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Roles of RNAkines in regulating glucose homeostasis

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Abstract: Under physiological conditions, the body maintains glucose homeostasis through interorgan communication between metabolic organs. As is well known, this crosstalk is mediated by traditional hormones or metabolites. Recently, a new type of secreted factor called RNAkine has become increasingly prominent in regulating glucose homeostasis. They are secreted non-coding RNAs that are mainly transported from the origin cells to the target cells through extracellular vesicles (EVs), participating in interorgan communication. In this review, we summarized the various organs involved in glucose homeostasis and their inter-organ crosstalk, and emphasized the important role of RNAkines which is of great significance for both the prevention and treatment of type 2 diabetes mellitus (T2DM).

Keywords: RNAkine; glucose homeostasis; miRNA; pancreatic islets

1. Introduction

The regulation of glucose homeostasis in the human body is a complex physiological process that involves the collaboration of multiple organs, including the pancreas, adipose tissue, muscles, and liver. This process is essential for maintaining blood glucose levels within an appropriate range, thereby ensuring the normal functioning of various bodily functions. The pancreatic islets play a central role in this regulation. When the level of blood glucose increases, the islets promote the absorption and utilization of glucose by various tissues, particularly the liver, muscles, and adipose tissue, by releasing insulin. Simultaneously, insulin can promote glycogen synthesis in the liver and muscle while inhibiting gluconeogenesis, which helps to lower blood glucose levels. Conversely, when blood glucose level decreases, the islets release glucagon to promote the decomposition of glycogen into glucose by activating enzymes in the liver, and stimulate gluconeogenesis, that is, the

transformation of substances that are non-sugar into glucose—thereby increasing blood glucose levels. Muscles and adipose tissues are the main target tissues of insulin. With the help of insulin, these tissues can take glucose from the bloodstream and utilize it for energy consumption or storage. Additionally, the small intestine is the primary location for glucose absorption. Carbohydrates in food are decomposed by digestive enzymes and absorbed by intestinal epithelial cells into the bloodstream, thus influencing blood glucose levels. Although the brain does not directly participate in the regulation of glucose metabolism, it perceives blood glucose levels through structures such as the hypothalamus and regulates the secretion of insulin and glucagon via the autonomic nervous system, thereby indirectly participating in blood glucose regulation. These organs work in concert to maintain the dynamic balance of blood glucose levels.

In recent years, microRNAs (miRNAs), which are 19–22 nucleotides in length, can not only exert their functions within the cells where they are produced [1,2], but also communicate with other cells or tissues through paracrine or endocrine pathways [3–6] as a new secreted factor. First, the genes encoding miRNAs are transcribed by RNA polymerase II in the nucleus to form primary miRNAs (pri-miRNAs), which are then cleaved by Drosha to form precursor miRNAs (pre-miRNAs) and transported to the cytoplasm by nuclear transporters; pre-miRNAs are cleaved by Dicer into mature miRNAs in the cytoplasm [7]. Subsequently, miRNAs can be selectively packaged into extracellular vesicles (EVs) and enter the bloodstream or other bodily fluids with the secretion of EVs. Once EVs reach the target cell, they can be taken up by the target cell through receptor-mediated endocytosis, phagocytosis, or direct fusion with the cell membrane. In this way, miRNAs can be transferred to the cytoplasm of recipient cells, where they can be specifically incorporated into RNA-induced silencing complexes (RISC) and downregulate the expression of target genes [8,9]. Given the role of miRNAs in transmitting information between cells, they are regarded as a new signaling molecule and defined as ‘RNAkine’ in a recent article [10].

RNAkines can be secreted by donor cells and taken by recipient cells via EVs [10], which are natural carrier systems that can transfer nucleic acids, lipids, and proteins, in autocrine, paracrine, and endocrine manners [11]. Moreover, RNAkines can circulate without the need for EVs and are usually associated with stabilizing proteins, such as high-density lipoprotein (HDL). Under the regulation of neutral sphingomyelinase, HDL can transport RNAkines and deliver them to receptor cells with functional targeting capabilities [12]. Unlike traditional signaling molecules (such as hormones, cytokines, and chemokines) that typically bind to receptors to exert their effects, RNAkines are a class of secreted non-coding RNAs (ncRNAs), that act as endogenous RNAs in recipient cells, regulating multiple genes and simultaneously modulating them. In addition to the miRNAs mentioned earlier, RNAkines also include long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) [10]. However, there is limited research on circRNAs or lncRNAs in the field of glucose homeostasis, and miRNA-mediated intercellular communication has become a significant molecule in promoting the regulation of glucose homeostasis. Therefore, here we focus on introducing the role played by miRNAs.

