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REVIEW

Peripheral origin exosomal microRNAs aggravate glymphatic system dysfunction in diabetic cognitive impairment

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Abstract Cognitive dysfunction is one of the common central nervous systems (CNS) complications of diabetes mellitus, which seriously affects the quality of life of patients and results in a huge economic burden. The glymphatic system dysfunction mediated by aquaporin-4 (AQP4) loss or redistribution in perivascular astrocyte endfeet plays a crucial role in diabetes-induced cognitive impairment (DCI). However, the mechanism of AQP4 loss or redistribution in the diabetic states remains unclear. Accumulating evidence suggests that peripheral insulin resistance target tissues and CNS communication affect brain homeostasis and that exosomal miRNAs are key mediators. Glucose and lipid metabolism disorder is an important pathological feature of diabetes mellitus, and skeletal muscle, liver and adipose tissue are the key target insulin resistance organs. In this review, the changes in exosomal miRNAs induced by peripheral metabolism disorders in diabetes mellitus were systematically reviewed. We focused on exosomal miRNAs that could induce low AQP4 expression and redistribution in perivascular astrocyte endfeet, which could provide an interorgan communication pathway to illustrate the pathogenesis of DCI.

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Furthermore, the mechanisms of exosome secretion from peripheral insulin resistance target tissue and absorption to the CNS were summarized, which will be beneficial for proposing novel and feasible strategies to optimize DCI prevention and/or treatment in diabetic patients.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by persistent hyperglycemia and insulin resistance. Due to the advancement of modern medical science, herbal medicine and chemical drugs are well developed[1], and glycolipid metabolism and macrovascular lesions are well controlled. However, some new complications are of increasing concern, and cognitive dysfunction is one of its main complications[2]. The pathogenesis of central nervous systems (CNS) complications in diabetes mellitus is multifactorial. To date, the pathogenesis of DCI is not clear, and there is no effective treatment. Some studies have found that DCI and Alzheimer's disease (AD) have similar clinical manifestations and pathological links[3]. Cumulative studies have confirmed the existence of a large number of toxic substances in diabetic brain tissues, such as amyloid peptide (Aβ), phosphorylated Tau, and advanced glycation end products[4–9]. Most previous research has focused on trying to stop the production of these toxic substances to treat cognitive dysfunction. Unfortunately, they hardly halt the progression of cognitive decline[10]. Therefore, the clearance pathway of toxic substances in brain tissue might be a potential prospect for DCI therapy.

The glymphatic system is a glial-dependent waste removal pathway in the brain that is specifically used to remove soluble waste protein and brain parenchymal interstitial metabolites[11–13]. Accumulated studies have shown that diabetic status induces glymphatic system dysfunction. Jiang et al.[11] and Zhang et al.[14] found that the clearance rate of hippocampal and hypothalamic interstitial fluid in type 2 diabetes is slowed, which may be an important cause of cognitive impairment. The expression and polarization of AQP4 on perivascular astrocyte endfeet plays a key role in maintaining the function of the glymphatic system, which could promote metabolic waste clearance from brain tissue[13,15]. Studies have found that AQP4 in perivascular astrocyte endfeet could be downregulated[16] and redistributed in diabetes[17]. However, the mechanism of AQP4 expression loss and redistribution around cerebral vessels in the diabetic state is not clear.

