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Review

The emerging roles of extracellular vesicles in diabetes and diabetic complications

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ABSTRACT

Diabetes and diabetic vascular complications are now the leading cause of death in the world. The effects of traditional medical treatment are usually limited and accompanied by many side effects, such as hypoglycemia, obesity, liver and kidney damage, and gastrointestinal adverse reactions. Thus, it is urgent to explore some new strategies for the treatment of patients with diabetes. Recently, extracellular vesicles have received increased attention because of their emerging roles of cell–to–cell communication under physiological and pathological conditions. In addition, because of their abundant existence in almost all body fluids, as well as their plentiful cargos of bioactive proteins and miRNAs they carry, extracellular vesicles have a strong potential for therapeutic and diagnostic applications in many metabolic diseases, such as obesity and insulin resistance. Here, with the aim of providing the basis for the development of new treatments for diabetes, we review current understanding of extracellular vesicles and the critical roles it has played in the onset and progression of diabetes and diabetic complications.

1. Introduction

The umbrella term extracellular vesicles (EVs) is defined as the lipid bilayer vesicles that carry bioactive proteins, lipids, nucleic acids that interact with and modify target cells [1,2]. Almost all cell types release EVs; thus, they are naturally present in all body fluids, such as blood, urine, saliva, ascites, cerebrospinal fluid, and semen [3]. At present, the extracellular vesicles are proposed to be divided into three parts–exosomes, ectosomes and apoptotic bodies–according to their size and biogenesis [4,5]. Recently, interest in extracellular vesicles has exploded with increasing evidence indicating that EVs play an important role in numerous metabolic diseases, such as obesity, diabetes, and cancer [6,7]. In addition, clinical studies have found that the difference in the number of of EVs and their composition might reflect the pathophysiological conditions of their parent tissue; thus, EVs might serve as potential diagnostic and therapeutic agents in these diseases [8–10]. Since exosomes and ectosomes have many features in common and they are the major causes for inducing metabolic changes in target cells, here, the term "EVs" will be used to refer to these two individual classes of vesicles and their mixture.

1.1. Exosomes

First described in the 1980s, exosomes (EXOs) are nanovesicles

Abbreviations: APCs, antigen presenting cells; AT, adipose tissue; ATM-EXOs, adipose tissue macrophages-derived exosomes; DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; DPP4, hepatocytes dipeptidyl peptidase 4; DR, diabetic retinopathy; ELVs, exosome-like vesicles; EMPs, endothelial microparticles; EPC, endothelial progenitor cells; ER, endoplasmic reticulum; EVs, extracellular vesicles; EXOs, exosomes; GAD65, glutamic acid decarboxylase; GLUT4, glucose transporter 4; IA-2, protein tyrosine phosphatase-like molecule IA-2; iEMPs, injured endothelial microparticles; IFN-γ, interferon-γ; IL-6, interleukin-6; ILVs, intraluminal vesicles; iMSCs, islet mesenchymal stem-like cells; IR, insulin resistance; MCP-1, monocyte chemoattractant protein-1; MPs, microparticles; MVs, microvesicles; MVBs, multivesicular bodies; PPARγ, peroxisome proliferator-activated receptors γ; PDR, proliferative diabetic retinopathy; SCs, Schwann cells; TNF-α, tumor necrosis factor α

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(30–100 nm in diameter) with bilayer membranes secreted by sheep reticulocytes during differentiation [11]. Exosomes are intraluminal vesicles (ILVs) formed by the inward budding of endosomal membrane to parcel up selective proteins, lipids, and nucleic acids [12]. When endosomes contain a large number of ILVs–also called multivesicular bodies (MVBs)–some of them will fuse with the plasma membrane and secret exosomes extracellularly [13,14].