This review systematically summarizes the roles of communication between pancreatic islets and insulin-sensitive tissues such as adipose tissue, muscle, and liver in regulating glucose homeostasis. Here, we focus on a new secretion factor—RNAkine, which plays a crucial role as a maintainer of glucose homeostasis by participating in interorgan communications mainly via EVs. The signaling molecules involved in glucose homeostasis across tissues are summarized in Figures 1 and 2, and will be discussed in more detail in this review (Tables 1 and 2). This review aims to summarize the role of multiple organs in regulating blood glucose homeostasis and the secretion factors involved, and emphasize the role of RNAkines.

2. The center role of pancreatic islets

The pancreas plays a vital role in regulating glucose homeostasis by releasing various hormones. The pancreatic islets, small clusters of cells located within the pancreas, are crucial for this process. Islets typically comprise five distinct cell types, namely, α cells (~20%), contain glucagon; β cells (~70%), contain the insulin, C-peptide and islet amyloid polypeptide (IAPP); γ cells (<5%), contain pancreatic polypeptide (PP); δ cells (<10%), contain the somatostatin and ε cells (<1%), contain the ghrelin [13–15]. Among these hormones, the islets maintain blood glucose levels mainly through glucagon and insulin. Glucagon secretion is inhibited by elevated levels of glucose and insulin, and stimulated by increased levels of fatty acids and amino acids during fasting. Between meals or during sleep, under the conditions of low blood glucose, α-cells secrete glucagon to stimulate the breakdown of liver glycogen. Additionally, during prolonged fasting, glucagon drives gluconeogenesis in the liver and kidneys to elevate endogenous blood glucose levels [16]. In contrast, after a meal, elevated glucose levels from external sources stimulate insulin release from pancreatic β cells [17], a process known as Glucose-stimulated insulin secretion (GSIS). Insulin can inhibit the secretion of glucose by the liver and enable glucose uptake into adipose tissue and muscle in an insulin-dependent manner, promoting lipid storage in fats and the formation of glycogen in muscles to lower blood glucose levels.

In addition to glucagon and insulin, which are directly involved in regulating blood glucose levels, other hormones secreted by the pancreas also play a role in this regulation by influencing insulin and glucagon secretion. For example, pancreatic PP acts as an appetite suppressant and stimulates enzyme secretion in the digestive tract, which can reduce gastric emptying and intestinal motility [18]. And has been demonstrated to suppress glucagon release at low glucose levels through the activation of PPYR1 receptors on α cells [19]. Somatostatin, secreted by islet δ cells and extra-islet neuroendocrine cells, serves as a paracrine inhibitor of both insulin and glucagon secretion [20,21]. Ghrelin, a peptide hormone primarily produced in the stomach and also in the pancreas, acts as a physiological regulator of glucose homeostasis and insulin secretion [22], functioning as an insulin-suppressive hormone [23]. IAPP, also known as amylin, is a peptide hormone that is stored and released by pancreatic islet-β cells. IAPP curbs appetite, delays gastric emptying, and helps lower the level of blood glucose [24]. Additionally, C-peptide, which is a byproduct

of insulin synthesis [25], can interfere with IAPP polymerization [26], thereby indirectly affecting blood glucose levels.

The pancreatic islets can also regulate blood glucose homeostasis through miRNAs. Both miR-375 and miR-124a are abundant in pancreatic islets and β cells. Overexpressed miR-375 impacts insulin secretion negatively by targeting Myotrophin (Mtpn) to reduce exocytosis [27], while miR-124a impairs insulin biosynthesis by downregulating Forkhead box a2 (Foxa2), a transcription factor essential for insulin secretion, β-cell differentiation, glucose metabolism, and pancreatic development [28,29]. Consistent with the function of miR-375, miR-9 has a negative regulatory effect on insulin secretion. MiR-9 is only expressed in the brain and pancreas. It negatively controls insulin release by reducing the expression of transcription factor Onecut-2, which in turn increases the level of Granuphilin/Slp4, a Rab GTPase effector associated with β-cell secretory granules [30]. Similarly, under the induction of thioredoxin-interacting protein (TXNIP) and diabetes, β cell miR-200 is overexpressed and promotes β cell apoptosis by inhibiting Zeb1, thereby negatively affecting insulin release [31].