Although the brain is an important target organ of insulin, and a large amount of evidence indicates that the dysfunction of insulin metabolism in the brain impairs the function of neurons and glial cells during diabetes mellitus[18,19], according to the progressive pathogenesis of diabetic encephalopathy, peripheral glucose and lipid metabolism disorders might be the initial pathological link of DCI because of the interorgan communication between peripheral and central organs[20–23]. Extracellular vesicles, especially exosomes with multiple miRNAs, are an important mode of intercellular communication and have attracted increasing attention in the development, homeostasis, injury and repair of the CNS. Indeed, the origin of the changed miRNAs in the brain would be available to multiple sources; in addition to peripheral exosomal miRNAs, exosomes from neurons, glial cells, endothelial cells and other sources in the brain themselves would also produce multiple miRNAs. Exosomes from the brain cells themselves produce multiple miRNAs when insulin metabolism is dysfunctional in the brain, which also affects the function of the glymphatic system. Circulating exosomes, which are mainly derived from adipose tissue, skeletal muscle, and liver[24,25], seem to be the initiating etiology of diabetic cognitive dysfunction in the pathological state of diabetes. Interestingly, the main organs that produce exosomes are also the organs that characterize the pathological changes in diabetes[26,27]. Moreover, the diabetic environment can lead to changes in exosome-miRNAs[28,29]. Moreover, cumulative studies have also confirmed that AQP4 is one of the key target genes of miRNAs[30]. Therefore, this review will be beneficial for elucidating the interorgan communication mechanism of glymphatic system function, regulation and providing a new strategy for the prevention and treatment of DCI.

2. Low expression and redistribution of AQP4 on perivascular astrocyte endfeet aggravates glymphatic system dysfunction in diabetes

Accumulating studies indicate that glymphatic system dysfunction is the ultimate common pathologic link in multiple neurodegenerative diseases (such as Parkinson's disease and AD)[31]. Clinical and preclinical studies have also confirmed the phenomenon of glymphatic system dysfunction in DM and associated neurological abnormalities[14,26,32,33]. By using diffusion tensor image analysis along with the perivascular space, Yang et al.[33] found lower water diffusivity along the perivascular space in type 2 diabetes mellitus patients, suggesting that glymphatic system dysfunction is associated with DM. Moreover, MRI was used to detect the contrast agent GD-DTPA injected into the cerebrospinal fluid (CSF) and hippocampus, which not only found that the CSF bulk speed slowed in the perivascular space but also confirmed that the clearance rate of the brain parenchyma decreased in DM rats[32]. Furthermore, Zhang et al.[11] and Kim et al.[12] also confirmed that diabetes-induced cognitive impairment is closely related to glymphatic system dysfunction.

The expression and localization of AQP4 on the perivascular astrocyte endfeet facilitates CSF and interstitial fluid exchange and plays a crucial role in the glymphatic system. Previous studies have confirmed that AQP4 deletion aggravates glymphatic system dysfunction in traumatic brain injury and subarachnoid hemorrhage[34,35]. Cumulative studies also found that AQP4 deletion accelerated the deposition of Aβ plaques in the APP/PS1 murine model[36,37]. In addition to AQP4 expression, the polarization distribution of AQP4 is also important for maintaining glymphatic system function. Harrison et al.[38] found that the polarization distribution of AQP4 in an AD model was highly correlated with abnormal deposition of phosphorylated Tau. In fact, there are few

direct studies on the role of AQP4 in DCI. Notably, increasing evidence has shown that DM affects AQP4 expression and polarization distribution. The insulin-resistant state could impair cognitive function, accompanied by astrocyte activation and AQP4 loss of polarization distribution[39,40]. In spontaneously diabetic Torii rats, the transition of perivascular AQPs from AQP4 to AQP1 was observed as hyperglycemia continued to increase[40]. Moreover, the expression of AQP4 in the hippocampus of diabetic rats was significantly reduced compared with that of normal rats[41]. In an intracerebral hemorrhage rat model, AQP4 was significantly downregulated by treatment with streptozotocin[42]. These studies suggest that AQP4 downregulated expression and redistribution on the perivascular astrocyte endfeet is important to maintain glymphatic system function in DCI.

3. Exosome-mediated peripheral−central communication affects brain homeostasis and glymphatic system dysfunction in DM

Given that interorgan communication plays critical roles in regulating brain homeostasis, it would be an ideal strategy to use peripheral IR tissues as the initial factors to treat CNS disease accompanied by DM. Skeletal muscle, adipose tissue and liver tissue are the main IR target organs that can secrete growth factors and miRNAs to mediate peripheral and central communication and affect cognitive function[43]. Previous studies on the improvement of neurological function through exercise have provided some understanding of the relationship between the peripheral and CNS[44]. Moreover, skeletal muscle atrophy caused by diabetes is associated with cognitive impairment[45]. Our previous studies have also shown that DCI mice had skeletal muscle atrophy, while their cognitive function decreased[46]. Adipose tissue IR has also been reported to cause synaptic damage in the hippocampus[47]. These findings suggest that peripheral pathological changes in diabetes may lead to progressive exacerbation of cognitive impairment through communication between peripheral and central regions.

