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# MicroRNAs and type 2 diabetes

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## Abstract

MicroRNAs (miRNAs) are non-coding single strand RNAs. MiRNAs are encoded by endogenous genes with a length of about 22 nucleotides. MiRNAs play a vital role in the inhibition of post-transcriptional translation of mRNAs. In recent years, studies have discovered that miRNAs play an essensial role in the pathogenesis of type 2 diabetes. In addition, the discovery of miRNAs in the serum and plasma also provides a potential target for the discovery of disease markers. Taken together, preliminary data suggest a potential role of miRNAs in type 2 diabetes, however more clinical trials need to be studied.

**Keywords:** microRNAs, Insulin resistance, Diabetes

## Background

### Type 2 diabetes and insulin signaling

The incidence of type 2 diabetes has increased year by year. The main reason of type 2 diabetes is insulin resistance. Insulin which maintains the stability of blood glucose levels, is a hormone produced and secreted by islet beta cells. Insulin is caused by an increase of nutrients in the blood, such as glucose. Under normal conditions, insulin acts mainly by binding to the receptors on the membrane, phosphorylating downstream IRS1 and IRS2, and then activating a series of downstream kinases, including PI3K, PDK1 and AKT, which act on a series of downstream proteins such as GSK3β, mTORC1 and the FOXO transcription factor family and so on [1]. It promotes liver glycogen synthesis, inhibits gluconeogenesis, and increases glucose absorption in adipose tissue and muscle tissue [2]. Insulin resistance refers to the insufficient response of target organs to insulin.

### MicroRNAs

MiRNAs are small, non-coding RNAs. MiRNAs were first found to regulate development time points in C.elegans. Now, from plants to humans, a lot of miRNAs are discovered, and functions of miRNAs are involved in various fields of biology. The formation of miRNAs begins with primary miRNA (pri-miRNA) in the nucleus [3]. The stem loop structure formed from Pri-mRNA can be identified and cut by the complex formed by Drosha and DGCR8 RNA enzyme III, and precursor miRNA (pre-miRNA) is formed [4]. Pre-miRNA relies on the transport mechanism to enter the cytoplasm and then is cut into a mature 22 nucleotides chain miRNA with the Dicer. The double stranded miRNA is formed after the formation of the AGO protein family, and the chain is melt and integrated into the silencing complex containing AGO (RISC). RISC-miRNA is formed by binding to the target gene sequence of miRNA and then affects target gene expression [5]. Two miRNAs from the opposite side of the pre-miRNA name -3p or -5p. In plants, miRNAs and target sequences are completely complementary, and miRNAs promote the cut and degradation of target genes. In multicellular animals, miRNA and target sequences are not completely matched, and the target gene is mainly inhibited during translation instead of degraded [6].

Under normal physiological conditions, miRNAs may be involved in various pathways to ensure the development process and maintain homeostasis. MiRNAs dysfunction caused by internal factors (genes) or external conditions (environment) can lead to abnormal development and metabolic disorders. The role of miRNAs in the development is relatively detailed, and the role in disease needs further study. In recent years, more and more specific types of miRNAs have been studied in metabolic diseases. This review mainly discusses the function of miRNAs in insulin signaling pathway and glucose homeostasis, and explores the possibility of serum and plasma miRNAs as an endocrine signal.

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### MicroRNAs and insulin signaling

MiRNAs can regulate the response of target tissues to insulin. For example, the expression of miR-29a and miR-29b are increased in the liver, fat and muscle of diabetic rats, and cell experiments also demonstrated to be associated with insulin resistance [7, 8]. MiR-29a and miR-29b mainly mediate insulin pathway by inhibiting proteins that enhance insulin signaling, including CAV2 [9], INSIG1, and PIK3R1 [7, 10]. MiR-126 can promote insulin resistance by inhibiting IRS1 [11]. In addition, miRNAs can also directly regulate glucose levels in cells, for example, miR-223 can regulate glucose uptake by inhibiting GLUT4 in muscle tissue. MiR-33a and miR-33b can regulate the insulin pathway by IRS2, SIRT6 and AMPKα1 [12, 13]. MiR-130a and miR-204 can improve glucose tolerance by inhibiting GRB10 and GLP1R respectively [14, 15]. MiR-378 and miR-93 lead to insulin resistance by targeting P110a and SIRT7 respectively [16, 17]. In conclusion, miRNAs can regulate the insulin signaling pathway and glucose absorption in target tissues.