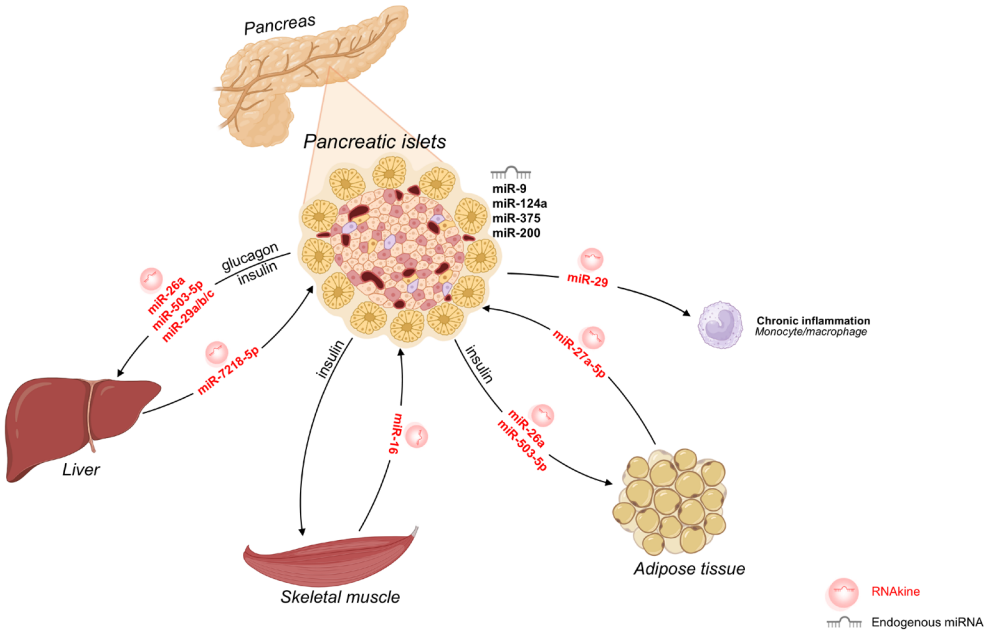

Figure 1. The center role of pancreatic islet. The diagram illustrates a pancreatic-centered metabolic regulatory network mediated by hormones, endogenous miRNAs, and RNAkines, primarily including RNAkines secreted by pancreatic islets and RNAkines targeting the pancreatic islets. Figure generated using BioRender (biorender.com/).

2.1. RNAkines secreted by pancreatic islets

Pancreatic β cells were previously thought to directly regulate blood glucose homeostasis solely by secreting hormones, but now it has been discovered that pancreatic β cells can also secrete RNAkines [10,32]. Pancreatic β cells can selectively and actively secrete RNAkines under certain stimulation conditions, such as high glucose, high free fatty acids (FFA), high

arginine, and high Kcl [32], to regulate blood glucose homeostasis. For example, β cell-released miR-26a can regulate peripheral insulin sensitivity in a paracrine manner. Secreted miR-26a from β cells could be taken up *in vivo* by the liver, visceral adipose tissue (VAT), and brown adipose tissue (BAT), and can improve insulin sensitivity in these tissues [33]. Besides, miR-26a can also modulate β cell replication and insulin secretion in an autocrine manner. Lack of miR-26a in mice leads to impaired β cell function and diminished efficacy of β cell-derived EVs, which in turn exacerbates obesity-related glucose intolerance and insulin resistance. In overweight individuals, serum EV levels of miR-26a are decreased and show an inverse relationship with clinical manifestations of type 2 diabetes mellitus (T2DM) [33]. Therefore, the function of miR-26a is expected to provide new opportunities for the treatment of T2DM. Additionally, β cells released miR-29 family members (miR-29a/b/c) are involved in the promotion of insulin resistance. When under conditions like fasting or a high-fat diet (HFD), the level of FFAs in the bloodstream will elevate, then pancreatic β cell-released miR-29a/b/c in response to elevated FFA levels. These miRNAs are then absorbed by the liver, where they target p85α, thereby regulating hepatic insulin sensitivity and controlling glucose homeostasis. It is worth noting that genetic deletion of miR-29a/b/c from β cells leads to lower circulating levels of miR-29 and improves HFD-induced hepatic insulin resistance [34]. Furthermore, prediabetic β cells that secrete miR-29 drive macrophage-induced inflammation, thus causing insulin resistance and diabetes via TNF-receptor-associated factor 3 (TRAF3). The overexpression of secreted miR-29 in β cells facilitates the recruitment and activation of circulating macrophages and monocytes. Then, these miR-29 molecules are absorbed by the macrophages that have been recruited. This induces a local inflammatory response in the pancreas and leads to glucose intolerance and insulin resistance. Conversely, blocking miR-29 effects can rescue this [35]. Besides, under aging and HFD conditions, β cells generate and release miR-503-5P to cause insulin resistance. Under this state of chronic inflammation, secreted miR-503-5p is delivered to the liver and adipose tissues, targeting insulin receptors and triggering insulin resistance. Moreover, highly expressed miR-503-5p in β cells activates JNK MAPK and p38 MAPK to decrease GSIS and compensatory β-cell proliferation by targeting JNK-interacting protein 2 (JIP2) inner β cells. Therefore, miR-503-5p is an intra- and inter-organ modulator, initially leading to insulin resistance in the liver and adipose tissue, and ultimately causing β-cell decompensation due to GSIS dysfunction and inability of compensatory β-cell proliferation. Additionally, targeting the miR-503 cluster within β-cells specifically can alleviate diabetes associated with aging by restoring GSIS and enhancing insulin sensitivity [36] (Figure 1).