Information exchange mediated by exosomal miRNAs has attracted increasing attention in nervous system development and physiology[48,49]. Exosomes, which can transfer nucleic acids, proteins, lipids and other signaling molecules and trigger phenotypic changes in recipient cells, are biological nanoscale spherical lipid bilayer vesicles secreted by donor cells[50]. They not only transmit signals over short distances between local cells but also mediate communication throughout the body[51]. Exosomes are produced by almost all cells, while circulating exosomes are mainly from liver, fat, and skeletal muscle[52]. As the main peripheral pathological organs in the diabetic environment, exosomes produced by these organs also change accordingly. A recent study showed that adipose tissue-derived EVs mediate interorgan communication between adipose tissue and the brain and induce cognitive impairment[53]. Therefore, exosome-mediated peripheral−central communication may be a key pathway affecting brain homeostasis.

4. DM induced abnormal exosome miRNA expression in peripheral tissues

A large number of studies have shown that the cargo of miRNAs in exosomes can be changed and then affect brain homeostasis in DM. Adipocytes, as key cells in regulating energy metabolism and glucose balance, release a large number of exosomal miRNAs into the blood (Table 1)[52,54−70]. High glucose treatment significantly increased the expression of miR-320 in adipocytes[54]. Moreover, miR-143, miR-221, and miR-27 were upregulated in adipose tissue of obese mice induced by a high-fat diet (HFD)[55,57,58]. Clinical studies have also shown decreased miR-130 concentrations in obese female subjects[60].

As another key pathological tissue of diabetes, exosomal miRNAs secreted by the liver are also significantly affected by the

Table 1 Some of the microRNAs associated with peripheral tissues in diabetic condition.

MicroRNA	Target tissue(s)	Function	Ref.
miR-320	Adipose tissue↑	Induced insulin resistance	54
miR-143	Adipose tissue↑	Regulate EPRK5 involvement in adipocyte differentiation;	55,56
	Liver↑	Target OPR8 inhibition insulin-stimulated Akt activation and impair glucose metabolism	
miR-221	Adipose tissue↑	Induced insulin resistance	57
miR-27a	Adipose tissue↓	Inhibit adipocyte differentiation; regulate liver lipid metabolism;	58,59
	Liver, muscle↑	Inhibit muscle glycogen decomposition	
miR-130	Adipose tissue↑	Inhibit PPARγ biosynthesis reduces adipogenesis	60
miR-122	Liver↓	Induce insulin resistance through the PPAR-α pathway	61
miR-451	Liver↑	Inhibit GYK expression reduce glucose output	62
miR-335	Liver↑	Regulate of biosynthesis of fatty acids and triglycerides	63
	Adipose tissue↑		
miR-103	Adipose tissue↓	Improve insulin resistance	64
	Liver↓		
miR-107	Adipose tissue↓	Improve insulin resistance	64
	Liver↓		
miR-27b	Liver↑	Network of genes that control lipid metabolism	65
miR-15b	Liver↑	Induce insulin resistance	66
miR-802	Liver↑	Target HNF1B regulate insulin sensitivity;	67,68
	Skeletal muscle↑	Regulate insulin sensitivity and glucose transport	
miR-19a	Liver↓	Regulate PTEN expression mediate glycogen synthesis in hepatocytes	69
miR-20b	Skeletal muscle↑	Disrupt glucose metabolism	70
miR-27a-3p	Skeletal muscle↑	Inhibition of glycogen phosphorylase, PGM and GAA, leading to glycogen accumulation	59

↑Increased; ↓Decreased.

