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PROSPECTS

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Molecular aspects of diabetes mellitus: Resistin, microRNA, and exosome

Mohammad Javad Saeedi Borujeni[1] | **Ebrahim Esfandiary**[1] | **Gholamreza Taheripak**[2] | **Pilar Codoñer-Franch**[3] | **Eulalia Alonso-Iglesias**[4] | **Hamed Mirzaei**[5]

[1] Department of Anatomical Sciences and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

[2] Faculty of Medicine, Department of Biochemistry, Iran University of Medical Sciences, Tehran, Iran

[3] Department of Pediatrics, Obstetrics and Gynecology, University of Valencia, Valencia, Spain

[4] Department of Biochemistry and Molecular Biology, University of Valencia, Valencia, Spain

[5] Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence
Ebrahim Esfandiary, Department of Anatomical Sciences and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
Email: esfandiari@med.mui.ac.ir
Hamed Mirzaei, Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
Email: mirzaeih911h@mums.ac.ir; h.mirzei2002@gmail.com

Abstract

Diabetes mellitus (DM) is known as one of important common endocrine disorders which could due to deregulation of a variety of cellular and molecular pathways. A large numbers studies indicated that various pathogenesis events including mutation, serin *phosphorylation*, and increasing/decreasing expression of many genes could contribute to initiation and progression of DM. Insulin resistance is one of important factors which could play critical roles in DM pathogenesis. It has been showed that insulin resistance via targeting a sequence of cellular and molecular pathways (eg, *PI3* kinases, *PPARγ* co-activator-1, microRNAs, serine/threonine kinase *Akt*, and serin *phosphorylation*) could induce DM. Among of various factors involved in DM pathogenesis, microRNAs, and exosomes have been emerged as effective factors in initiation and progression of DM. A variety of studies indicated that deregulation of these molecules could change behavior of various types of cells and contribute to progression of DM. Resistin is other main factor which is known as signal molecule involved in insulin resistance. Multiple lines evidence indicated that resistin exerts its effects via affecting on glucose metabolism, inhibition of fatty acid uptake and metabolism with affecting on a variety of targets such as CD36, fatty acid transport protein 1, Acetyl-CoA carboxylase, and AMP-activated protein kinase. Here, we summarized various molecular aspects are associated with DM particularly the molecular pathways involved in insulin resistance and resistin in DM. Moreover, we highlighted exosomes and microRNAs as effective players in initiation and progression of DM.

KEYWORDS
diabetes mellitus, exosome, insulin resistance, microRNA, resistin

Abbreviations: ADP, adenosine diphosphate; AMP, 5′ adenosine monophosphate; AT, adipose tissue; ATP, adenosine triphosphate; BMI, body mass index; CAP'1, cyclase associated actin cytoskeleton regulatory protein 1; ChIP, chromatin immunoprecipitation; DM, diabetes mellitus; EMPs, endothelial microparticles; eNOS, endothelial nitric-oxide synthase; GAD65, glutamic acid decarboxylase 65 kDa; GLUT-4, glucose transporter 4; Hsp 90, heat shock protein 90; IR, insulin resistance; IRS, insulin receptor substrate; JNK, C-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; miRNAs, microRNAs; MMP, matrix metalloproteinase; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3-kinase, phosphatidylinositol-4,5-bisphosphate 3-kinase; PKC, protein kinase C; *PPARγ*, peroxisome proliferator-activated receptor gamma; RLM, resistin-like molecules; SNP, single nucleotide polymorphism; SOCS, suppressors of cytokine signaling; T1D, type 1 diabetes; T2D, type 2 diabetes; TGF-β, transforming growth factor β; Tregs, regulatory T cells; VEGFR, vascular endothelial growth factor receptor.

1 | INTRODUCTION

Diabetes mellitus (DM) is one of the common metabolic disorders which could due to insufficiency in insulin secretion or action or both of them. It has been showed that DM is associated with a variety of symptoms such as hyperglycemia, glycosuria, polydipsia, and polyuria. There are two main types of DM. Type 1 diabetes (T1D; insulin-dependent diabetes mellitus) characterized by destruction of pancreatic beta cell and type 2 (T2D; non-insulin dependent diabetes mellitus) characterized by insulin resistance (IR) and insulin deficiency.[1–4] Due to growth in aging population, low physical activity, obesity, and urbanization in developed countries, the prevalence of T2D has been increasing for the last years and will continue to increase.[5,6]

Various studies indicated that cell therapy, gene therapy, drug delivery, using of natural products, and medical nutrition therapy could be used as effective therapeutic platform for various disease including cancer and metabolic disorder (ie, various types of diabetes).[7–15] Hence, identification of various cellular and molecular pathways involved in DM pathogenesis could help to choice better treatment portions for DM patients.

Adipocytokines are cytokines secreted mainly by adipose tissue (AT) that play an important role in various metabolic functions such as short and long term energy homeostasis, immunity, regulation of lipid and glucose metabolism, and endocrine functions.[16–19] Relating DM, adipocytokines have been involved in resistance of cells to insulin hormone and some of their associated metabolic conditions such as hypertension and dyslipidemia.[20,21] One of the most important adipocytokines implicated in insulin resistance is resistin, proposed as one of the main bridges between obesity and IR.[22,23] Investigation of pathophysiological aspects of resistin on DM has raised considerable research interest in recent decades.