2.2. RNAkines targeting the pancreatic islets

Secretion of RNAkines can also directly target the pancreas, establishing communication between other organs and pancreatic islets. For example, in adipose tissue, miR-27a-5p secreted by visceral adipocytes impairs insulin secretion in obesity. These secreted miR-27a-5p molecules are taken up by the pancreatic islets, where they target L-type Ca^{2+} channel subtype CaV1.2 (Cacna1c), reducing insulin release from β cells. In db/db mice, depletion of miR-

27a-5p levels markedly ameliorates glucose intolerance and enhances insulin secretion [37]. Similarly, the crosstalk between skeletal muscle and β cells plays a role in glucose homeostasis. For example, under a high palmitic acid diet (HPD), miR-16, which is overexpressed in muscle-released EV-like vesicles (ELVs) is taken up by β cells and during insulin resistance, participates in adaptations in β cell mass. This process influences blood glucose levels indirectly [38]. Additionally, the crosstalk between hepatocytes and β cells also plays a role in glucose homeostasis. For example, hepatocytes secret miR-7218-5p to islet β cells could promote the β cell proliferation ability during obesity, thereby improving insulin sensitivity. miR-7218-5p affects β cell line-MIN6 cell proliferation by targeting the CD74 gene and mediates compensatory hyperplasia of islets. This could represent a mechanism for the compensatory hyperplasia of pancreatic β-cells in response to insulin resistance and obesity [39] (Figure 1).

3. Adipose tissue

The main function of adipose tissue is to store triglycerides when calorie intake exceeds energy needs and release them during fasting to affect glucose metabolism in the liver and muscles, thereby regulating blood glucose levels indirectly [40]. Adipose tissue functions as an endocrine organ, playing a role in regulating systemic metabolic homeostasis and in the secretion of various bioactive adipokines, hormones, inflammatory mediators, and signaling lipids [41]. For example, leptin induces lipolysis by regulating sympathetic neurons in white adipocytes [42], indirectly affecting blood glucose homeostasis. Adiponectin can enhance adipocyte lipid storage and insulin sensitivity [43]. The function of adipose tissue is also regulated by miRNAs. In obese mice, silencing the expression of miR-103/107 will improve insulin sensitivity and glucose homeostasis by targeting caveolin-1 to reduce downstream insulin signaling. Conversely, enhancing the function of miR-103/107 in the liver or adipose tissue is sufficient to lead to impaired blood glucose homeostasis. These findings provide a novel therapeutic target for managing T2DM and obesity [44].

The RNAkines secreted by adipose tissues play crucial roles in regulating blood glucose homeostasis, through endocrine and paracrine communication with other organs. Generally speaking, the adipose tissue in obesity mostly secretes “harmful” RNAkines, resulting in insulin resistance. For example, in obesity, adipose tissue releases miR-27a into the bloodstream, which then induces insulin resistance in skeletal muscle through repression of peroxisome proliferator-activated receptor γ (PPARγ) [45]. Besides, in obesity, adipose tissue also releases lower levels of miR-141-3p, significantly inhibiting insulin sensitivity and glucose uptake. These miR-141-3p molecules are absorbed by hepatocytes and induce insulin resistance by increasing the phosphorylation level of AKT and impairing insulin signaling [46]. In overweight/obesity, adipocytes secreted miR-130b during adipogenesis. MiR-130b can directly target muscle cells and decrease the expression of PGC-1α (also known as PPARGC1A), a gene that is pivotal for lipid oxidation within the muscle, thereby indirectly impairing glucose tolerance [47]. Additionally, mature adipocytes secrete EVs, which transport miR-34a to macrophages and inhibit polarization of M2 macrophages by

suppressing the expression of Krüppel-like factor 4 (Klf4). MiR-34a indirectly resists glucose intolerance and insulin resistance caused by obesity through its paracrine action as a key mediator [48].