1.2. Ectosomes

The terminology of ectosomes is derived from the definition of ectocytosis, introduced in 1991 by Stein and Luzio to depict the vesicles shedding from the plasma membrane of stimulated neutrophils [15]. Ectosomes–also known as microvesicles (MVs), exosome–like vesicles (ELVs) and microparticles (MPs)–are small bilayer membrane vesicles ranging from 100 to 1000 nm in diameter; they can be released by several types of cells, including endotheliocytes, platelets, and monocytes. In contrast with exosomes, ectosomes are formed by outward budding of small plasma membrane domains to wrap special cargos with the assistance of endosomal sorting complex required for transport (ESCRT), and then they are shed from the cell surface [16,17].

Despite differences in their size and generation mechanism, the two classes of EVs have similar functions after releasing (Table 1). Generally, the internalization of EVs by recipient cells occurs mainly through three methods: direct fusion with plasma membranes, ligand–receptor binding, or the endocytic pathway [18]. Once EVs are translated into target cells, such bioactive cargos (mRNA, miRNA, and proteins) as those EVs carried will extensively regulate important metabolic processes, including inflammation and glucose and lipid metabolism. It has been reported, for example, that EVs are released by hepatocytes in response to lipotoxic signals that contribute to local macrophage activation, inflammation and fibrosis [19]. In addition, adipose–derived EVs may modulate insulin–signaling pathways in skeletal muscle and hepatocytes, contributing to obesity associated systemic insulin resistance [20,21]. Thus, given the massive facts that EVs involve in the development of numerous metabolic diseases, as well as the published article which focused on the roles EVs played in the development and treatment of diabetes [22], we will review here the different mechanisms involved in EVs–mediated diabetes and diabetic complications. In doing so, we hope to lay the groundwork for future research and development of EVs in the treatment of diabetes, cancer, obesity, and other metabolic diseases.

2. EVs in type 1 diabetes

Type 1 diabetes is a T cell–mediated autoimmune disease characterized by the destruction of pancreatic beta cells that lead to insulin deficiency. Type 1 diabetes results from a complicated interaction between genetic and environmental factors. However, the initial trigger for autoimmune processes in type 1 diabetes remains unclear. Lymphocyte infiltration of the islets has been recognized as the onset of type 1 diabetes [24]. Recently, it was found that there are other abnormalities that arise in non–obese diabetic mice before the lymphocyte infiltration, such as upregulated inflammatory cytokines in the pancreatic islet [25] and increased endoplasmic reticulum (ER) stress [26] in beta cells. Normally, the islet mesenchymal stem–like cells (iMSCs) are located at the periphery of normal islets but permeate into beta cell areas when insulitis occurs. In addition, iMSCs can release highly immunostimulatory exosomes that are able to activate T and B cells to produce numerous cytokines, including interleukin-6 (IL-6), interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) through a TLR4/MyD88mediated pathway [27]. These inflammatory cytokines are highly irritating to beta cells, which can induce cellular endoplasmic reticulum (ER) stress [28]. Thus, EVs that contain large amounts of intracellular autoantigens, including the 65 kDa isoform of glutamic acid decarboxylase (GAD65) and the protein tyrosine phosphatase-like molecule IA-2, are secreted by beta cells [29]. Once the intracellular autoantigens are recognized and taken up by the antigen presenting cells (APCs), self–reactive T cells are activated and beta cell destruction follows (Fig. 1).

Moreover, recent studies have found that infiltrative T lymphocytes can directly induce beta cells apoptosis by secreting exosomal microRNAs (miR-142-3p, miR-142-5p, miR-155) and increase the production of beta cells chemokines, which can promote the recruitment of immune cells to destroy beta cells [28,30]. However, it is still unclear what induces the iMSCs to permeate the beta cell area and how iMSCs–derived EVs interact with and activate different lymphocytes to mediate beta cell death. Clearly, further studies are needed to clarify the roles that exosomes play in the development of type 1 diabetes.