diabetic environment. Liver cells can selectively encapsulate miR-122 into MVs and secrete it out of cells in a high lipid environment, resulting in an increase in miR-122 levels in serum and a decrease in miR-122 content in the liver of type 2 diabetic mice[61]. Zhou et al.[62] found that the increased expression of miR-451 in diabetic mouse hepatocytes may be caused by inhibiting the expression of glycerol kinase Gyk. Moreover, the expression of miR-335, miR-103, miR-107, miR-27a, and miR-27b was increased in the liver of HFD-induced obese mice[63–65]. In SFA-induced obese mice, overexpression of miR-15b acts on insulin receptors, which is an important cause of liver IR[66]. Similarly, miR-143 expression levels in the liver were significantly upregulated in a mouse model of dietary obesity[56]. Increased hepatic miR-802 expression was also found in both obese mouse models and obese humans[67]. Furthermore, some of the miRNAs (*e.g.*, miR-19a) could be downregulated in the livers of diabetic mice[69].

The exosomal miRNAs from skeletal muscle, as an important sensitive tissue of diabetes, are also abnormally expressed in diabetes. Xiao et al.[70] reported that miR-20b expression was significantly upregulated in skeletal muscle under diabetes. miR-802, as a potential therapeutic target for type 2 diabetes, regulates insulin sensitivity and glucose transport in skeletal muscle cells, which was significantly increased in L6 cells cultured under high lipid conditions[68]. Chemello et al.[59] also found that miR-27a-3p expression was increased in all muscles of HFD mice.

These findings suggest that in diabetic states, peripheral IR tissue-derived EVs and their cargo miRNAs could be changed and mediate the pathophysiologic processes of CNS disease (Fig. 1). Therefore, it is necessary to further clarify which abnormal miRNAs influence brain function and AQP4 abnormal changes.

5. Peripheral tissue-derived exosomal miRNAs induce AQP4 loss or redistribution in DM

As a class of endogenous regulators, miRNAs play an important role in mediating the progression of brain injury diseases. Exosomal miRNAs, which can avoid degradation by RNase when released by donor cells, can be absorbed by the brain and regulate the expression of posttranscriptional genes[71]. Considering that the expression and localization of AQP4 on perivascular astrocyte endfeet is the main biomolecular basis of the glymphatic system, to further elaborate the hypothesis that peripheral tissue-derived exosomal miRNAs could induce AQP4 loss or redistribution, some of the miRNAs that target AQP4 are summarized in Table 2[30,72–89]. These miRNAs have multiple effects on DCI progression. For example, the microRNA-29 family was associated with memory function and might serve to identify older patients with end-stage renal disease and Parkinson disease at risk of cognitive decline[79,80]. MiR-29a mitigated oxygen glucose deprivation (OGD)-induced damage to astrocytes by mediating the