Resistin is a member of resistin-like molecules (RLM), a small family of proteins which play crucial roles in the activation of inflammatory processes. Expression of resistin gene is induced during differentiation of adipocytes. One of the proposed functions of resistin is the coordination between adipose tissue as an energy storage organ and target organs of insulin such as the fat, liver, and muscle.[24–26] Some animal studies indicate that administration of resistin disturbs glucose homeostasis and insulin action in normal mice. By contrast, neutralization of resistin decreased blood glucose and increased insulin action in animal models of T2D.[24,27]

It has been showed that a variety of cellular and molecular pathways could be involved in DM pathogenesis. Among of various cellular and molecular targets, microRNAs (miRNAs) have been emerged as important molecules which could regulate a variety of cellular and molecular pathways.[28–33] MiRNAs are known one class of small non-coding RNAs which could anticipate in various biological processes such as growth, differentiation, and angiogenesis.[34–37] Multiple lines evidence indicated that deregulation of these molecules could be related with DM pathogenesis.

Hence, identification of them could contribute to better understanding of different molecular aspects of DM. It has been showed that miRNAs could regulate various biological processes associated with DM such as insulin synthesis in β-cells, insulin release, and effect on signals associated with regulating cellular membrane electrical excitability (ATP: ADP ratio), and β-cell fate, islet mass formation and insulin granule exocytosis.[38]

Recently, some studies indicated that exosomes and their cargos could have critical roles in DM pathogenesis. Exosomes are nano-carriers which could be released from various types of cells such as normal cells, stem cells, and tumor cells.[39,40] It has been showed that these nano-vehicles via targeting their cargos in host cells are able to change behavior of host cells. Therefore, exosomes could be identified as key players in DM pathogenesis. For example, exosomal miRNAs is one of important exosome's cargos which could affect on various cellular and molecular targets involved in DM pathogenesis.[41] In this review, we summarize recent findings on the molecular roles of resistin, miRNAs, and exosomes in DM.

2 | INSULIN SIGNALING AND INSULIN RESISTANCE

Insulin is a proteic hormone of 6 KDa secreted by pancreatic beta cells. It is composed of two polypeptidic chains linked together by disulfide bonds.[42] Secretion of insulin from the pancreatic beta cell is a primary response to elevated blood glucose concentration.[43] Insulin elicits its biological effects by decreasing glucose production in liver and increasing the rate of glucose utilization in adipose tissue (AT) and striated muscle.[44–46] Many molecular signaling pathways are involved in the ability of insulin in sustaining whole-body energy balance. Binding of insulin to the extracellular domain of insulin receptor elicits a complex series of signaling events which conclude in translocation of the major insulin responsive glucose transporter 4 (GLUT-4) from cytoplasmic vesicles to the plasma membrane.[47–49] The insulin receptor has a crucial role in glucose homeostasis for mice with insufficient insulin receptor died shortly after birth because of severe hyperglycemia.[50,51] Expression of the insulin receptor is performed in almost all mammalian tissues, but maximally in skeletal muscle, adipose tissue, and liver.[52] Among the insulin targeted organs, skeletal muscle is responsible for more than 80% of glucose disposal induced by insulin.[53,54] Insulin receptor is a heterotetrameric protein composed of two extracellular alpha subunits and two trans-membrane beta subunits with kinase activities at their intracellular domain.[50,55] Interaction of insulin with alpha subunits activates the tyrosine kinase

activity in beta subunits. Cross-autophosphorylation of beta subunits leads to the amplification of the kinase activity. Phosphorylation of insulin receptor substrate (IRS) is a critical step in insulin action so that most of the physiological effects of the insulin are mediated by the signaling pathways involving the phosphorylation of the IRSs.[51,56]

IR implies the resistance to the insulin effects on glucose hemostasis. IR in obese subjects and patients with T2D is manifested by decreased glucose transport and metabolism in adipose tissue and skeletal muscle and also by impaired suppression of glucose output in liver.[57,58] In obese and diabetic patients, the resistance of AT, muscle, and liver to insulin is the crucial pathophysiological event in worsening of disease.[59–61] Many theories have been proposed for explaining the pathophysiological link between obesity and IR. A recent theory implicates the relations between obesity, inflammation, and IR.[62–64] Based on this theory, ectopic accumulation of lipids in liver and skeletal muscle disturbs the insulin signaling pathways, leading to reduced glucose usage in muscles and decreased glycogen synthesis in liver. One of the undesirable consequences of muscle and liver IR is increased hepatic de novo lipogenesis and hyperlipidemia. The infiltration of macrophages into white AT in obesity also leads to increased lipolysis and consequently, increased hepatic triglyceride synthesis, and esterification of fatty acids. Macrophage-related AT lipolysis also stimulates gluconeogenesis in liver, promoting hyperglycemia, increased fatty acid delivery to the liver, and enhanced glucose synthesis from glycerol. Based on above impair insulin signaling in AT plays a critical role in obesity, inflammation, and IR.[61,65–68]

From the molecular perspective, the most important and identified cause of IR is a defective post-receptor signaling in insulin target organs.[69] Some studies reported that autoactivation of insulin receptor was decreased in patients with T2D.[60] Additionally, reduced expression of PI3-kinase has been showed in skeletal muscle of obese subjects.[70] Reduced phosphorylation of insulin signaling molecule in insulin target organs in obesity and DM2 is one of the primary events in the IR process.[71] It seems that serine phosphorylation of IRS proteins lead to some events such as disconnection between the insulin receptor/IRS-1 and IRS-1/PI3-kinase, inhibition of the activation of PI3-Kinase, enhanced degradation of IRS-1, and decreased IRS-1 tyrosine phosphorylation. C-Jun N-terminal kinase (JNK) and protein kinase C (PKC) are some of the serine kinases involved in phosphorylation of serine residues on IRS-1 and in abating the insulin signal transduction.[72–74] Suppressors of cytokine signaling (SOCS) induction is another probable mechanism of IR.[75,76] Moreover, de-phosphorylation of insulin signaling molecules by phosphatases is another proposed underlying mechanism of IR.[73] Figure 1 is a simple schema of various signaling pathways involved in insulin resistance and DM.