3. EVs in type 2 diabetes

Type 2 diabetes results from a progressive defect in insulin production and insensitive response of the body to insulin (also termed insulin resistance, IR). Type 2 diabetes is the most common type of diabetes, and it accounts for 90–95% of all cases of diabetes [31]. Type 2 diabetes is a complex metabolic disorder caused by multiple pathogenic factors, but the mechanisms are not completely understood. Recent studies found that inadequate blood provision to hypertrophic adipose tissue, [32] as well as the obesity–induced overexpression of hepatocytes dipeptidyl peptidase 4 (DPP4) [33] corporately induces the formation of a chronic low–grade inflammation in adipose tissue (AT) [34,35]. This leads to the induction of more inflammatory cells infiltrating AT and the secretion of numerous inflammatory cytokines, such as TNF-α and IL-6 [36]. Some earlier studies suggested that those cytokines could directly block insulin action in adipocytes, hepatocytes and muscle cells, thereby, leading to systemic insulin resistance [37,38]. However, anti–TNF-α antibody therapies have not obtained a satisfactory result in recovering the insulin sensibility [39,40], suggesting there may be other mechanisms implicated in the development of insulin resistance.

Recently, adipose tissue macrophages–derived exosomes (ATM-EXOs) were found to represent a new mechanism in modulating insulin signaling. It was discovered that injection of ATM-EXOs isolated from obese mice caused lean mice to develop cellular and systemic insulin resistance and glucose intolerance. Conversely, great improvements of these disorders were observed in obese mice who were injected with ATM-EXOs that were isolated from lean mice [20]. Further analyses of ATM-EXOs composition with RNA sequencing found that among the dozens of differentially expressed miRNAs within lean and obese ATM-

Table 1
Comparison of exosomes and ectosomes.

Characteristic	Exosomes	Ectosomes
Origin	Storing in late endosomes as ILVs before fusing with the plasma membrane [3]	Outward budding of small plasma membrane domains [5]
Diameter	30–100 nm [4]	100–1000 nm [14]
Membrane markers	CD63, CD9, CD81, flotillin-1, ESCRT-3, TSG-101, HSP70, HSP90, Rab5a/b [2]	flotillin-2, selections, β1 integrins, annexin V, CD40, caveolin [4]
Compositions	Cholesterol, miRNAs, mRNAs, Ceramide, proteins [12]	Cholesterol, miRNAs, proteins, Phosphatidyserine, mRNAs [17]
Extraction methods	Ultracentrifugation, Immunomagnetic bead separation, Density gradient centrifugation, Kit extraction, acoustofluidics technology [23] (the integration of acoustics and microfluidics)	