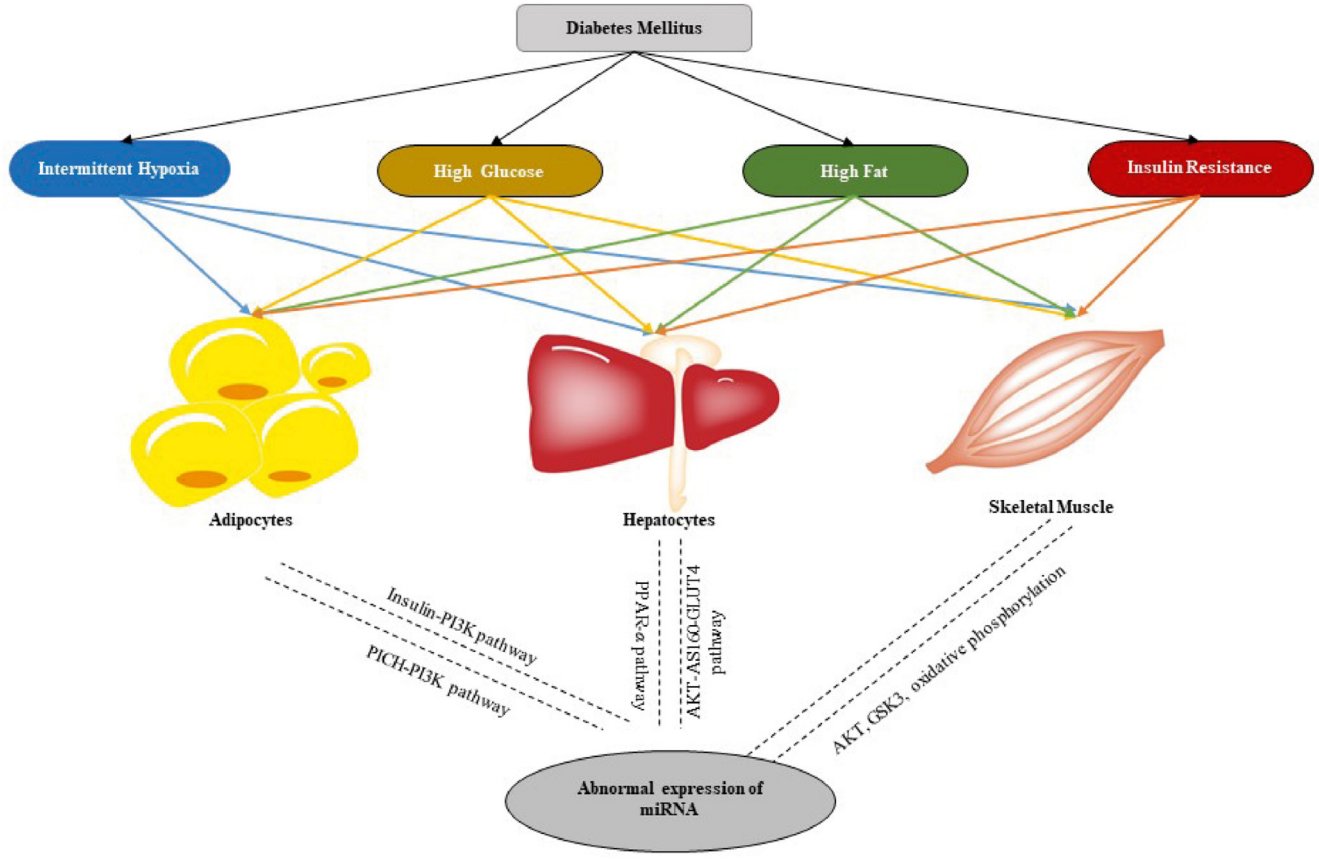

Figure 1 The diabetic environment induced abnormal exosome miRNA expression in peripheral organs. Hypoxia, high glucose, hyperlipemia, insulin resistance and other key pathological factors of diabetes affect exosomes secreted by adipose tissue, skeletal muscle and liver in target organs of diabetes, leading to abnormal expression of miRNAs. PI3K, phosphatidylinositol-3-kinase; PICH, PLK1-interacting checkpoint helicase; PPAR, peroxisome proliferator-activated receptors; AS160, AKT substrate of 160 kDa; GLUT4, glucose transporter member 4; GSK3, glycogen synthase kinase-3.

Table 2 Some of the microRNAs by directly targeting AQP4 after brain injury.

MicroRNA	Effect	Changes of miRNAs in diabetic patients	By modulating AQP4-mediated brain injury diseases	Ref.
miR-29a	Down-regulation of AQP4	Skeletal muscle↑[72], liver↑[73]	Reduced (OGD)-induced astrocyte injury	79
miR-29b	Down-regulation of AQP4	Skeletal muscle↑, adipose tissue↑[74]	Reduces the destruction of the blood−brain barrier due to ischemic stroke	80
miR-29b-3b	Redistribution of AQP4		Affect brain edema	81
miR-130b	Redistribution of AQP4	Adipose tissue↑[75]	Alleviate the neuroprotective function of cerebral ischemia and reperfusion injury	82
miR-145	Down-regulation of AQP4		Treatment of ischemic stroke and protection of astrocytes from injury	83,84
miR-24	Redistribution of AQP4		Reduce cerebral ischemia reperfusion injury	85
miR-93	Down-regulation of AQP4		Inhibition of neuronal apoptosis, alleviation of cerebral edema and neurological function after cerebral ischemia	86
miR-383-5P	Down-regulation of AQP4	Liver↑[76]	Weightlessness can increase miR-383-5p and decrease AQP4 to induce dementia	30
miR-130a	Redistribution of AQP4	Skeletal muscle↑[77], adipose tissue[78]	Reduce cerebral infarction; Decrease AQP4 (M1/M23) ratio, restore AQP4 polarization, improve cognition	87,88,89