3 | RESISTIN MOLECULE: ORIGIN AND STRUCTURE

Steppan et al, for the first time used the name resistin (based on insulin resistance) to describe a small protein that was specifically expressed and secreted by mouse adipose tissue and which serum levels increased markedly in experimental models of obesity. They indicated that adipocytes could release a unique signaling molecule (called resistin) and this molecule is associated with diabetes. Their results confirmed that the level of resistin could be decreased via using anti-diabetic drug rosiglitazone. Moreover, injection of anti-resistin antibody could enhance blood sugar and insulin action in mice with diet-induced obesity.[27]

Resistin is a member of "Resistin Like Molecules" (RLM) with a molecular weight of 12.5 KDa.[77] At the genomic level, the gene coding for resistin (*RETN*) is located on human chromosome 19p13.2 and spans 1369 bp with three introns and four exons.[78,79] It has been recently suggested that some miRNA which bind to the 3′UTR regions of aforementioned genes are related to glucose homeostasis, adipogenesis, and inflammation of white adipose tissue.[80] Among these miRNAs, miR-492 seems to be the most important, but the issue is open to discussion.[81,82] The common feature of RLM protein is the existence of a motif (10-11 cysteine-rich) at the carboxyl terminus that could support the globular domain of the resistin monomer via formation of 5 disulfide bridges.[83–85] Disulfide and non-disulfide bonds also playing an important role in the formation of dimers, trimmers, and hexamers forms of circulating resistin.[86]

Human resistin induces low inflammation by monocytes stimulation.[87,88] Chronic inflammation mediated by resistin can lead to some metabolic disease such as obesity, atherosclerosis, and cardiovascular diseases.[89–92] According with the recent fundamental study of Lee et al, adenylyl cyclase associated protein 1 (CAP1) is a functional receptor for human resistin. Binding of human resistin to CAP1 in monocytes up-regulates cyclic AMP (cAMP) concentration, protein kinase A (PKA) activity, and NF-kB-related transcription of inflammatory cytokines.[86] Furthermore, CAP1-overexpressing monocytes elicited inflammation of adipose tissue whereas CAP1-suppressed expression revoked the resistin- induced inflammatory activity. Based on above basic findings, Lee et al presented CAP1 as a bona fide receptor for human resistin.[86]

4 | RESISTIN: PROPOSED BIOLOGICAL EFFECTS

Considerable debate exists regarding the role of resistin in physiological and pathological conditions both in humans and animals. As previously mentioned Steppan et al[27] showed that insulin resistance and glucose intolerance were induced by

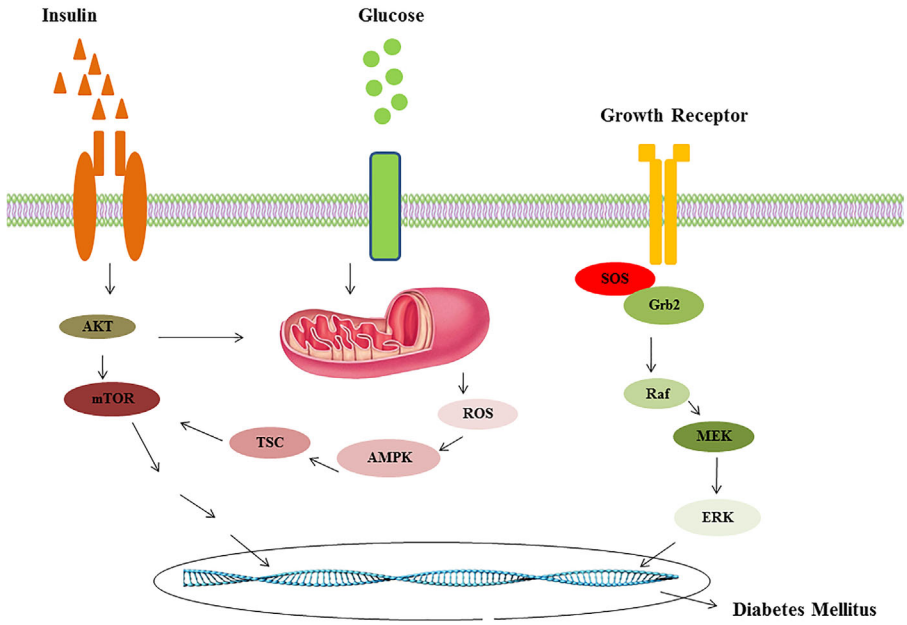

FIGURE 1 A schema of various signaling pathways in volved in DM

resistin injection to normal mice. However the causative mechanism was unclear. It has been suggested that disrupting the insulin signaling in insulin target tissues is the basis of insulin resistance induced by resistin.[67,93–96] Resistin induces proliferation and migration of human endothelial cells, activation of endothelial cells by promoting endothelin-1 release, increases the expression of vascular endothelial growth factor receptors (VEGFRs) and matrix metalloproteinases (MMPs), stimulates the capillary tube formation and activates ERK1/2 and p38 pathways.[97] Thus, it seems that resistin plays a key role in angiogenesis related vascular disorders.[98–101] Potential roles for resistin in the pathogenesis of atherosclerosis, non-alcoholic fatty liver disease, rheumatic diseases, cardiovascular disease, and kidney disease, inflammation associated with obesity, cancer, and asthma have already been exposed.[25,87,102] In addition, resistin can modulate several molecular signaling pathways involved in autoimmune disorders.[103,104] Resistin also interferes with the chemotactic movement and the stimulation of the oxidative burst of polymorphonuclear cells. By this way, resistin may contribute to the disturbed immune response in patients with hyperinsulinemia, including uremic, and diabetic subjects.[105]

5 | RESISTIN AND INSULIN RESISTANCE

Since its first description as a new adipocytokine with an impact on insulin responsiveness and glucose hemostasis, the probable role of resistin on IR induced by obesity is a puzzling issue. To date, many experimental and clinical studies have surveyed the possible relationship between resistin levels and IR in obese patients and excellent reviews have been published in this issue. However, the main factors linking obesity, inflammation, and IR are not fully understood. The correlation between high body mass index (BMI) and IR is a matter of controversy and relationship between resistin levels, obesity, and IR[106–109] are supported by some studies but not by others that failed to identify any significant correlation between aforementioned parameters.[110–112] In this part we summarize some molecular aspects about the correlations between resistin levels, inflammation, obesity, IR, and DM2.