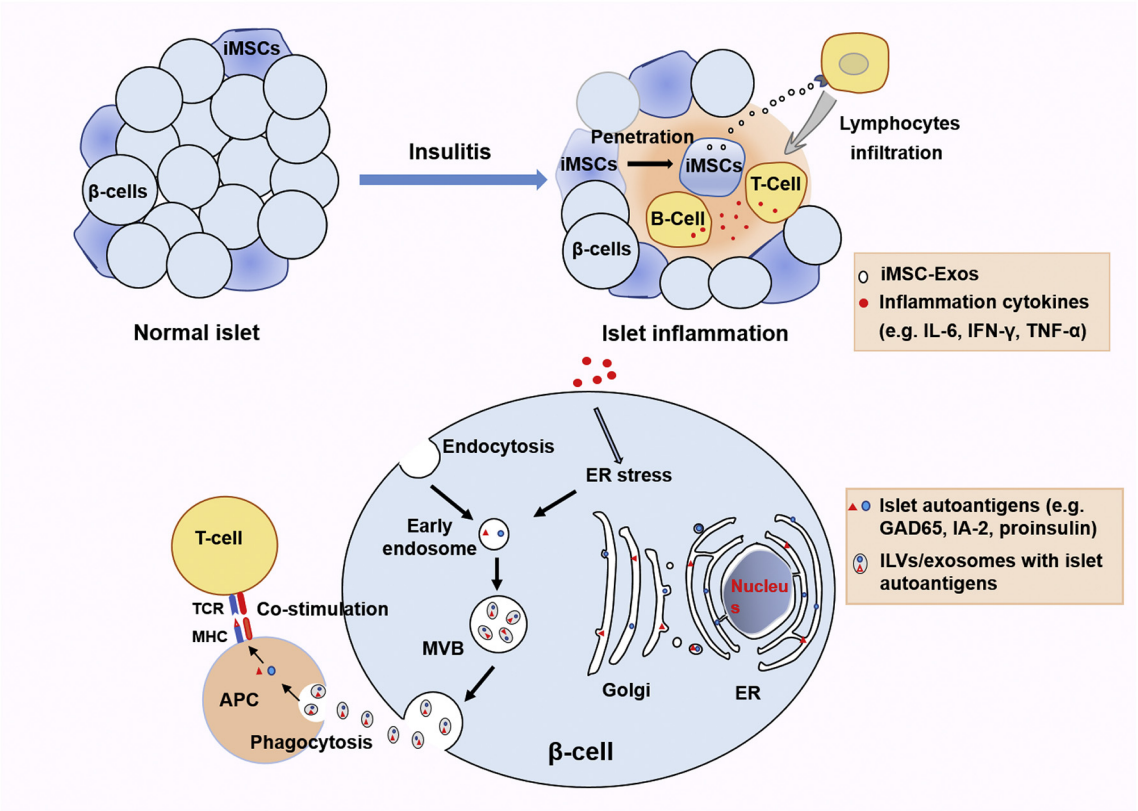

Fig. 1. The initial events of Type 1 diabetes. Islet mesenchymal stem-like cells (iMSCs) invade the central beta cell area from the periphery of normal islets and release exosomes to activate lymphocytes to generate inflammatory cytokines, such as IL-6, IFN-γ and TNF-α, which can induce the ER stress of beta cells. ER stress stimulates the production of ILVs/exosomes loaded with beta cell autoantigens (e.g., GAD65, IA-2), which can be taken up by APCs and presented to self-reactive T cells to cause beta cell destruction.

EXOs, the enrichment of miR-155 in obese ATM-EXOs was identified as the cause that induced these disorders. It has been shown that miR-155 can directly inhibit the expression of peroxisome proliferator–activated receptors γ (PPARγ) [41] and its downstream target genes, such as glucose transporter 4 (GLUT4) [42]. These genes are related to the differentiation and maturation of adipocytes [43] and insulin-stimulated glucose uptake [44], respectively, and there repression could directly affect cellular glucose uptake and insulin sensitivity, especially in the liver, adipose tissue, and skeletal muscle (Fig. 2). However, it is inappropriate to assert that miR-155 is the only explanation for insulin resistance in lean mice treated with obese ATM-EXOs, since there are still a number of differentially expressed miRNAs as well as protein cargos within these ATM-EXOs that may also influence cellular metabolism.

In addition, Jalabert et al. recently found a beneficial effect of exosome-like vesicles (ELVs) derived from high palmitate diet (HPD) induced obese mice on type 2 diabetes. Data from their work showed that muscle ELVs can induce beta cell proliferation, which may promote adaptations of beta cell mass during insulin resistance [45]. Interestingly, there are no answers to the question of whether EVs derived from other insulin–responsive tissues, like adipose tissue and liver, also have this proliferative effect and and somehow delay or prevent the progression of type 2 diabetes before the pancreatic islet fully loss its compensatory roles. Clearly, further studies are needed to uncover the full extents of roles that EVs play in type 2 diabetes.

4. EVs in diabetic vascular complications

Generally, diabetic vascular diseases involve macrovascular (coronary artery disease, peripheral arterial disease, and cerebrovascular disease) and microvascular (nephropathy, retinopathy, and neuropathy) complications [46,47]. Common risk factors for diabetic micro–/macrovascular complications include hyperglycemia, hyperinsulinemia, hypertension, inflammation, dyslipidemia, and blood hypercoagulability [48,49]. Recently, a large number of studies have shown that EVs might contribute to the development of diabetic–related vascular disease through their procoagulant, proinflammatory and proangiogenic properties [50–52]. In the following sections, we will focus on the relationship between EVs and diabetic vascular diseases.

