostly people over 45 years of age with obesity and cardiovascular problems [5].

Three basic mechanisms underlie development of type 2 diabetes. The first is a progressive disorder of insulin secretion by pancreatic β cells. Next, insulin resistance and increased glucose production in liver are listed [6].

It is worth noting that this type of diabetes occurs with increasing frequency in children and adolescents. Over the years knowledge concerning the etiology of both type 1 and type 2 diabetes was extended, which enabled implementation of new methods of treatment and prevention [7, 8].

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Since a monogenic factor conditioning the emergence of this disease has not been isolated, scientists more often focus on regulators of expression of various metabolic proteins, e.g. miRNA, which are one of the more important factors regulating expression. First reports concerning the role of miRNA in metabolism of animal organisms come from observations of miR-14 mutants in *Drosophila melanogaster*. They were characterized by enlarged lipid droplets in body fat, which is one of the more important places of lipid accumulation in this species of insects [9].

MicroRNA includes a group of single-stranded, non-coding, endogenous molecules with a length of 19–150 nucleotides. MiRNA's primary function is post-transcriptional regulation of expression of various genes, made possible through complementarity of miRNA and mRNA sequences [10, 11]. A number of research demonstrated that miRNA plays a very important role in organism, participating in many biological processes, e.g. oncogenesis, angiogenesis, apoptosis, cell division and cellular differentiation, among others [12]. A single miRNA molecule can excite expression of several genes, inhibit it, or excite some and inhibit others [13, 14]. Furthermore, fairly mild effects of reducing activity of miRNA biogenesis pathway components suggest that these molecules are characterized by relatively high stability and long lifetime in the cell, which limits the possibilities of utilizing such a strategy in short-term therapeutic modulation of miRNA levels [15].

A number of already conducted research suggests that miRNA may serve as diagnostic and prognostic factors in multiple disorders, including diabetes, where abnormalities in expression of particular miRNA may indicate pathogenesis of a disease or the disease itself. Most recent research informs that new isoforms of miRNA circulating in the serum may be good indicators of particular diabetic disorders. Considering availability of material for research, diagnostic procedures, as well as shortening of the time it takes to perform them, this can potentially be of great significance for early diagnosis of this type of diabetes and understanding its molecular mechanisms.

MicroRNA regulates the process of insulin secretion, cellular differentiation of beta cells in pancreatic islets and additionally influences glucose and lipid metabolism.

All these issues are potential subjects for further research. For many years scientists have been looking for both genetic and environmental causes of this disorder.

The purpose of this work is to show the role of microRNA in type 2 diabetes.

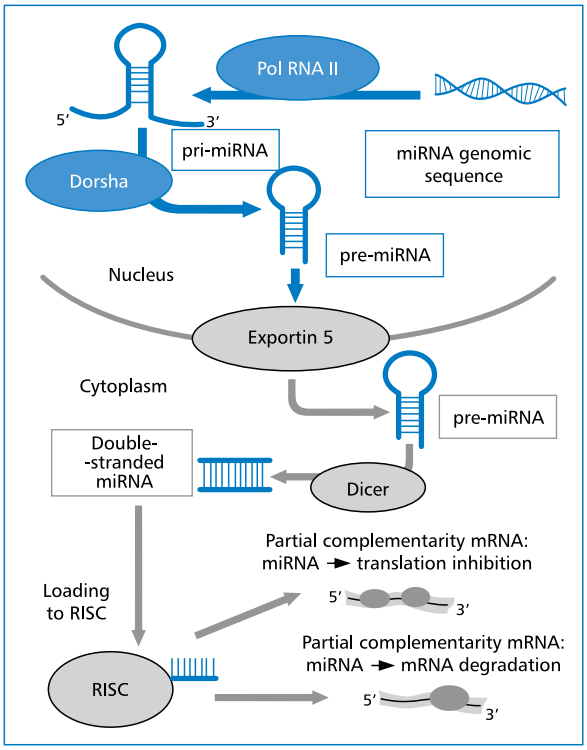

Figure 1. MiRNA biogenesis pathway [modified 25]

miRNA biois

Formation of miRNA consists of several phases (Fig. 1). The first phase is transcription, leading to the formation of primary transcript of miRNA (pri-miRNA, primary miRNA). Next, pre-miRNA is formed through post-transcriptional modification of pri-miRNA. These processes take place in the cell nucleus; subsequently, pre-miRNA is transferred to cytoplasm. Within it, pre-miRNA is subjected to processes leading to the formation of a mature, functional miRNA molecule with a length of ~20 nt [16]. The primary transcripts (pri-miRNA) form interconnected hairpin structures with a 5′ end; characteristically, they contain multiple stem-loops and may be several thousand base pairs long [17, 18]. Double-stranded pri-miRNA structures are recognized by the DGCR8 (Di George syndrome critical region gene 8) nuclear protein, which is bound to Drosha ribonuclease (enzyme belonging to the RNase III group). Together, they form the microprocessor complex, which participates in processing of primary transcripts of miRNA in the cell nucleus. In this complex, DGCR8 binds to single-stranded ends of pri-miRNA and orients catalytic domain of ribonuclease so it can cleave the transcripts and release pre-miRNA hairpin structures with a length of ~60–100 nucleotides [19, 20]. In such a form they are transferred