Many miRNAs also play a role in other metabolic diseases with abnormal insulin response, including obesity and NAFLD. For example, recently, miR-103 and miR-107 were found to be increased in the liver of *ob/ob* mice and diet induced obese mice. Inhibition of miR-103 and miR-107 could increase insulin sensitivity. Overexpression of miR-103 and miR-107 may cause imbalance of glucose homeostasis [18]. If miR-103 and miR-107 are studied in nonhuman primates and humans, it can provide the therapeutic target for obesity induced insulin resistance [19].

The other miRNAs were also found to be increased in the obesity model. These miRNAs also regulate the insulin signaling pathway. Similar to miR-103 and miR-107, miR-143 is up-regulated in *db/db* mice and diet induced obese mice. Overexpression of miR-143 can reduce insulin sensitivity by inhibiting ORP8 [20]. The let7 miRNA family is up-regulated in *ob/ob* mice and diet induced obese mice [18]. Let7, a tumor suppressor, is widely studied in the field of cancer. However, the recent article has found that let7 plays a role in glucose metabolism. Let7 Overexpression in muscle can lead to insulin resistance by inhibiting IGF1R, INSR and IRS2 [21].

In conclusion, miRNAs can affect insulin signaling pathway and influence glucose homeostasis by affecting insulin signaling and insulin sensitivity. However, in pathological conditions, such as obesity induced insulin resistance, more in vivo tests need to do to prove the role of miRNA as a drug target for treatment.

### MicroRNAs and insulin secretion

MiR-375 in pancreas is found to play a role in pancreatic development in zebrafish [22], and has a regulatory effect on pancreatic islet alpha and beta cell volume [23]. MiR-375, on the one hand, can reduce the secretion of insulin by inhibiting myotrophin (Mtpn), and on the other hand, it can affect the insulin signaling pathway by inhibiting the PDPK1 [24]. MiR-124a is found to be co-expressed with miR-375 in cultured cells, and can also act on Mtpn. It also indicates that Mtpn may be coordinated by a variety of miRNAs [25]. MiR-124a is also involved in pancreatic development and insulin secretion by regulating FOXA2 transcription factors and RAB27A [26, 27]. Other kinds of miRNAs have also been found to regulate insulin secretion. For example, miR-9 can regulate insulin secretion by inhibiting OC2 and SIRT1 [28, 29]. MiR-29a and miR-29b can prevent the insulin secretion by inhibiting monocarboxylate transporter 1 (MCT1) [30]. MiR-184 can increased pancreatic beta cell proliferation and mass [31]. In conclusion, all these studies indicate that miRNAs can affect insulin secretion by affecting pancreatic development and insulin exocytosis.

### MicroRNAs in serum and plasma

In recent years, studies have discovered that miRNAs exist in serum and plasma, suggesting that serum and plasma miRNAs may become a new biomarker of disease and may regulate target cells as secretory miRNAs [32, 33]. In serum and plasma, miRNAs were initially found in the exocytosis vesicles and particles secreted by donor cells [34]. Later studies showed that miRNA also existed in apolipoprotein assembly bodies, such as combining with miRNA processing enzyme AGO2 [35–37]. MiRNAs in serum and plasma are major progress in the discovery of disease markers, and changes in miRNAs are associated with disease status, for example, miR-122 is related to liver injury and non-alcoholic fatty liver [38], miR-223 is related with atherosclerosis [39], miR-126 is associated with type 2 diabetes [40], let7e plays a role in hypertension [41]. MiR-486, miR-146b and miR-15b in the circulation are augmented in T2D patients [42]. MiR-199-3p is increased in plasma of patients with diabetes [43]. MiR-424 is up-regulated in serum of T2D patients by targeting Keap1 and Nrf2 [44]. MiR-146b is decreased in plasma of *db/db* mice [45]. More miRNA associated with metabolism disease may be found in the future and the underlying mechanisms need to be explored.