4.1. Diabetic macrovascular complications

Diabetes is a generally accepted risk factor for inducing and accelerating atherosclerosis in large and moderate arteries, especially in coronary and cerebral arteries. Generally, the endothelial dysfunction is considered to be an initial event of diabetic macrovascular complications [53,54]. Recent studies show that EVs engage in the processes of endothelial damage.

MicroRNA-126, which was thought to be an important post-transcriptional regulator in the control of proliferation and migration of endothelial progenitor cells (EPC) into the injured vascular endothelium, was significantly declined in circulating microparticles isolated from diabetic patients [55,56]. Moreover, researchers found that injured endothelial microparticles (iEMPs) isolated from diseased vascular walls were highly detrimental to murine endothelium, compared to healthy endothelial microparticles (EMPs). Further investigation found that NADPH oxidase activity was increasingly upregulated in iEMPs, which could increase the production of ROS in normal endothelial cells and thus induce endothelial apoptosis in an ROS–dependent activation of ASK1–JNK/p38 pathways [57]. It was also reported that foam cell–derived microparticles, which were associated

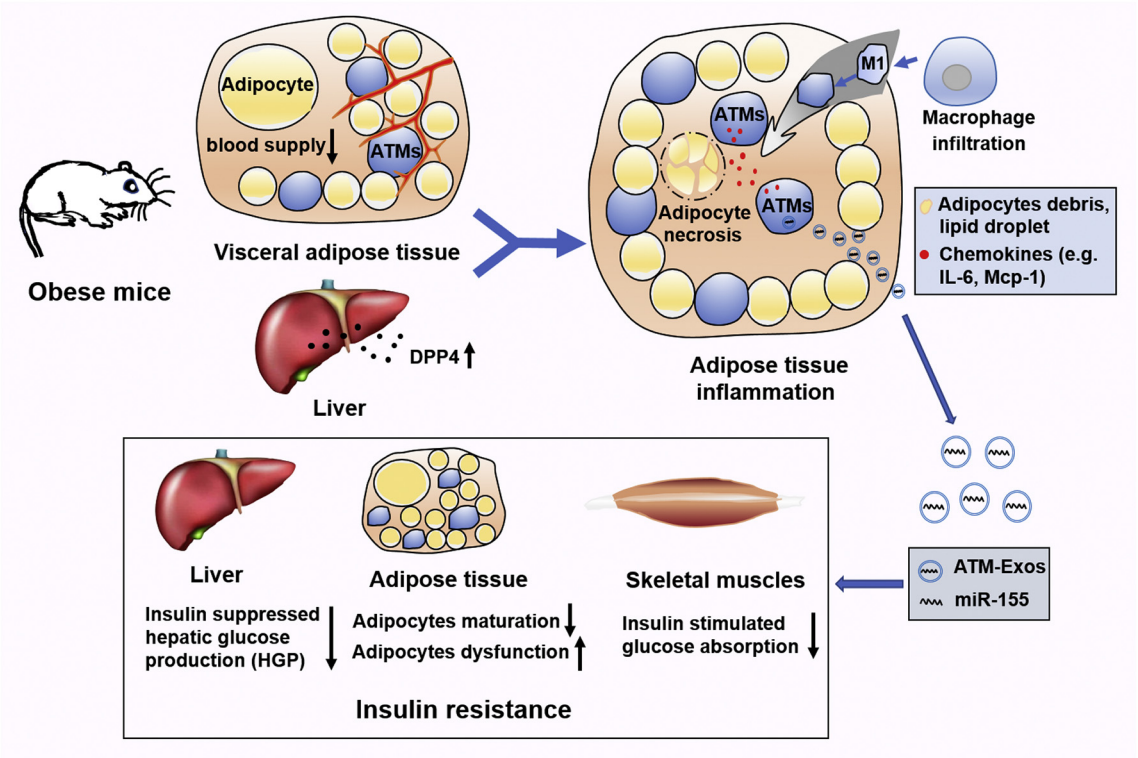

Fig. 2. The crosstalk between obesity and insulin assistance. Obesity induce overexpression of liver DPP4 and relatively insufficient blood supply in adipose tissue, which could directly inflame ATMs by acting with plasma factor Xa and induce the hypoxia and necrosis of adipocytes, respectively, thereby, promoting the formation of adipose tissue inflammation and inducing marked macrophages infiltration into AT. Those ATMs could release enormous exosomes loaded with miR-155, which could cause cellular and systemic insulin resistance by suppressing its target gene, PPARγ, particularly in the liver, adipose tissue, and skeletal muscles.