Recently some studies suggest that regulation of insulin function initiated in hypothalamic nuclei involved in energy balance.[113–115] The intended hypothalamic nucleus receives signals from AT (adipokines) and pancreatic beta cells (insulin). Among the adipokines secreted from AT, leptin, adiponectin, and resistin have a critical role in the regulatory loop involving AT and the hypothalamic nucleus to control energy homeostasis.[114,116] As previously mentioned, resistin is defined as a potential factor in obesity-related IR, inflammation and DM, but the issue is open to discussion. Benomar et al[117] in animal studies investigated the effects of resistin on insulin sensitivity and insulin signaling. Their results demonstrated that resistin deeply impairs insulin sensitivity and signaling in the hypothalamic nuclei, AT, liver, and skeletal muscles. Furthermore, at the molecular level, activation of JNK and p38 MAPK, increased serine phosphorylation of IRS-1, and enhanced IL-6 expression in the hypothalamic nuclei and insulin-sensitive organs were induced by resistin.

Some studies indicated that expression of resistin could be associated with other disorders such as nonalcoholic fatty

liver disease (NAFLD). In a study, Pagano et al[118] indicated that levels of resistin were significantly increased in patients with NAFLD patients than with controls.

6 | RESISTIN AND PANCREATIC BETA CELL FUNCTION

Pancreatic beta cells are located on Langerhans islets and the main function of them is to adapt insulin secretion to the fluctuations in circulating levels of glucose in the blood.[119] The balance between insulin secretion and insulin action determined the glucose tolerance.[120] One of the critical subjects associated with beta cell function is the ability of these cells to generate in the face of IR, because it prevents the onset of DM2. Saldeen[121] reported that several hormones, metabolites, growth factors, and cytokines are involved in the regulation of pancreatic beta cell viability.

Increases in the mass of adipose tissue are known to have an adverse effect on the function of beta cell.[122–126] As previously mentioned, the results of Steppan et al[27] indicated that administration of resistin to mice caused glucose intolerance and that resistin neutralization enhanced insulin action. Based on the results of Steppańs study, other researchers suggested that resistin is probably expressed in pancreatic beta cells. For the first time, Minn et al[127] demonstrated that resistin is expressed in Langerhans islets and up-regulated in IR condition. Considering resistin expression in normal human pancreatic islets it seems that this protein plays a main role in islet function. In addition, islet resistin expression was increased in animal models of IR. In other study, Nakata et al[128] presented that resistin prompts IR in pancreatic beta cell through the induction of SOCS-3 expression and impairing insulin secretion induced by glucose. Pham et al[129] investigated the relationship of some adipokines with beta cell function in patients with type DM1; their findings indicated that the serum levels of resistin associated positively with fasting and stimulated beta-cell function in T1D patients. Brown et al, examined the effects of resistin on insulin secretion, insulin receptor gene expression and beta cell function, and viability in vitro. Their results showed that resistin caused significant decrease in insulin receptor gene expression both at the mRNA and protein level, but did not affect the secretion of insulin. Furthermore, at low concentrations, resistin caused significant increases in the viability of pancreatic beta cell. Their data implicate resistin as a factor that may control beta-cell function and viability.[130]

7 | RESISTIN AND TYPE 2 DIABETES MELLITUS

Since the initial discovery of resistin, numerous studies were performed for determining the effects of this adipocyte secreted hormone on the pathogenesis of DM. As previously mentioned, the skeletal muscle is the major site of glucose uptake induced by insulin. The animal study performed by Palanivel et al[131] showed that treatment of diabetic rats with recombinant resistin caused reduced insulin-stimulated glucose uptake in skeletal muscles and decreased translocation of GLUT-4 following insulin stimulation. They results also indicate that resistin regulates the IRS-1 function by affecting its tyrosine phosphorylation. In another study, researchers investigated the effects of continued exposure of rat skeletal muscle cells to resistin on GLUT-4 translocation and glucose uptake; their results showed that resistin decreased both GLUT-4 translocation and skeletal muscle glucose uptake in response to insulin.[132] Aforementioned studies demonstrated the probable role of resistin on glucose homeostasis in rodents. But in contrast, Way et al[133] indicated that resistin gene expression was considerably reduced in adipose tissue of ob/ob, db/db, tub/tub, and KKAy models of obesity.