Brown adipose tissue (BAT) is a regulator of metabolism and energy expenditure through non-shivering thermogenesis. It can secrete traditional molecules such as lipids and peptides [49], as well as RNAkines. RNAkines derived from BAT can regulate the expression of liver genes. For example, under cold exposure (physiological states), BAT-secreted miR-378a-3p is selectively packaged into EVs and delivered into the liver, enhancing gluconeogenesis by targeting p110α. This mechanism reprograms systemic glucose metabolism by promoting hepatic gluconeogenesis, thereby helping to maintain systemic glucose homeostasis [50]. BAT secretes miR-99b, which downregulates the level of fibroblast growth factor 21 (Fgf21) mRNA in the liver to improve insulin sensitivity. In adipose tissue-specific DICER knockout (AdicerKO) mice, the disruption of miR-99b secretion results in higher expression of Fgf21 in the liver, thereby improving glucose tolerance and insulin sensitivity [51]. Besides miR-99b, gonadal white adipose tissue (gWAT) releases miR-222, which then enters the liver and skeletal muscle, impairing the insulin signaling pathway by targeting insulin receptor substrate 1 (IRS1), thereby reducing insulin sensitivity [52].

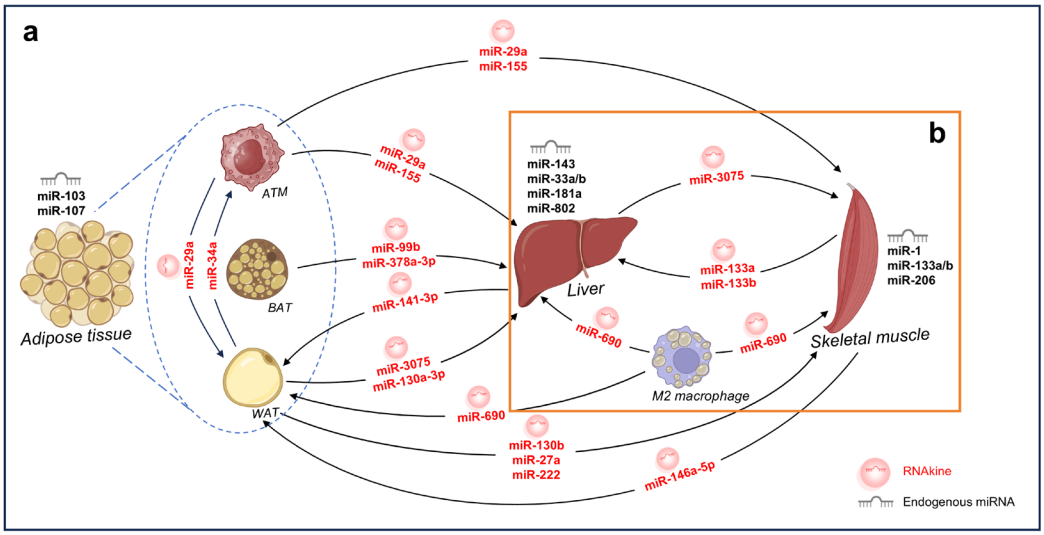

Figure 2. A metabolic regulatory network composed of adipose tissue, skeletal muscle, and liver in regulating glucose homeostasis. (**a**) The diagram illustrates adipose tissue, as the donor and recipient of RNAkine, participates in the regulation of glucose homeostasis. (**b**) RNAkine-mediated metabolic regulatory network in skeletal muscle and liver. It also involves the participation of M2 macrophage. Figure generated using BioRender (biorender.com/).

Adipose tissue macrophages (ATMs) also secrete RNAkines to regulate insulin sensitivity. In obese mice, an elevated secretion of miR-155 from ATM (with no specification of whether it is M1 or M2 macrophages) leads to a decline in glucose tolerance and insulin sensitivity in insulin-target tissues, including the skeletal muscle and the liver, by targeting

PPARγ [53]. Consistent with the function of miR-155, miR-29a secreted by obese ATM promotes insulin resistance in hepatocytes, adipocytes, and myocytes [54]. On the contrary, miR-690 secreted by M2 macrophages can systematically enhance glucose tolerance and insulin sensitivity by targeting NADK. MiR-690 can function as an insulin sensitizer and could be a novel insulin sensitizer for the treatment of metabolic disease [55] (Figure 2a).

4. Skeletal muscle and liver

Skeletal muscle is an endocrine organ, capable of producing and releasing various myokines that help regulate glucose homeostasis. Such as IL-6, acute exercise can cause an increase in IL-6 levels [56], which increases basal glucose uptake [57] and enhances the sensitivity of muscles to insulin. Additionally, after 12 weeks of endurance exercise, there are four miRNAs (miR-133a/b, miR-206, and miR-1) are associated with improved insulin sensitivity. They are negatively modulated in the vastus lateralis muscle of humans, and their downregulation may play an important role in regulating different contracting skeletal muscles [58].