Table 1. MicroRNA which play a role in development of type 2 diabetes, along with genes whose expression they regulate

miRNA	Genes	References
miRNA-181a	IRS2, ESR1, SITR1; reduction of insulin signal reaching the cell	31; 32
miRNA-146a	PTEN, PTEN1	33
miRNA-144	IRS1	32
miRNA-182	Encodes genes responsible for hepatic enzymes in gluconeogenesis	27
miRNA-29	Akt, Collagens	34–36
miRNA-320	Akt, P85, PPARγ, VEGF	35
miRNA-192	Cbl/CAP; encodes genes responsible for insulin receptor	27, 35
miRNA-30d	Encodes genes responsible for insulin transcription	37, 38
miRNA-375	Encodes genes responsible for insulin secretion	29
miRNA-9	Encodes genes responsible for insulin secretion, Onecut2	32, 39
miRNA-96	Encodes genes responsible for insulin secretion and Noc-2	40
miRNA-124a	Encodes genes responsible for insulin secretion and Foxa2, Kir-6.2 and Sur-1	23, 29, 32, 40
miRNA-15a	Biosynthesis of insulin with inhibition of endogenous UCP2 protein	41
miRNA-122	AMPK, FANS, ACC1, SCD1	42
miRNA-33a/b	IRS2, involved in oxidation of fatty acids, including CROT, CPT1A, HADHB and PRKAA1 — showed increased expression, involved in regulation of fatty acid synthesis, such as SREBF1, FASN, ACLY and ACACA — showed decreased expression	27
miRNA-222	P27KIP1, P5KIP2	34
miRNA-503	cdc25A cyclin, CCNE1	35, 43
miRNA-34a	VAMP2, Bcl2, PPARγ	44
miRNA-335	Stxbp1, aP2, PPARγ	32
miRNA-133a	IGF1, SGK1, Glut4	45, 46
miRNA-126	VEGF, IGF2	41
miRNA-103	Differentiation and growth of adipocytes, regulation of insulin sensitivity	38, 47
miRNA-107	Regulation of insulin sensitivity	38, 47

to cytoplasm by a transferase: exportin-5 (Exp-5) [21–23]. In the cytoplasm, pre-miRNA processing by the enzyme Dicer (as a result of whose activity double-stranded miRNA-miRNA duplexes are formed in cytoplasm) leads to the formation of a double-stranded molecule with a length of ~20 nucleotides [19, 23]. RISC (microRNA-induced silencing complex) is the complex taking part in silencing gene expression. It is formed of proteins and RNA. Single-stranded miRNA binds to the RISC protein complex, which contains, among others, Dicer. Active RISC complex, which contains single-stranded antisense RNA, is formed [24]. Gene silencing may occur via either degradation of specific mRNA or as a result of inhibiting translation of the transcript. miRNA molecules are bound to 3' untranslated region (3'UTR or 5'UTR) of the target mRNA [25, 26]. Despite considerable progress in molecular biology, processes concerning translation blocking are not fully understood.

miRNA in type 2 diabetes

MicroRNA-375, microRNA-75, microRNA-29 and microRNA-122 are related to type 2 diabetes [27, 28]. During research, mainly concerning physiology of mammals, the role of miR-375 which controls glucose-dependent insulin secretion through regulation of myotrophin gene, was discovered. For this reason, this molecule is considered a possible target for developing new strategies of treatment of diabetes [28–30].

A list of all microRNA in type two diabetes and genes whose expression they regulate is presented in Table 1.

Other research provided information concerning a group of miRNA in the serum which are deregulated in type 2 diabetes. They were marked using real-time PCR (qPCR). They are: miR-9, miR-29a, miR-30d, miR-34a, miR-124a, miR-146a and miR-375 [37].

Summary

Expansion of knowledge concerning microRNA and its role in disease processes is a target for devising new therapeutic strategy, and therefore utilization in production of drugs. Most researches are currently in their initial phase, but even preliminary results are highly promising. They helped develop a profile of miRNA isoforms in the serum and identify specific isoforms of miRNA characteristic for patients with type 2 diabetes. As these researches progress, it will be possible to gain a better understanding of molecular basis underlying development of this lifestyle disease. This may translate to prevention of development of type 2 diabetes. Profiles of certain isoforms of miRNA occurring in the serum of patients with type 2 diabetes have been included in this work.

The main assumption for utilizing microRNA in treatment is gaining influence over control of protein expression. There are multiple reports indicating the possibility of indirect modification of expression of proteins involved in pathogenesis of various diseases. Research considered in this work confirms the fact that this family of micromolecules affects receptors, insulin transcription and secretion. It should also be remembered that insulin resistance is one of the most important and significant factors of development of type 2 diabetes. In conclusion, it is highly likely that the significance of microRNA in predicting development of type 2 diabetes will greatly increase.

Conflict of interest

Authors do not report any conflict of interest.

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