Scientific Research Publishing

Journal of Biosciences and Medicines, 2022, 10, 1-11
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Advances in the Study of Exosomal miRNAs in Diabetes and Its Complications

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How to cite this paper: Xiang, F. and Wu, H.Y. (2022) Advances in the Study of Exosomal miRNAs in Diabetes and Its Complications. *Journal of Biosciences and Medicines*, **10**, 1-11.
https://doi.org/10.4236/jbm.2022.1012001

Received: November 3, 2022
Accepted: December 2, 2022
Published: December 5, 2022

Abstract

Diabetes mellitus is a group of metabolism-related diseases characterized by elevated plasma glucose levels, and the course of diabetes mellitus is closely linked to the development of diabetes-related complications, which can be life-threatening due to poor glycemic control. Exosomes are small vesicles that encapsulate intracellular molecules and are composed of a variety of bioactive proteins, lipids and nucleic acids (including microRNAs, lncRNAs, and circ-RNAs), and recent studies have increasingly shown that miRNAs in exosomes are an important mode of intercellular and intertissued communication and play a key role in the development and progression of various diseases. This review presents the progress of the application of exosomal miRNAs in type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and diabetes-related complications.

Keywords

miRNAs, Diabetes, Diabetes-Related Complications, Insulin Resistance, Biomarkers

1. Introduction

Diabetes mellitus is a multifactorial chronic disease characterized by the presence or absence of progressive insulin resistance and elevated blood glucose levels due to relative insulin deficiency [1]. According to the results of the International Diabetes Federation Diabetes Consultation, 9th edition, the global prevalence of diabetes in 2019 is 9.3% (463 million people), and given that nearly 500 million people have diabetes, there is an urgent need to develop and implement multisectoral strategies to address diabetes. Without urgent and adequate action, 579 million people are expected to have diabetes in 2030, a figure that will increase by 51% (700 million) by 2045 [2]. And on December 6, 2021, the Interna-

tional Diabetes Federation (IDF) officially released the 10th edition of the Global Diabetes Map, in which the core content indicates that in 2021, 537 million (10.5%) adults aged 20 - 79 will have diabetes - 1 in 10 people. The total number of people with diabetes is projected to increase to 643 million (11.3%) by 2030 and to 783 million (12.2%) by 2045 [3]. In recent decades, almost all regions of the world have shown a significant increase in the prevalence of diabetes. Diabetic complications are diseases secondary to diabetes. Diabetic complications can involve all organ systems of the body, including cardiovascular, brain, kidney, nerve, retina, skin and extremities, and can result in serious disabling and even life-threatening complications such as myocardial infarction, cerebrovascular disease, renal failure, ketoacidosis, and non-ketotic hyperosmolar coma. The increase in the number of people with diabetes or the prolongation of the duration of diabetes may change the disease status of many populations worldwide, and as the base of people with diabetes increases year by year, the incidence of diabetes-related complications also increases year by year [4]. Diabetes is one of the top 10 causes of death among adults, causing an estimated 4 million deaths worldwide in 2017, and global health expenditures for diabetes were estimated at $727 billion in 2017 [5]. Macrovascular complications of diabetes, including coronary heart disease, stroke and peripheral vascular disease, microvascular complications, such as end-stage renal disease (ESRD), retinopathy and neuropathy, and lower extremity amputation (LEA), are the leading causes of diabetes-related burden.

Exosomes are small extracellular vesicles of 50 - 150 nm in diameter, which originate in the late endonuclear pathway and are secreted in the extracellular space when the multivesicular vesicles fuse with the plasma membrane [6]. It is a small extracellular vesicle of 50 - 150 nm in diameter, which is secreted in the extracellular space when the multivesicular vesicles fuse with the plasma membrane. Many studies have shown that all cell types in the human body can secrete exosomes [7]. It has been shown that exosomes are naturally present in body fluids. In addition, there is also growing evidence that exosomes are an important mode of intercellular and intertissued communication [8] [9]. For example, bone marrow mesenchymal stromal cells are a major source of cellular and tissue communication. For example, bone marrow MSC-derived exosomes regulate aging-related insulin resistance [10]. Exosomes from human umbilical cord MSCs can alleviate type 2 diabetes by reversing peripheral insulin resistance and reducing cell destruction [11]. Adipocyte-derived microRNA-34a exosomes inhibit the polarization of M2 macrophages and promote obesity-induced adipose inflammation [12]. The exosomes of cardiomyocyte origin can directly transfer excess proteins and glycolytic enzymes to endothelial cells and thus regulate glucose transport [13] etc. Thus, it is clear that exosomes do play an important role in regulating body metabolism and signaling.