↑Increased; ↓Decreased.

overexpression of AQP4 target proteins[81]. Conversely, miR-29b overexpression can reduce blood−brain barrier damage caused by ischemic stroke by downregulating AQP4[82]. Similarly, miR-29b-3b directly regulates AQP4 to affect brain edema in mice[83]. MiR-130b was found to reduce AQP4 expression to exert a neuroprotective effect against cerebral ischemia−reperfusion injury[84]. The downregulation of miR-145 in participants with cognitive dysfunction is due to overproduction of proinflammatory cytokines[85]. MiR-145 has also been confirmed to protect astrocytes by downregulating AQP4[86]. Overexpression of miR-24 in exosomes derived from mesenchymal stem cells can reduce ischemia−reperfusion injury by targeting AQP4 regulation[87]. Meanwhile, it was found that downregulation of miR-93 expression could inhibit neuronal apoptosis in cerebral ischemia rats, alleviate cerebral edema and regulate neural function by regulating AQP4 expression[88]. Zhang et al.[30] found that the mechanism of microgravity-induced hippocampal neuron injury may be related to the altered expression level of the target protein AQP4 mediated by miR-383-5p. Furthermore, it is noteworthy that miR-130a could regulate the phenotypic transformation and protein expression of AQP4[89]. These studies have confirmed that miRNAs can regulate the expression of AQP4.

By integrating the abnormal expression of miRNAs that target AQP4 in peripheral organs of diabetes, we summarized that abnormal expression of miR-29a[72,73,81], miR-29b[74,82], miR-130b[75,85] and miR-383[30,76] induced by diabetes can reduce AQP4 expression. Moreover, Zhang et al.[90] found that intermittent fasting treatment in AD can significantly upregulate the level of miR-130a to promote Aβ clearance and improve cognitive impairment. These results confirmed that miR-130a could induce AQP4 redistribution. Most importantly, some studies have reported abnormal expression of miR-130a in skeletal muscle[77] and liver cells[78] in diabetes mellitus. These studies confirm that abnormal expression of peripheral miRNAs in the diabetic environment might induce glymphatic system dysfunction by regulating AQP4 expression and redistribution. Therefore, further determining the source of miRNAs and making it clear how the miRNAs are delivered in the circulation is necessary to elucidate AQP4-targeted miRNAs in diabetic environments.

6. The regulatory mechanisms of exosomal miRNAs on AQP4 expression and localization

miRNAs are noncoding RNAs that are involved in the post-transcriptional regulation of target gene expression play an important role in the regulation of physiological functions, and exploiting brain-specific miRNA−target interactions could accelerate the search for prognostic targets of brain diseases[91]. Multiple sources of miRNAs in the brain can regulate the expression and localization of AQP4 in astrocytes and thus participate in the corresponding pathological processes, leading to the occurrence of cognitive dysfunction. Regulation of astrocyte AQP4 starts with AQP4 gene regulation, and miRNAs targeting AQP4 have been confirmed to be a useful application[92]. Bioinformatics analysis is usually used to predict the target genes of certain miRNAs first, and then the targeted binding sites of miRNAs on the AQP4 mRNA 3′UTR can be predicted by the TargetScan website. Finally, the predicted results should be verified by a dual-luciferase assay. Accumulated studies have confirmed that different miRNAs regulate AQP4 expression by a dual-luciferase reporter system. These results confirmed that AQP4 was the direct target of many miRNAs, which resulted in a direct effect on the expression of mAQP4[82,83]. In addition, miR-130a has been shown to inhibit the expression of its direct target gene AQP4 M1 subtype and reduce the ratio of AQP4 (M1/M23), which could induce AQP4 redistribution. These results indicated that the exosomal miRNAs regulated AQP4 expression