with the instability of arterial plaques, might serve as a potential biomarker for acute myocardial infarction (MI) and stroke [58,59]. Other studies showed that the accumulation of cholesterol in human monocyte/macrophage cells increased the generation of tissue factor (TF) positive microparticles, which have a high procoagulant activity and might contribute to the formation of artery thrombosis [60].

Collectively, these studies indicate that circulating microparticles might be potential pathogenic factors that cause endothelial dysfunction and vascular diseases; therefore, MPs might serve as biomarkers and potential therapeutic targets for diabetic macrovascular complications.

4.2. Diabetic microvascular complications

4.2.1. Nephropathy

Diabetic nephropathy (DN) is one of the most common complications of diabetes. DN is also the major cause of end–stage renal failure, and nearly one in three people with diabetes have chronic kidney disease [61,62]. The number of patients with diabetes–related chronic kidney disease has significantly increased with the global epidemics of obesity and diabetes [63]. The major pathological alterations of DN are mesangial matrix expansion and glomerular basement membrane thickening caused by excessive deposition of extracellular matrix in glomerular, tubulointerstitial, and vascular spaces, which result in glomerulosclerosis, tubulointerstitial fibrosis, and vascular remodeling, respectively. As the disease progresses, it will eventually lead to a complete loss of kidney function.

Recently, EVs have received extensive attention in DN pathogenesis because of their protective or deleterious effects on renal function. On one hand, it was found that MPs isolated from monocytes and endothelial cells could induce an inflammatory phenotype in podocytes and accelerate their apoptosis, which might lead to the development of proteinuria [64]. On the other hand, the EXOs secreted by mesenchymal stem cells was found to have an anti–inflammatory property, which might have a potential renal–protective effect [65]. Moreover, it was reported that the exosomes isolated from urine–derived stem cells could reduce the loss of nephrons in diabetic rats because of the cargos they carry, such as growth factor, transforming growth factor-β1, bone morphogenetic protein-7 and angiogenin, which could increase glomerular endothelial cell proliferation and promote vascular regeneration [66]. In addition, urinary exosomes have attracted the attention of nephrologists because nearly all nephrons can secret miRNA–containing EVs, which might serve as potential non–invasive biomarkers to reflect renal function and damage [67,68].

4.2.2. Retinopathy

Diabetic retinopathy (DR) is the primary cause for blindness in adult populations, especially in developed countries [69]. DR is characterized by excessive proliferation of endothelial cells in the retina, leading to proliferative diabetic retinopathy (PDR) and the impairment of retinal vascular function. The increase of retinal vascular permeability results in the exuding of fluid and lipids into the retina and yellowish–white areas, if continued, this can lead to blindness. Previous studies have found a positive correlation between the monocyte/platelet–derived microvesicles (MVs) and the progression of diabetic retinopathy, especially in patients with retinal vascular occlusion [70,71]. These MVs can stimulate the coagulation cascade in retinal vessels and thus aggravate microvascular damage [71]. In addition, it was reported that vitreous MVs may accelerate the progress of PDR by stimulating endothelial proliferation and promoting angiogenesis [72]. Therefore, MVs may have pathogenic roles in the progression and development of retinopathy through their pro-angiogenic and pro-endothelial effects.