One of the key processes in the adjustment of the plasma glucose level is the regulation of hepatic gluconeogenesis and disturbed glucose production in the liver is a central characteristic in T2D.[134] Under normal conditions, hepatic glucose production was inhibited by insulin action and resistin has been shown to decrease the insulin effects by promoting increases in plasma glucose levels. It seems that increasing the rate of gluconeogenesis in the liver is a crucial step of resistin action in patients with T2D.[135] However, some surveyed indicated that resistin did not affect glucose production in rat derived hepatocytes.[136] One of the commonly used anti-diabetic drugs that decrease glucose production in the liver is metformin. In the animal study performed by Fujita et al metformin treatment was reported to improve the worse effects of DM such as hyperglycemia and hyperinsulinemia, but results also surprisingly showed that resistin gene expression at protein level was increased after treatment with metformin.[136]

In genetic knowledge, a polymorphic variant of a gene may lead to the abnormal expression or to the production of an atypical form of the gene product; this condition may be associated with some diseases. One of the proposed factors that affect the level of cytokines and adipocytokines in biological fluids is the presence of functional polymorphism in the promoter and intron regions of their corresponding genes.[137,138] Recently the effects of the resistin gene (*RETN*) polymorphisms on DM have become a focus of interest to researchers. Based on previous studies, up to 70% of the variations in circulating resistin levels by genetic factors and some surveys reported a positive correlation between single nucleotide polymorphisms (SNPs) and plasma resistin levels.[27,139] Hivert et al founded the relation between SNPs in the 3′ region of *RETN* and circulating resistin levels and plasma glucose levels. Based on Cho et al study, the SNP 420C/G in the

promoter region of *RETN* plays a critical role in resistin gene expression and determination of plasma resistin concentration in humans.[140] The most recent study performed by Fawzy et al[141] indicates that SNPs of *RETN* and increased serum resistin levels may be associated with increased IR and consequent susceptibility to T2D in offsprings of DM patients.

It has been showed that resistin could be known as one of main risk factors for T2D patients. Fontana et al[142] indicated that levels of serum resistin could be related with mortality risk in patients with T2D. High levels of resistin could be associated with progression of T2D in various patients.[142] Serum and polymorphism assessments confirmed that resistin could has critical roles in T2D and could be known as important risk factor for this disease.[142,143]

It seems that more assessment of resistin roles in patients with DM could help to understanding of depth insights into pathways involved in pathogenesis of DM and could contribute to better treatment of patients with DM.

8 | MicroRNA AND INSULIN RESISTANCE

MiRNAs are a class of non-coding RNAs which are known as epigenetic regulators.[144–148] These molecules exert their regulatory effects via affecting of a variety of cellular pathways such as MAPK, AKT, apoptosis, TGF-β, VEGF, and STAT.[144,149,150] It has been showed that miRNAs have critical roles in various biological processes such as angiogenesis, metastasis, invasive, growth, differentiation, and apoptosis.[151–154] A large number studies indicated that deregulation of them could lead to initiation and progression of various diseases such as stroke, cancer, cardiovascular diseases, Infammatory diseases, and diabetes.[155–158] Several studies confirmed that miRNAs have critical roles in diabetes pathogenesis.[155,159] They showed that deregulation of a variety of miRNAs including miR-15, miR-21, miR-144, miR-150, and miR-192 could affect on diabetes pathogenesis (Figure 2).[155,159] Hence, identification of various miRNAs could contribute to better understanding of molecular pathways involved in diabetes pathogenesis. Moreover, several studies indicated that miRNAs could be used as diagnostic, prognostic, and therapeutic biomarkers in various diseases such as diabetes.[155,159]

Pancreatic b-cells have critical roles in glucose homeostasis, and releasing insulin in response to glucose levels in the bloodstream.[159] It has been showed that absence or inactivation of b-cells could lead to T1D, or T2D. A large number studies indicated that deregulation of a variety of miRNAs such as miR-15a/b, miR-16, miR-195, miR-503, miR-541, miR-214, miR-9, miR-124a, miR-7, miR-376, and miR-375 could affect on pancreas (and therefore b-cell) development.[159]

It has been showed that deregulation of miRNAs affect on autoimmune destruction of b-cells which could lead to T1D.[159] In a study, Hezova et al[160] assessed the alteration of various miRNAs in regulatory T cells (T-reg cells) in subjects with T1D. Several studies indicated that T-reg has critical roles in autoimmune disease. Their results indicated that miR-191 and miR-342 down regulated and miR-510 up regulated in T-reg cells of patients with diabetic than healthy subjects.[160]

MiR-342 is other important miRNAs which deregulation of it are associated with hematological disease.[161] These findings suggested that these miRNAs via targeting a variety of cellular and molecular pathways involved in autoimmune destruction of b-cells could provide disease condition in patients with T2D. It has been showed, when high levels of glucose are available, miR-375 was down regulated in adult b-cell islets.[162] Down regulation of miR-375 could prompt secretion of insulin via de-repression of its targets such as Mtpn and PDK1.[162–164] Up regulation of miR-375 could decrease proliferation and insulin gene transcription and decrease secretion of glucose-induced insulin.[164]

These findings showed that ectopic expression of miR-375 could lead to increasing of susceptibility to fatty acid which leads to inducing apoptosis in diabetic pancreatic b-cells.[164] These results suggested that miR-375 acts as negative regulatory of cellular growth and proliferation and deregulation of this miRNA could lead to reduction of b-cell mass, low levels of insulin, hyperglycemia, and thus diabetes.[165]

Resistin is known as one of important molecules which are associated with insulin resistance. Hence, identification of cellular and molecular mechanisms related with resistin could contribute to the development of novel therapies for patients with DM. Multiple lines evidence indicated that miRNAs could affect on cellular and molecular mechanisms associated with resistin.[166,167] In a study, Wen et al[166] indicated that miR-145 could be involved in the development of resistin-induced insulin resistance in HepG2 cells. They found that up regulation of miR-145 could inhibit glucose uptake in HepG2 cells via phosphorylation of Akt and IRS-1, and leads to inducing of insulin resistance in hepatocytes. Moreover, their results indicated that p65 has critical roles for the up-regulation of miR-145 by resistin. Chromatin immunoprecipitation (ChIP) showed that p65 bind to the promoter region of miR-145. These findings suggested that miR-145 has important roles in the development of resistin-induced insulin resistance via employing p65 pathway.[166]

In other study, Ying et al[167] found that miR-492 could reverse high glucose-induced insulin resistance in HUVEC cells via affecting on resistin. Their results showed that high glucose stress could affect on miR-492 expression (down regulation) and resistin expression (up regulation). According