2. Exosomal miRNAs and Type 1 Diabetes Mellitus (T1DM)

Type 1 diabetes mellitus (T1DM), one of the types of diabetes, is a complex au-

toimmune disease that primarily affects children and adolescents [14]. Elevated blood glucose levels in patients with T1DM result from absolute insulin deficiency and lead to hyperglycemia and life-threatening diabetic complications [15]. Although much research has been conducted on the pathogenesis of this type one diabetes mellitus (T1DM), its exact pathogenesis remains unclear. There is growing evidence that small extracellular vesicles, exosomes, are involved in intercellular communication and regulate interorgan dialogue, thereby regulating various metabolisms in the body [8] [9]. Exosomes are extracellular nanoparticles secreted by cells, containing proteins, lipids and nucleic acids (miRNA, lncRNA, circRNA, etc.) bioactive molecules [16]. More importantly, many studies have shown that exosomes and their cargo—proteins, lipids and nucleic acids (miRNA, lncRNA, circRNA, etc.) bioactive molecules are associated with the development of T1DM, and miRNA (microRNA) among the different components of exosomes have attracted special attention [17]—miRNAs, one of the main substances transported by exosomes, are abundant small noncoding RNAs (19 - 22 nucleotides in length), which are key post-transcriptional regulators of gene expression and can be transferred to recipient cells in an active form via exosomes [18] [19] [20] [21]. They play a key role in many biological processes by binding to target molecules, inducing their degradation or inhibiting translation [22]. It is now well understood that miRNAs play a key role in many biological processes by binding to target molecules, inducing their degradation or inhibiting translation. It is now well known that miRNAs are secreted by cells and can be delivered to recipient cells as endogenous miRNAs. Although miRNAs are rapidly degraded by ribonucleases in plasma, miRNAs encapsulated by extracellular vesicles are highly stable in circulation [23]. MiRNAs play an important role in the regulation of pancreatic β-cell activity. Indeed, they are involved in β-cell differentiation and functional maturation and regulate insulin secretion and cell survival [24] [25]. Dysregulation of miRNAs expression is associated with the development of T1D and T2D and with an age-related decrease in β-cell proliferation [26] [27]. In addition, in rodent and human islets, some miRNAs such as miR-23a-3p, miR-23b-3p and miR-149-5p were found to regulate the expression of the pro-BH3-only proteins DP5 and PUMA in human pancreatic β-cells, thereby inducing β-cell dysfunction and death under inflammatory conditions [28]; T-lymphocyte-derived exosomal miRNAs, in type 1 diabetes mellitus (T1DM), can cause pancreatic β-cell apoptosis [29]. In recent years, some exosomal miRNAs have also been found to be differentially expressed in T1DM patients through studies [30], it was also found that in the plasma-derived exosomal mRNA expression profile of T1DM patients, a total of 112 plasma-derived exosomal miRNAs were detected, of which 66 miRNA expressions were upregulated and 46 miRNA expressions were downregulated [31]. In addition, it has been shown that plasma exosome-rich extracellular vesicles from lactating mothers with type 1 diabetes contain abnormal levels of miRNAs postpartum. Real-time qPCR validation confirmed that compared

with lactating healthy mothers, hsa-miR-146a-5p, hsa-miR-26a-5p, hsa-miR-24-3p and hsa-miR-30d-5p were significantly upregulated in lactating mothers with type 1 diabetes [32]. Overall, the above research evidence suggests that exosomal miRNAs are increasingly associated with the formation and progression of type 1 diabetes mellitus (T1DM). However, there is a lack of diagnostic and therapeutic measures for early prevention, early diagnosis and early treatment of type 1 diabetes mellitus (T1DM) in clinical practice. In recent years, the emergence of a new research hotspot—exosomal miRNAs—has provided a new possibility for early prevention of type 1 diabetes mellitus (T1DM) through early screening of differentially expressed miRNAs in exosomes to identify high-risk groups, and exosomal miRNAs play an important role in regulating pancreatic β-cell activity, which provides a new opportunity to target type 1 diabetes mellitus (T1DM) patients for early prevention. This provides a new guiding direction for the restoration of targeted therapies to regulate islet β-cell activity, modulate islet β-cell activity, and prevent islet β-cell apoptosis in patients with type 1 diabetes mellitus (T1DM).