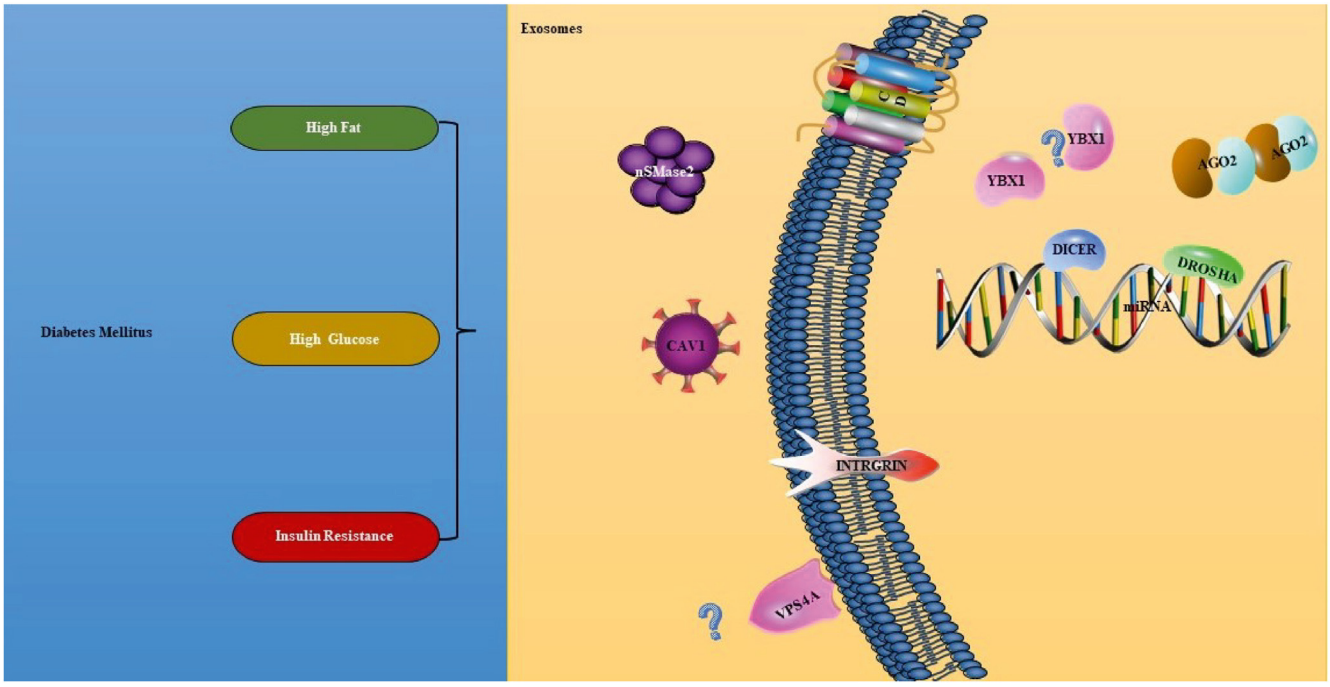

Figure 2 The diabetic environment affects the synthesis of exosome miRNAs in peripheral and exosome uptake in brain tissues, including the III RNA enzymes DROSHA and DICER, which control miRNA production, RNA-binding proteins (YBX1 and AGO2) and exosome encapsulated membrane proteins (nSMase2, CAV-1 and VPS4A). YBX1, Y-box binding protein 1; AGO2, Argonaute 2; nSMase2, type 2-neutral sphingomyelinase; CAV-1, Caveolin-1; VPS4A, vacuolar protein sorting 4A.

and localization by directly targeting AQP4 and its subtype gene[90].