### MicroRNAs and insulin resistance in type 2 diabetes

The main reason of type 2 diabetes is insulin resistance. As shown in Table 1, microRNAs can regulate insulin resistance by affecting proteins in insulin signaling.

## Conclusions

The regulation of insulin pathway and glucose homeostasis by miRNAs suggests that miRNAs plays a regulatory

**Table 1** The functions of miRNAs

| miRNAs | Mechanisms | Functions | Tissues |
|---|---|---|---|
| miR-29a and miR-29b | inhibit CAV2, INSIG1, PIK3R1 | inhibit insulin signaling | liver |
| miR-126 | inhibit IRS1 | inhibit insulin signaling | liver |
| miR-223 | inhibit GLUT4 | inhibit glucose uptake | muscle |
| miR-33a and miR-33b | inhibit IRS2,SIRT6,AMPKa1 | inhibit insulin signaling | liver |
| miR-130a | inhibit GRB10 | promote insulin signaling | liver |
| miR-204 | inhibit GLP1R | promote insulin signaling | pancreas |
| miR-378 | inhibit p110a | inhibit insulin signaling | liver |
| miR-93 | inhibit Sirt7,Tbx3 | inhibit insulin signaling | null mice |
| miR-103 and miR-107 | inhibit caveolin-1 | inhibit insulin signaling | liver |
| miR-143 | inhibit ORP8 | inhibit insulin signaling | liver |
| Let7 | inhibit IGF1R,INSR,IRS2 | inhibit insulin signaling | muscle |
| miR-375 | inhibit MTPN | reduce insulin secretion | pancreas |
| miR-124a | inhibit MTPN,FOXA2,RAB27A | reduce insulin secretion | pancreas |
| miR-9 | inhibit OC2,SIRT1 | reduce insulin secretion | pancreas |
| miR-29a and miR-29b | inhibit MCT1 | reduce insulin secretion | pancreas |
| miR-184 | inhibit AGO2 | increase insulin secretion | pancreas |
| miR-122 | | liver injure and NAFLD | serum |
| miR-223 | | atherosclerosis | plasma |
| miR-126 | | type 2 diabetes | plasma |
| let7e | | hypertension | plasma |
| miR-486, miR-146b and miR-15b | | type 2 diabetes | serum |
| miR-199-3p | | type 2 diabetes | plasma |
| miR-424 | Keap1 and Nrf2 | type 2 diabetes | serum |
| miR-146a | | type 2 diabetes | plasma |

role in type 2 diabetes. The discovery of serum and plasma miRNAs not only provides a new marker for the disease, but also suggests that miRNAs may secrete to the target organ from donor cells.

The discovery of the role of miRNAs not only provides new ways of scientific research, but also provides a new perspective for clinical research. The treatment of type 2 diabetes has been devoted to the inhibition of drug targets (enzymes). Important discoveries in the metabolism of miRNAs provide potential treatments for type 2 diabetes, such as the role of miR-33a and miR-33b in the disease. While other miRNAs, such as miR-103 and miR-107, provide drug targets for treatment intervention.

The role of miRNAs in type 2 diabetes still needs to be explored. For example, multiple target genes are often found in mRNAs, and many miRNAs synergies are likely to inhibit the expression of target genes. Therefore, a new method of combining system biology is needed to study the regulation of miRNA networks. MiRNAs often have multiple target genes and different target genes involved in different processes, and whether miRNAs can regulate glucose metabolism and other processes, such as proliferation, is very important. Finally, in view of the fact that miRNAs usually participates in multiple pathways, the long-term effects of miRNAs as a target therapy need to be considered. These existing problems need to be solved in the research of miRNAs.

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## Publisher's Note



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