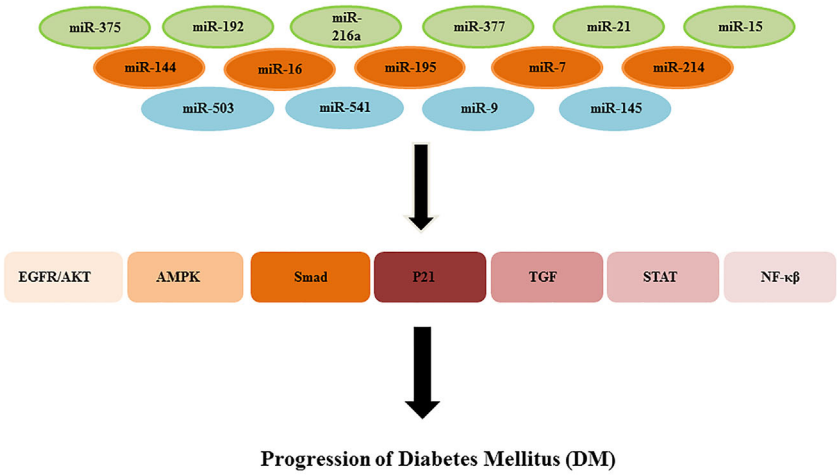

FIGURE 2 Various miRNAs and their cellular and molecular targets involved in DM

to these results, resistin is an important target for miR-492.[167] Up-regulation of miR-492 could decrease endothelial cells migration and lipid accumulation which induced by high glucose stress. It has been showed that up-regulation of some cellular targets such as p-STAT3, SOCS, and P-selectin activation could be induced by high glucose stress via affecting on up-regulation of miR-492. These results suggested that miR-492 could contributes to insulin resistance and endothelial dysfunction induced by high glucose, via down regulation of resistin, which due to STAT3 phosphorylation, SOCS, and P-selectin activation.[167]

Circulating miRNAs are one of important types of miRNAs which could be used as prognostic, diagnostic, and therapeutic biomarkers.[33] Utilization of them are associated with several advantages such as fast detect in body fluids, accessible, and non-invasive.[168] Hence, identification of them