7. Peripheral exosome synthesis and central exosome absorption were impaired in DM

The secretion of exosomal miRNAs from donor cells initiates peripheral and central cell communication and is regulated by a variety of signals, including the III RNA enzymes DROSHA and DICER, which control miRNA production[93], RNA-binding proteins (Y-box binding protein 1 and Argonaute 2) and exosome-encapsulated membrane proteins [(type 2-neutral sphingomyelinase), Caveolin-1 (CAV-1) and (vacuolar protein sorting 4A)][94]. Interestingly, cumulative studies have demonstrated that diabetes could lead to abnormal expression of miRNA synthase and miRNA-sorted proteins, leading to changes in miRNAs in exosomes[95,96]. Diabetes induced downregulation of DROSHA and DICER protein expression[97,98]. Drosha and Dicer expression is inhibited by high glucose treatment of primary skeletal muscle microvascular endothelial cells in mice[99]. Related studies have shown that in insulin-resistant mouse models, reduced levels of Argonaute 2 in β cells aggravate the diabetic phenotype and block self-growth[100]. These studies indicated that exosome synthesis and their cargos are changed in diabetes. Therefore, the expression of exosome synthetic proteins in peripheral tissues, which are perceived as the most important source of circulating exosomes, would be a potential therapeutic target for early intervention in DCI.

Due to the limitation of the blood−brain barrier and circulating RNase, the delivery of drugs and genetic information (DNA, miRNA, etc.) to the brain has always been an important challenge for the prevention and treatment of brain diseases. Exosomes possess many favorable bioactivities and are excellent carriers for targeting brain tissue. Exosomes are able to cross the blood−brain barrier from the blood to the CNS as well as from the brain to the blood[101]. A targeted drug delivery system would also be a feasible treatment strategy for neurodegenerative diseases[102]. Circulating exosomes cross the BBB through a variety of clathrin-dependent and nondependent endocytosis pathways, such as CAV-1-mediated uptake and lipid raft mediated internalization[103]. CAV-1, Flotillin1, P21 (RAC1) activated kinase 1, RAC family small GTPase 1 and Dynamin-2 are the main proteins that mediate exosome uptake. CAV-1 is enriched in endothelial cells and plays a major role in the regulation of trafficking *via* the blood−brain barrier. Yue et al.[104] found that neuronal knockout of CAV-1 reduced exosome uptake and eliminated EV-mediated neuronal protection under OGD conditions. Conversely, neuronal overexpression of CAV-1 increases exosome intake, confirming that CAV-1 expression is key to exosome intake both in intercellular communication and in peripheral and central communication. Notably, the diabetic environment can affect CAV-1 expression in endothelial cells, and CAV-1 expression is downregulated in the brains of type 2 diabetes mellitus patients[96] and diabetic rats[105]. In addition, exposure of skeletal muscle C2C12 cells to high glucose concentrations increased the phosphorylation of PAK-1[106]. These studies suggest that the diabetic environment could induce abnormal exosomal miRNAs by affecting the synthesis of exosomal miRNAs in peripheral tissues and exosome uptake in the brain (Fig. 2).

8. Conclusions

The diabetic environment could induce abnormal changes in circulating exosomal miRNAs by affecting exosome synthesis and miRNA sorting in peripheral IR tissues, and these changes in exosomal miRNAs when absorbed into the brain could lead to the

loss of AQP4 and relocalization to perivascular astrocyte endfeet, which has been proposed to be the molecular basis of maintaining the normal function of the glymphatic system. Then, the concept was first derived in this review that peripheral and central communication in diabetes mediated by exosomal miRNAs could induce glymphatic system dysfunction by regulating AQP4 expression and localization, and this concept proposes a potential therapeutic strategy for the early intervention of DCI.

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Author contributions

Lin Zhang and Dongna Li extracted data, prepared figures and tables, and wrote the manuscript, Pengwei Zhuang, Dingbin Liu and Yanjun Zhang conceived of the review and provided diabetic cognitive impairment expertise. Pengrong Yi, Jiangwei Shi, Mengqing Guo and Qingsheng Yin prepared the article. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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