Skeletal muscle-secreted RNAkines also play an important role in glucose homeostasis. Under exercise stimulation, miRNAs secreted by skeletal muscles can improve blood glucose homeostasis. For example, during high-intensity interval training (HIIT), muscle-derived miR-133a and miR-133b enhance liver insulin sensitivity and glucose tolerance by inhibiting the transcription factor Forkhead box O1 (FoxO1) in the liver [59]. Similarly, miR-146a-5p, abundant in EVs derived from skeletal muscle, mediates fatty acid absorption and significantly impairs glucose tolerance. This occurs through its targeting of the growth and differentiation factor 5 (GDF5) gene as an inhibitor of the PPARγ signaling pathway [60]. Therefore, miR-146a-5p indirectly affects glucose homeostasis and may serve as a new target for developing therapies for metabolic diseases such as obesity.

The liver is the metabolic center of the body, maintaining energy balance throughout the body by driving endocrine and metabolic secretions. Insulin-like growth factor 1 (IGF-1), predominantly produced in the liver [61], is classified primarily as a mitogenic hormone and insulin metabolic hormone [62], indirectly affecting blood glucose levels. In the liver, overexpression of miR-181a reduces the level and activity of sirtuin-1 (SIRT1) protein, and leads to insulin resistance in hepatic cells [63]. Additionally, liver expression of miR-802 is upregulated in two obese mouse models (HFP and Leprdb/db) as well as in obese humans. In mice, the inducible overexpression of miR-802 leads to diminished insulin sensitivity and compromised glucose tolerance [64]. Similarly, miR-33a and miR-33b also reduce insulin signaling by targeting insulin receptor substrate 2 (IRS2) in the liver insulin signaling pathway [65]. In addition, overexpression of miR-143-induced obesity, suppresses AKT activation in response to insulin and disrupts glucose homeostasis by targeting ORP8. Therefore, the miR-143-ORP8 signaling axis could emerge as a promising therapeutic target for diabetes associated with obesity [66].

RNAkines released by hepatocytes also contribute to the regulation of blood glucose homeostasis. For example, in early onset obesity (4wk HFD), hepatocytes secret miR-3075

that promotes insulin sensitivity. The secreted miR-3075 are taken up by primary hepatocytes, skeletal muscle cells (L6 myocytes), and adipocytes, where they target fatty acid 2-hydroxylase (FA2H). So, miR-3075, acting as a specific insulin-sensitizing miRNA represents a compensatory mechanism in the initial phases of caloric surplus to avert insulin resistance induced by long-term obesity. However, in chronic obesity (16–18 weeks HFD), this compensatory effect is diminished in chronic obese mice, and hepatocyte-derived EVs from these mice no longer contain high levels of miR-3075. These EVs contribute to insulin resistance by activating proinflammatory responses in macrophages [67]. Besides, hepatic EV-derived miR-130a-3p mitigated dysregulated glucose metabolism by reducing the levels of pH domain and leucine-rich repeat protein phosphatase 2 (PHLPP2) expression and activating the AKT-AS160-GLUT4 signaling pathway in adipose cells [68]. The interaction between adipose tissue and the liver facilitates glucose transport in adipocytes, which is helpful to effectively prevent and treat insulin resistance (Figure 2b).

RNAkines can function within recipient cells, suggesting their involvement in endocrine cell-cell communications and organ interactions. Major organs such as the pancreas, adipose tissue, skeletal muscle, and liver play crucial roles in glucose homeostasis. These organs rely on RNAkines to maintain coordination between organs, which is essential for maintaining metabolic homeostasis (Table 1). Additionally, the roles of some endogenous miRNAs in regulating glucose homeostasis are listed in Table 2.

Table 1. RNAkines involved in glucose homeostasis.