3. Exosomal miRNA and Type 2 Diabetes (T2DM)

Type 2 diabetes mellitus (T2DM) is a metabolic chronic disease characterized by insulin resistance and elevated blood glucose levels [1]. Type 2 diabetes mellitus (T2DM) has the highest prevalence and incidence of all diabetes cases, is a complex disease with a rising global prevalence, and is rapidly increasing worldwide [5]. Type 2 diabetes mellitus (T2DM) is a multifactorial disease with genetic, environmental, and obesity correlates. Obesity is one of the prevalent and predisposing factors of type 2 diabetes mellitus (T2DM) and is a major influence on global health and economic burden. And in recent years, it has been shown that insulin resistance is a common feature of obesity and type 2 diabetes, and type 2 diabetes mellitus (T2DM) is closely related to obesity [2] [33] [34] [35]. Adipose tissue is considered to be a dynamic endocrine organ that regulates the energy balance of the entire body by releasing a variety of hormones that regulate glucose and lipid metabolism [36]. In addition, adipose tissue is a dynamic endocrine organ. In addition, adipose tissue is an important source of exosomes, especially exosomal miRNAs, which can regulate gene expression in distant tissues such as the liver [37]. In recent years, more and more experimental studies have shown that exosomes and their carriers (proteins, mRNAs and microRNAs) contribute to the alteration of crosstalk between skeletal muscle, liver and adipose tissue during the development of insulin resistance and that miRNAs, which are non-coding RNAs, play a key role in regulating glucose metabolism and tissue cell insulin resistance in the body. Studies have shown that exosomal miRNAs derived from adipose tissue macrophages can regulate insulin sensitivity in vivo and *in vitro* [38]. Recently, it was reported that adipose tissue endothelial cells produce large amounts of exosomes in response to glucagon, and this study confirmed the importance of exosome-mediated intra-adipose and

inter-organ communication in energy metabolism [39]. The liver is also a dynamic endocrine organ that secretes a variety of proteins, nucleic acids [40] and it plays a key role in many physiological processes, including the regulation of systemic glucose and lipid metabolism [41]. Exosomal miRNAs are produced by a wide range of cells and are inextricably linked to insulin resistance and islet cell autoimmunity. It has been demonstrated that exosomal MiR-29b-3p from bone marrow MSCs can regulate aging-related insulin resistance exosomes, and exosomal MiR-29b-3p released from bone marrow MSCs can be taken up by adipocytes, myocytes and hepatocytes, thus leading to insulin resistance in vivo and *in vitro* [10]. The adipocyte-derived exosome MiR-27a induces skeletal muscle insulin resistance by inhibiting PPARγ [42] [43]. ExosomalmiR-375 prevents high-fat diet-induced insulin resistance and obesity by targeting the aryl hydrocarbon receptor and bacterial tryptophanase (tnaA) genes [44]. In addition, recent studies have shown that exosomal miRNA-351, miR-1249-3p, and miR-26a all play important roles in the regulation of cellular insulin sensitivity, respectively [45] [46] [47]. In conclusion, through the in-depth research on exosomal miRNAs in various fields in recent years, it is easy to find that exosomal miRNAs play a key role in the formation and development of type 2 diabetes mellitus (T2DM).

According to the World Health Organization, the number of adults with diabetes is expected to increase, with the majority of people with diabetes (approximately 90% - 95%) having type 2 diabetes mellitus (T2DM). Type 2 diabetes mellitus (T2DM) is rapidly increasing worldwide, and as the prevalence base increases each year, the type 2 diabetes epidemic requires the development of new treatment and prevention strategies to attenuate this debilitating disease the expansion [48]. It is important to identify individuals at risk for diabetes. Identifying individuals at risk for diabetes is important because early intervention may delay or even prevent the full progression of the disease, and new biomarkers are needed for type 2 diabetes mellitus (T2DM) to identify high-risk individuals in the population for early prevention and early diagnosis [49]. In recent years, a new class of non-coding RNAs, microRNAs (miRNAs), has emerged as important regulators of many biological functions, including cell signaling and the essential maintenance of tissue structure. Exosomal miRNAs are small endogenous noncoding RNAs, and their potential as biomarkers has been extensively studied in recent years because they are stable and easy to quantify [23] [50]. And an increasing number of experimental studies have shown that disruption of miRNA levels not only leads to the development of chronic inflammation in obese diabetic patients, but also to pancreatic ß-cell dysfunction and loss, as well as insulin resistance in metabolic tissues. MiRNA-level disruption seems to be reflected in the patient's serum, which may prove to be diagnostic for patients before clinical manifestations of the disease, thus improving the management of diabetes and its associated management of complications. These metabolites have a significant predictive correlation with T2D

prodromal diabetes, T1D and/or T2D. In contrast, changes in plasma metabolites can be identified by metabolomics techniques and used to identify and analyze T1D and T2D biomarkers. Therefore, the results of metabolomics studies can be used to help develop effective interventions to manage these diseases [51]. Thus, it appears that exosomal miRNAs not only show promise as early biomarkers of disease, but many of them show therapeutic potential, some of which are already in preclinical development [52].