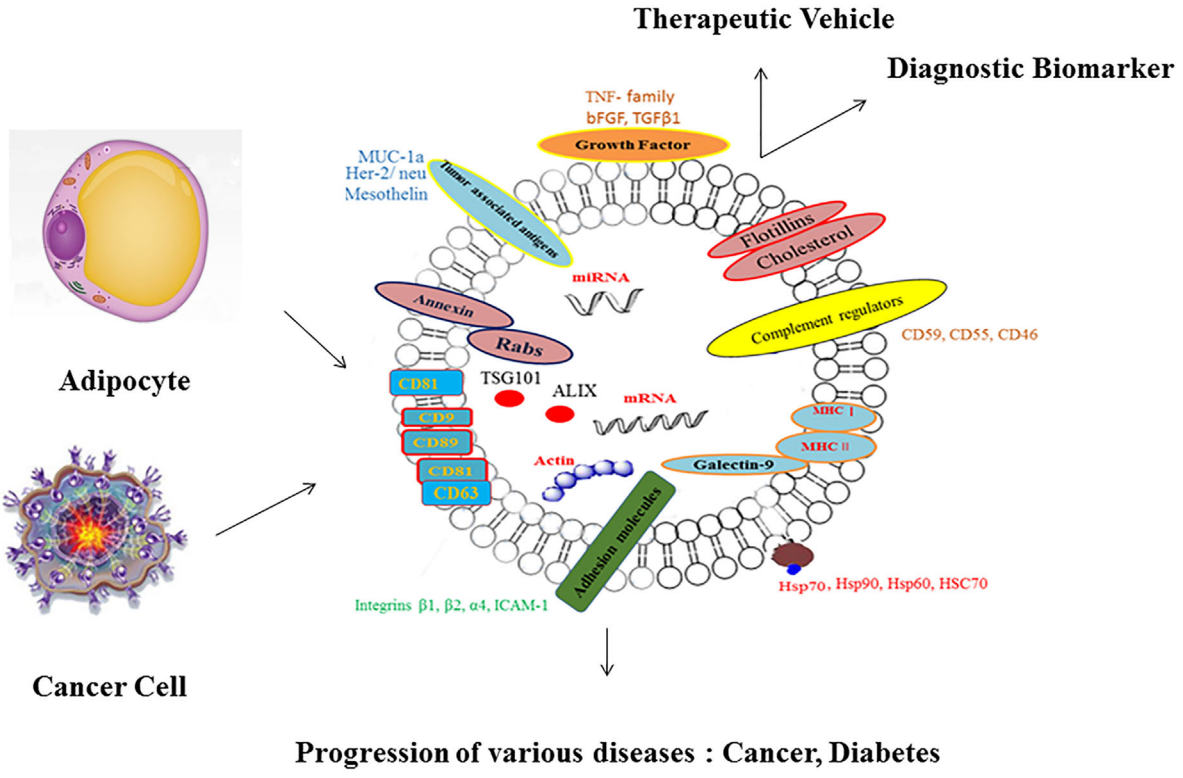

FIGURE 3 A schema of exosome and its cargoes

TABLE 1 Various microRNAs (miRNAs) involved in DM

MicroRNA	Expression in DM	Material	Sample (n)	Citation
miR-463-3p	Up regulation	Pancreatic islets	68	Hou et al[179]
miR-15a	Up regulation	Plasma	119	Wang et al[180]
miR-21	Up regulation	Plasma	119	Wang et al[180]
miR-144	Up regulation	Plasma	119	Wang et al[180]
miR-150	Up regulation	Plasma	119	Wang et al[180]
miR-486-5p	Up regulation	Plasma	119	Wang et al[180]
miR-451a	Up regulation	Serum	96	Ding et al[181]
miR-4534	Up regulation	Serum	96	Ding et al[181]
miR-27a	Up regulation	Whole blood	96	Karolina et al[182]
miR-150	Up regulation	Whole blood	96	Karolina et al[182]
miR-192	Up regulation	Whole blood	96	Karolina et al[182]
miR-320a	Up regulation	Whole blood	96	Karolina et al[182]
miR-375	Up regulation	Whole blood	96	Karolina et al[182]
miR-661	Up regulation	Serum	184	Wang et al[183]
miR-571	Up regulation	Serum	184	Wang et al[183]
miR-770-5p	Up regulation	Serum	184	Wang et al[183]
miR-892b	Up regulation	Serum	184	Wang et al[183]
miR-1303	Up regulation	Serum	184	Wang et al[183]
miR-15a	Up regulation	Serum	184	Wang et al[183]
miR-16	Up regulation	Serum	184	Wang et al[183]
miR-125b	Up regulation	Serum	184	Wang et al[183]
miR-221	Up regulation	Serum	184	Wang et al[183]
miR-17	Up regulation	Whole blood	36	Karolina et al[184]
miR-23a	Up regulation	Whole blood	36	Karolina et al[184]
miR-23b	Up regulation	Whole blood	36	Karolina et al[184]
miR-29b	Up regulation	Whole blood	36	Karolina et al[184]
miR-29c	Up regulation	Whole blood	36	Karolina et al[184]
miR-99b	Up regulation	Whole blood	36	Karolina et al[184]
miR-106b	Up regulation	Whole blood	36	Karolina et al[184]
miR-125a-5p	Up regulation	Whole blood	36	Karolina et al[184]
miR-125b	Up regulation	Whole blood	36	Karolina et al[184]
miR-130a	Up regulation	Whole blood	36	Karolina et al[184]
miR-130b	Up regulation	Whole blood	36	Karolina et al[184]
miR-142-3p	Up regulation	Whole blood	36	Karolina et al[184]
miR-151-3p	Up regulation	Whole blood	36	Karolina et al[184]
miR-151-5p	Up regulation	Whole blood	36	Karolina et al[184]
miR-183	Up regulation	Whole blood	36	Karolina et al[184]
miR-185	Up regulation	Whole blood	36	Karolina et al[184]
miR-190	Up regulation	Whole blood	36	Karolina et al[184]
miR-193a-3p	Up regulation	Whole blood	36	Karolina et al[184]
miR-194	Up regulation	Whole blood	36	Karolina et al[184]
miR-299-3p	Up regulation	Whole blood	36	Karolina et al[184]
miR-335	Up regulation	Whole blood	36	Karolina et al[184]
miR-361-3p	Up regulation	Whole blood	36	Karolina et al[184]

(Continues)

TABLE 1 (Continued)

MicroRNA	Expression in DM	Material	Sample (n)	Citation
miR-375	Up regulation	Whole blood	36	Karolina et al[184]
miR-502-3p	Up regulation	Whole blood	36	Karolina et al[184]
miR-550	Up regulation	Whole blood	36	Karolina et al[184]
miR-550	Up regulation	Whole blood	36	Karolina et al[184]
miR-589	Up regulation	Whole blood	36	Karolina et al[184]
miR-620	Up regulation	Whole blood	36	Karolina et al[184]
miR-629	Up regulation	Whole blood	36	Karolina et al[184]
miR-665	Up regulation	Whole blood	36	Karolina et al[184]
miR-886-5p	Up regulation	Whole blood	36	Karolina et al[184]
miR-1285	Up regulation	Whole blood	36	Karolina et al[184]
miR-1301	Up regulation	Whole blood	36	Karolina et al[184]
miR-30d	Up regulation	Plasma	31	Seyhan et al[185]
miR-34a	Up regulation	Plasma	31	Seyhan et al[185]
miR-21	Up regulation	Plasma	31	Seyhan et al[185]
miR-148a	Up regulation	Plasma	31	Seyhan et al[185]
miR-487b	Down regulation	Islet	49	Kameswaran et al[186]
miR-495	Down regulation	Islet	49	Kameswaran et al[186]
miR −539-3p	Down regulation	Islet	49	Kameswaran et al[186]
miR-655	Down regulation	Islet	49	Kameswaran et al[186]
miR-656	Down regulation	Islet	49	Kameswaran et al[186]
miR-10a,	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-10b	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-15a	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-27b	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-30e	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-95	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-100	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-128	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-133a	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-152	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-154	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-190	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-196a	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-199a-3p	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-199b-5p	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-206	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-208a	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-331-3p	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-342-3p	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-362-3p	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-374a	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-374b	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-378	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-422a	Down regulation	Skeletal muscle	92	Gallagher et al[187]

(Continues)

TABLE 1 (Continued)