4.2.3. Neuropathy

Seeing as more than 50% of subjects suffer from diabetic peripheral

neuropathy (DPN), this long-standing disease is clearly the most common complications of diabetes [73]. Generally, long–term hyperglycemic exposure is considered to be the primary cause of DPN, with other risk factors such as hexosamine, inflammation, anoxia, and ischemia also taken into consideration [74]. However, clinical trials targeting these factors have been unsatisfactory [75], suggesting that there may be other mechanisms that lead to the development of DPN. In an early protocol, researchers found that exosomes derived from healthy Schwann cells (SCs) promoted regeneration of injured peripheral axons [76]. Until recently, it was believed that HG–stimulated SC-EXOs could be internalized by distal axons of dorsal root ganglia neurons and suppress axonal growth, which might partially explain the formation of diabetic neuropathy [77]. However, at present, studies on EVs and diabetic neuropathy are considerably limited. It is uncertain whether EVs derived from other sources participate collectively in the pathogenesis of DPN, or whether healthy SC-EXOs have an improving effect on DPN. Therefore, more studies are needed to explore the correlation of EVs with DPN formation.

5. Applied prospect of EVs as biological tools for diagnosis and therapy

Today, about 451 million people around the world suffer from diabetes, and the figure is estimated to increase to 693 million by the year 2045 as a result of the worldwide prevalence of obesity [63]. Great expenditures of time and money, as well as resources, both human and material, are put toward preventing and curing diabetes and diabetic complications every year. However, With the gradual deepening studies on EVs, researchers have found some new and promising characteristics of EVs in clinical applications.

In the field of oncotherapy, EVs developed as vehicles for drug delivery have made great progress in inhibiting tumor growth and reducing the side effects of drugs [8,78]. It was reported that by taking advantage of the RNA ligand for specific targeting and extracellular vesicles for efficient membrane fusion, the resulting ligand-displaying extracellular vesicles were able to deliver siRNAs to cancer cells, which efficiently ihibited the growth of patient–derived colorectal, breast, and colorectal cancer xenograft in mouse models [8]. Regarding diabetes, researchers have developed highly efficient nanovesicle drug delivery vectors for patients with diabetic mellitus, aiming at packaging insulin into nanovesicles, which can be taken orally, without daily insulin injection [79]. Also, studies with rats have shown that the therapeutic effect of certain liposomal formulations loaded with insulin is better than traditional insulin injections [79]. Moreover, with the appearance of a newly developed product, named as “aptamer-conjugated extracellular nanovesicles”, the dilemma of EVs in future applications and clinical translations limited by low yield and inadequate targeting effects will soon be solved. As researchers have reported, this new product was generated by mechanically extruding donor cells labeled with aptamers; thus, a large number of targeted EVs could be conveniently acquired within one hour [78]. The quantitative production of targeted EVs will hopefully take the clinical applications of EVs a step further.

EVs also occupy an important place in the field of liquid biopsy [80]. With the protection of the lipid bilayer membrane, biomarkers such as miRNAs and proteins can be preserved more steadily in EVs, which makes EVs a potential liquid biopsy source in several diseases, including diabetes and diabetic complications, inflammation and ischemic diseases [81,82] However, given the non–negligible defects in current technologies for isolating EVs–lack in purity, low extraction rate, and time-consuming [4,5]–there is still a long way to go before EVs can be diagnostically applied in a wider range. Encouragingly, it was reported that a new separation method based on acoustofluidics was able to effectively isolate exosomes from blood. This acoustofluidic platform works in two steps: cell–removal model and exosome–separation model. Through the integration of acoustics and microfluidics, exosomes with high purity and yield can be isolated in a non–contact, non–damaging, and rapid method [23]. This is good news for the application of EVs in health monitoring, medical diagnosis, and personalized medicine.

6. Conclusion

In summary, EVs play important roles in the onset and progression of diabetes and diabetic complications. As EVs are natural means of transportation that generate by all kinds of cells, they can be absorbed by their target tissues in a safer and more moderate way than common drug deliveries. It is worth nothing that EVs themselves are not pathogenic for these diseases; it is the different miRNAs and proteins that EVs carry that endow them with bad or good effects. Thus, we should make good use of their special properties and apply EVs in clinic in a wider range as soon as possible.

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Declaration of Competing Interest

All authors declare that no conflict of interest exists.

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