RNAkine	Donor	Recipient	Target(s)	Mechanism	Function	Refs
miR-26a	Pancreatic β cell	Liver VAT, BAT	ACSL3, ACSL4, TCF7L2, PCK1, GSKβ, PKCδ, PKCθ	Activating insulin signaling pathway, inhibiting gluconeogenesis	Improving peripheral insulin Sensitivity; promoting insulin secretion and β cell replication	[33]
miR-29 a/b/c	Pancreatic β cell	Liver	p85α	Inhibiting PI3K/AKT signaling pathway	Impairing insulin sensitivity	[34]
miR-29	Pancreatic β cell	Monocyte/macrophage	TRAF3	Inducing inflammation in T2DM	Promoting insulin resistance	[35]
miR-503-5P	Pancreatic β cell	Liver, adipose tissue	JIP2	Activating JNK MAPK and p38 MAPK	Promoting insulin resistance and β-cell decompensation	[36]
miR-27a	WAT	Skeletal muscle	PPARγ	Impairing insulin signaling pathway Glut 4 expression	Impairing insulin sensitivity	[45]

Table 1. *Cont.*

RNAkine	Donor	Recipient	Target(s)	Mechanism	Function	Refs
miR-141-3P	Adipose tissue	Hepatocytes	–	Improving the level of phosphorylation of AKT and enhancing insulin signal transduction	Improving insulin sensitivity and glucose uptake	[46]
miR-130b	Adipocytes	Muscle cells	PGC-1α	Reducing muscle oxidative capacity	Impairing glucose tolerance	[47]
miR-34a	Adipocytes	Macrophage in adipose tissue	KLF4	Downregulating KLF4 mRNA	Improving insulin sensitivity	[48]
miR-27a-5p	Visceral adipocytes	Pancreatic islets	Cacna1c	Inhibiting insulin secretion	Improving glucose intolerance	[37]
miR-378a-3P	BAT	Liver	p110α	Inhibiting PI3K/AKT signaling pathway	Improving glucose output during cold exposure	[50]
miR-99b	BAT	Liver	FGF21	Downregulating FGF21 mRNA and circulating FGF21	Impairing insulin sensitivity	[51]
miR-222	WAT	Liver, skeletal muscle	IRS1	Impairing insulin signaling pathway	Impairing insulin sensitivity	[52]
miR-155	ATM	Liver, skeletal muscle	PPARγ	Impairing insulin signaling pathway	Impairing insulin sensitivity	[53]
miR-29a	ATM	Adipocyte, myocyte, hepatocyte	PPARδ	Impairing insulin signaling pathway	Impairing insulin sensitivity	[54]
miR-690	M2	Adipose tissue, liver, skeletal muscle	NADK	Improving insulin responses	Improving insulin sensitivity	[55]
miR-133a miR-133b	Skeletal muscle	Liver	–	Inhibiting gluconeogenesis through upregulating FoxO1	Improving insulin sensitivity	[59]
miR-146a-5p	Skeletal muscle	Adipose tissue	GDF5	Inhibiting PPARγ signaling	Impairing glucose tolerance	[60]
miR-16	Skeletal muscle	Pancreatic β cells	–	Regulating Ptch1	Participating in pancreatic development positively	[38]
miR-3075	Hepatocytes	Adipocytes, skeletal muscle cells, primary hepatocytes	FA2H	Downregulating FA2H mRNA	Improving insulin sensitivity in early onset obesity	[67]

Table 1. *Cont.*

RNAkine	Donor	Recipient	Target(s)	Mechanism	Function	Refs
miR-434-3p	Hepatocytes	ATM	–	Activating proinflammatory responses	Promoting insulin resistance in chronic obesity	[67]
miR-130a-3p	Liver	Adipocyte	PHLPP2	Activating AKT-AS160-GLUT4 signaling pathway	Improving glucose tolerance	[68]
miR-7218-5p	Hepatocytes	Pancreatic β cells	CD74	Downregulating CD74 mRNA	Promoting compensatory hyperplasia of islets	[39]

Abbreviations: ACSL, acyl-CoA synthetase long-chain; ATM, adipose-associated macrophage; BAT, brown adipose tissue; Cacna1c, Calcium voltage-gated channel subunit alpha1 C; CD74, cluster of differentiation 74; FA2H, fatty acid 2-hydroxylase; FGF21, fibroblast growth factor 21; GDF5, Growth Differentiation Factor 5; JIP2, JNK interacting protein 2; KLF4, Kruppel-like factor 4; TCF7L2, transcription factor 7-like 2; PCK, phosphoenolpyruvate carboxykinase (PEPCK); PGC-1, peroxisome proliferator-activated receptor gamma coactivator 1; PHLPP2, pH domain and leucine rich repeat protein phosphatase 2; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; IRS1, insulin receptor substrate 1; VAT, visceral adipose tissue; TRAF3, tumor necrosis factor receptor (TNFR) associated factor 3; NADK, NAD+ Kinase; WAT, white adipose tissue.