MicroRNA	Expression in DM	Material	Sample (n)	Citation
miR-423-3p	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-424	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-455-5p	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-519d	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-768-3p	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-768-5p	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-801	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-126	Down regulation	Skeletal muscle	92	Gallagher et al[187]
miR-21	Down regulation	PBMC	15	Meng et al[188]
miR-27a	Down regulation	PBMC	15	Meng et al[188]
miR-27b	Down regulation	PBMC	15	Meng et al[188]
miR-126	Down regulation	PBMC	15	Meng et al[188]
miR-130a	Down regulation	PBMC	15	Meng et al[188]
miR-23a	Down regulation	Serum	24	Yang et al[189]
let-7i	Down regulation	Serum	24	Yang et al[189]
miR-486	Down regulation	Serum	24	Yang et al[189]
miR-96	Down regulation	Serum	24	Yang et al[189]
miR-186,	Down regulation	Serum	24	Yang et al[189]
miR-191	Down regulation	Serum	24	Yang et al[189]
miR-192	Down regulation	Serum	24	Yang et al[189]
miR-146a	Down regulation	Serum	24	Yang et al[189]

could provide new insights in the prognosis, diagnosis, and therapeutic biomarkers related with DM patients.[168] In a study, Osipova et al[169] assessed the expression levels of circulating miR-21, miR-126, and miR-210 in plasma and urine from pediatric patients with T1D and using of them as new risk factors for pediatric patients with T1D. Their results revealed that levels of miR-21 and miR-210 were significantly up-regulated in the plasma and urine of pediatric patients with T1D, whereas, urinary miR-126 levels were significantly decreased. This data suggested that circulating miRNAs such miR-21, miR-210, and miR-126 could be used as new diagnosis biomarkers for pediatric patients with T1D. These miRNAs might show an early onset of diabetic-associated diseases.[169]

In other study, Yang et al[170] indicated that a variety of serum miRNAs could be employed for monitoring patients with T2D. Their results showed that expression levels of various miRNAs including miR-455-5p, miR-454-3p, miR-144-3p, and miR-96-5p were increased and expression levels of miR-409-3p, miR-665, and miR-766-3p were decreased in patients with T2D. Moreover, they showed that these miRNAs could affect on various pathways involved in T2D pathogenesis. These findings proposed that circulating miRNAs could be applied as new biomarkers in T2D patients.[170]

9 | EXOSOME AND INSULIN RESISTANCE

Exosomes are known as nano-vesicles 30-120 nm in diameter which could be released from many cell types such as stem cells, normal cells, and tumor cells.[39,171] These vehicles could carry various cargos including proteins, lipids, mRNA, and microRNA (Figure 3). It has been showed that exosomes via targeting their cargo in host cell could change behavior of cell.[39,40] Exosome's cargos exert their effects via targeting a sequence of cellular and molecular pathways involved in various physiological events.[39,40] It has been showed that exosomes released from adipocytes could have important roles role in cell-to-cell communication during the development of metabolic diseases such as DM[172,173] (Table 1).

It has been indicated that exosomes released from beta pancreatic cells could be associated with cytokine stimulation.[174] These results suggested that these exosomes could have critical roles in the development or the progression of diabetes via affect on various cellular and molecular targets such as cytokines.[174] DM could decrease the bioavailability of nitric oxide (NO) via regulating endothelial nitric-oxide synthase (eNOS) activity. It has been showed that eNOS could be regulated by various mechanisms including its interaction with heat shock protein 90 (Hsp 90). Likely,

exosomes containing Hsp90 could be considered as an alternative mechanism in the diabetic pathological state.[175] In addition to proteins, miRNAs are other important molecules could be transferred by exosomes. A large number studies that miRNAs anticipate in various molecular mechanisms involved in DM pathogenesis. Hence, targeting of these molecules by exosomes could be considered as other important mechanisms for progression of DM.[176]

In a study, Sheng et al indicated that exosomes contain diabetes auto-antigens such as glutamic acid decarboxylase 65 kDa (GAD65) could induce inflammatory cytokine secretion via targeting MyD88-mediated TLR-signaling pathway which could lead to T-cell proliferation. These findings suggested that these exosomes act as strong players in specific autoimmunity events which could lead to diabetes in susceptible individuals.[177]

Several studies indicated that exosomes could be used as effective diagnostic and therapeutic biomarkers in various diseases such as cancer. Few studies assessed the role of exosomes in DM pathogenesis.

Tramontano et al indicated that endothelial microparticles (EMPs) containing CD31, CD105, and CD106 were increased in DM patients than healthy subjects. These findings suggested that circulating EMPs could be used as diagnostic biomarkers for DM patients.[178]

In other study, Santovito et al[41] assessed exosomal miRNAs as one of important players in the adiponectin pathway in 18 patients with DM. Their results indicated that expressions of four miRNAs were increased whereas expression 21 miRNAs were decreased. Quantitative RT-PCR validation revealed the significant down regulation of let-7a and let-7f levels and up-regulation of miR-326 levels. Moreover, they showed that there was a negative association between circulating miR-326 and its target adiponectin. Their data revealed that levels of miR-326 were unaffected fter 12 months of anti-diabetic treatment, whereas levels of let-7a and let-7f were significantly increased. These data suggested that regulation of circulating miRNAs expression (exosomal miRNAs) could be considered as new targets in DM therapy.

10 | CONCLUSION

DM is known as one of major metabolic disorders which are associated with a variety of Envirmental and gentical factors. Identification of cellular and molecular pathways involved in DM pathogenesis, could contribute to better understanding of disease condition and could provide new therapeutic approaches. Resistin is a hormone which plays critical roles in DM pathogenesis. Unlike the proven role of resistin in rodents, the main function of this hormone in relation to energy balance and IR in DM2 is not consistent in humans. Some surveys have reported enhanced *RETN* expression levels in T2D, IR, obesity, inflammation, and metabolic syndrome, while some studies failed to identify any alteration in circulating resistin levels in aforementioned conditions. Further clinical studies are necessary to clarify the correlation between resistin levels and T2D. MicroRNAs and exosomes are other important molecules involved in DM pathogenesis. These molecules could exert their effects via targeting a sequence of cellular and molecular pathways involved in different stages of DM pathogenesis. Hence, identification of these molecules cold lead to better drawing of cellular and molecular targets involved in DM. Moreover, numerous studies indicated that miRNAs and exosomes could be used as powerful diagnostic and therapeutic biomarkers in DM therapy.

ORCID

Hamed Mirzaei http://orcid.org/0000-0002-9399-8281

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