4. Exosomal miRNA and Diabetic Complications

Macrovascular complications of diabetes, including coronary heart disease, stroke, and peripheral vascular disease; microvascular complications, such as end-stage renal disease (ESRD), retinopathy and neuropathy, and lower extremity amputation (LEA), are the leading causes of diabetes-related burden [53]. In recent decades, almost all regions of the world have shown a significant increase in the prevalence of diabetes mellitus [3] [5] [54]. The increase in the number of people with diabetes or the prolonged duration of diabetes may alter the disease status of many populations worldwide, especially due to the high prevalence of diabetes-specific complications such as renal failure and peripheral arterial disease [4]. The epidemiology of other diseases often associated with diabetes, including infections and cardiovascular disease, may also change, with direct implications for quality of life, health service needs, and economic costs. Hypertension and type 2 diabetes are common comorbidities, and people with diabetes develop hypertension twice as often as non-diabetic people. In addition, people with hypertension tend to exhibit insulin resistance and are at greater risk of developing diabetes than normotensive people [55]. Patients with type 2 diabetes mellitus (T2DM) are at high risk for macrovascular complications, and hypertension exacerbates cardiovascular disease, which is the leading cause of morbidity and mortality in diabetes mellitus [56]. The widespread burden of complications in people with diabetes will ultimately be influenced by efforts to prevent diabetes.

In recent years, a new class of non-coding RNA, microRNA (miRNA), has emerged as an important regulator of many biological functions. These functions include cell signaling and the basic maintenance of tissue architecture. Disruptions in miRNA levels not only lead to the development of chronic inflammation in obese diabetic patients, but also to pancreatic ß-cell dysfunction and loss, and insulin resistance in metabolic tissues. These major events set the stage for dysfunction in other tissues, including the retina, kidney, peripheral nerves, heart, and the entire vascular system [57]. Here again, miRNAs are shown to play a decisive role in the development of disease in a range of diabetic complications. Whereas disturbed miRNA levels appear to be reflected in the serum of patients, this may prove to be diagnostic of patients prior to clinical manifestations of the disease, thereby improving the management of diabetes and its associated complications [58]. It has been shown that exosomal miR-320 plays a key role in the

induction of diabetic cardiomyopathy, and this study demonstrates that CD36 (fatty acid translocase) is a key target gene of this miRNA and suggests that induction of CD36 expression is responsible for increased fatty acid uptake, which leads to cardiac lipotoxicity [59]. Among the complications of diabetes, diabetic nephropathy (DKD) remains one of the major causes of shortened life expectancy in diabetic patients, but its pathogenesis is not particularly well understood. However, it has been shown that miR-145 expression is increased in the urine of patients with early diabetic nephropathy and experimental animals with early diabetic nephropathy by experimental assays [60]. However, it has been shown that miR-145 expression is increased in the urine of early diabetic nephropathy patients and early diabetic nephropathy experimental animals. Moreover, in recent years, an in-depth study of exosomal miR-145 has demonstrated that miR-145 does play an important role in the formation and development of diabetic nephropathy [61] [62].

5. Current Problems with the Diabetes and Exosomal miRNA

Diabetes starts with the inability of the pancreas to maintain blood glucose concentrations within the normal physiological range, and there are no clinical indicators used to screen people at risk for early diabetes. It can only be observed through clinical features when the symptoms of diabetes are already in the middle to late stages and the islets have begun to fail or have undergone irreversible damage. In addition to this, there is no clinically validated test to distinguish type 1 from type 2 diabetes. The treatment for type 1 diabetes is relatively single, and there are no effective treatments other than insulin injections. In contrast, exosomal miRNAs have now been shown in various studies to improve cellular tissue insulin resistance, prevent islet cell apoptosis, and differentially expressed in plasma in healthy and diabetic populations. This provides a direction of choice for screening early indicators of people at risk for diabetes, a possible differential diagnosis between type 1 and type 2 diabetes, and a possible new option for a therapeutic approach to type 1 diabetes. At present, although the specific mechanisms of exosomal miRNAs in regulating human glucose metabolism and related pathways are not clear, we believe that their specific mechanisms will be clarified in the future as the related research progresses.

6. Summary and Prospect

The purpose of this review is to demonstrate the potential future use of exosomal miRNAs in the detection of prediabetes and/or staging progression and diabetes patterns and to provide a new therapeutic idea for the clinical treatment of diabetes and related complications.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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