Table 2. Endogenous miRNAs involved in glucose homeostasis.

miRNA	Tissue	Target(s)	Mechanism	Function	Refs
miR-9	Pancreas	Onecut-2	Increasing granuphilin levels and playing a negative modulatory role on insulin exocytosis	Inhibiting insulin secretion	[30]
miR-375	Pancreas	Mtpn	Impairing insulin exocytosis	Inhibiting insulin secretion	[27]
miR-200	Pancreas	Zeb1	Promoting beta cell apoptosis	Inhibiting insulin secretion	[31]
miR-124a	Pancreas	Foxa2	Downregulating Foxa2 protein	Impairing insulin biosynthesis	[28]
miR-103 miR-107	Adipose, liver	Caveolin-1	Diminishing the number of insulin receptors	Impairing insulin sensitivity and enhancing hepatic glucose production	[44]
miR-181a	Liver	SIRT1	Downregulating SIRT1 protein	Impairing insulin sensitivity	[63]
miR-802	Liver	HNF1b	Downregulating HNF1b mRNA (G6pc and Pck1 expression)	Impairing glucose tolerance and insulin sensitivity	[64]
miR-33a/b	Liver	IRS2	Inhibiting AKT and ERK activation	Impairing insulin sensitivity	[65]
miR-143	Liver	ERK5 ORP8	Inhibiting AKT activation	Promoting insulin resistance	[66]

Abbreviations: ERK5, Extracellular signal-regulated kinase 5; Foxa2, Forkhead box a2; HNF1, Hepatic nuclear factor 1; Onecut-2, One cut homeobox; Mtpn, Myotrophin; ORP8, Oxysterol-binding protein-related protein 8; SIRT1, Sirtuin 1; Zeb1, Zinc finger e-box binding homeobox 1.

5. Conclusion

In this review, we summarized the role of interorgan communication in regulating glucose homeostasis and highlighted the centrality of the pancreatic islets. Currently, the global prevalence of T2DM is rising rapidly, making it a global epidemic [69]. The pathogenesis of this disease mainly includes pancreatic β cell dysfunction and insulin resistance [70]. However, the traditional signaling molecule's action pathway is very limited. Here, we highlight a new signaling molecule, RNAkine, which has emerged as a critical regulator of glucose homeostasis. At present, various RNAkines with therapeutic potential have been extensively studied in animal models. For example, four RNAkines that are highly expressed in the serum EVs of obese mice, miR-192, miR-122, miR-27a-3p, and miR-27b-3p, were artificially synthesized and introduced into normal mice-derived EVs. When injected into normal mice, these EVs can induce glucose intolerance [71]. In addition, miR-143-3p was significantly increased in the circulatory system of T2DM patients and obese mice, and played an important role in the occurrence of insulin resistance. The injection of anti-miR-143-3p through the tail vein can inhibit the content of miR-143-3p in the circulatory system of obese mice and alleviate insulin resistance caused by obesity [72]. These findings indicate that miR-192, miR-122, miR-27a-3p, miR-27b-3p, miR-155, and miR-143-3p may all become therapeutic targets for T2DM in the future. In T2DM, RNAkines have the therapeutic prospect of reducing insulin resistance, protecting islet function, and inhibiting chronic obesity-related inflammation. These effects can be achieved by promoting or blocking the level or action of RNAkines. Although a large number of studies have found many miRNAs with clinical potential in the treatment of T2DM, so far, the only miRNA-targeted therapeutic drugs that have reached the Phase I clinical trial are anti-miR-103/107 (RG-125/AZD4076), which are used to treat T2DM patients with nonalcoholic fatty liver disease (NAFLD). This drug can inhibit the expression levels of miR-103 and miR-107, and increase the sensitivity of insulin signaling pathways in liver and adipose tissue [44,73]. But this drug ultimately failed to be marketed.

To sum up, RNAkines have greatly expanded the signal transduction between tissues and have great potential in the diagnosis and treatment of T2DM. However, because microRNAs typically have a large number of unknown targets, there are often unknown risks such as off-target effects during treatment. Therefore, the use of RNAkine-based therapies in clinical trials or practice often encounters many unexpected potential risks. At present, researchers ensure the targeting specificity of miRNA drugs by chemically modifying them or using drug delivery systems with stronger targeting properties (such as using EVs modified with surface proteins to encapsulate drugs and improve drug delivery targeting) [73]. Despite numerous difficulties, significant progress has been made in the development of drugs based on RNAkines. In the future, RNAkines will bring great hope for the diagnosis and treatment of metabolic diseases such as T2DM.

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Conflicts of interests

The authors have no other conflicts of interest to declare.

Authors' contribution

Conceptualization, J.L.; writing—original draft preparation, Y.W.; writing—review and editing, J.L. and C.Y.Z.; visualization, Y.W.; supervision, J.L.; project administration, J.L.; funding acquisition, J.L. and C.Y.Z. All authors have read and agreed to the published version of the manuscript.

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