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MicroRNAs in control of gene regulatory programs in diabetic vasculopathy

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1. ABSTRACT

Diabetes is generally associated with vasculopathy, which contains both microvascular and macrovascular complications, associated with high morbidity and mortality. Currently, despite interventional therapy, the overall prognosis for patients with diabetic vasculopathy remains unsatisfactory. Angiogenesis and vascular injury and repair are associated with a variety of cells. However, the molecular mechanisms of the cells that are involved in pathogenesis of diabetic vasculopathy remain largely unknown. As novel molecules, microRNAs (miRs) take part in regulating protein-coding gene expression at the post-transcriptional level, and contribute to the pathogenesis of various types of chronic metabolism disease, especially diabetic vasculopathy. This allows miRs to have a direct function in regulation of various cellular events. Additionally, circulating miRs have been proposed as biomarkers for a wide range of cardiovascular diseases. This review elucidates miR-mediated regulatory mechanisms in diabetic vasculopathy. Furthermore, we discuss the current understanding of miRs in diabetic vasculopathy. Finally, we summarize the development of novel diagnostic and therapeutic strategies for diabetic vasculopathy related to miRs.

2. INTRODUCTION

Diabetes has become a major public health problem worldwide. According to the China National Diabetes and Metabolic Disorders Study Group report, the prevalence of diabetes has been increasing alarmingly throughout China, and the age-standardized prevalence of total diabetes and pre-diabetes is estimated to rise to 9.7% and 15.5%, respectively (1). Diabetes has many short-term and long-term complications. With the improvement of medical treatment, short-term complications are coming under effective control, but long-term complications are still a major problem. Among chronic complications, vasculopathy remains the major cause of morbidity and mortality in patients with diabetes (2). These complications can be divided into micro- and macro-complications. The major microvascular complications are nephropathy, retinopathy, and neuropathy, whereas the macrovascular complications manifest themselves as accelerated atherosclerosis, resulting in premature ischemic heart disease, increased risk of cerebrovascular disease, and severe peripheral vascular disease (3). Although various therapies have emerged during past decades, the clinical prognosis of diabetic vasculopathy remains far from ideal (4). Early impairment of glucose metabolism remains below the threshold for diagnosis of type 2 diabetes mellitus (T2DM); a state known as impaired glucose tolerance (5). Atherosclerotic lesion formation is initiated by endothelial cell damage leading to endothelial dysfunction (6). It is well known that diabetes and cardiovascular disease have a close relationship. Recent studies have suggested that metabolic syndrome is related to the incidence of peripheral arterial disease (7). *In vitro* studies have shown that high glucose levels can damage endothelial cell function, inhibit proliferation and migration, and promote apoptosis (8). Emerging evidence suggests that circulating stem or progenitor cells play an important role in endothelial cell regeneration (9). Hill *et al*. suggested that the number of circulating progenitor cells is reduced sharply in patients

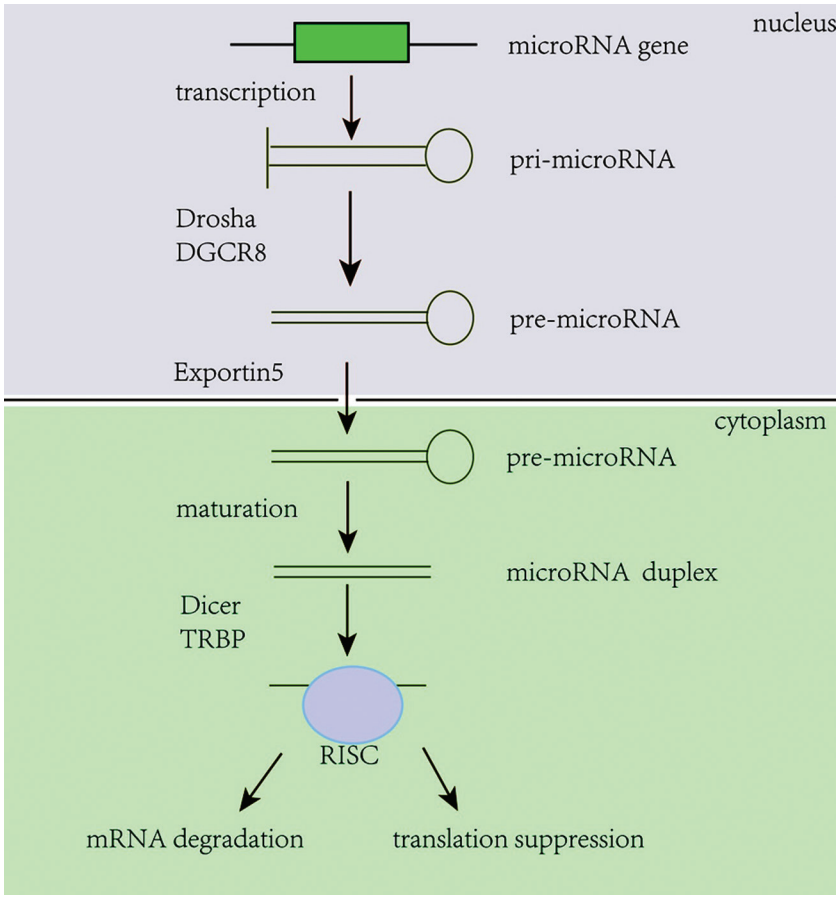

Figure 1. Physiological features of miRs and their mechanisms of action. DGCR8 = dsRBD domain binding partner protein; dsRBP=a double strand RNA binding protein; RISC = RNA-induced silencing complex; TRBP = HIV-1 TAR RNA binding protein.

with diabetes or other chronic metabolic diseases (10). In addition, the function of endothelial progenitor cells (EPC) is impaired (11, 12). The currently accepted theory is that endothelial progenitor cells are damaged in patients with diabetes, and their ability to home to damaged areas is limited, leading to an abnormal repair process (13, 14). High glucose and advanced glycation end products (AGEs) can also damage other important cells, such as mesenchymal stem cells, which contribute to tissue regeneration, differentiation and immunomodulation (15). Diabetes mellitus is a prothrombotic condition, with persistent endothelial cell dysfunction with suppression of nitric oxide and prostacyclin synthesis, combined with platelet resistance, leading to loss of control over platelet activation (16). MicroRNAs (miRs) belong to the family of non-coding RNAs, which are ~22 nucleotides (nt) in size and regulate gene expression at the post-transcriptional level, and numerous studies have established a wide range of critical roles for miRs (17, 18). It is now well established that miRs are important for vascular development, physiology and disease (19). Many studies have found that miRs may be the key regulators of endothelial progenitor cell proliferation and migration (12, 20, 21). For example, our previous studies have found specific miRs downregulating EPCs in the cardiovascular system in patients with diabetes, which impairs their functional properties. Many other studies have shown that EPC functions are temporally and spatially regulated by miRs in many aspects (20, 22, 23). In this review, we highlight miR-dependent regulation of diabetic vasculopathy, exploring new mechanisms that could be used for miR-based therapeutic approaches for diabetic vasculopathy.

3. PHYSIOLOGICAL FEATURES OF MIRS AND THEIR MECHANISMS OF ACTION

The physiological features of miRs and their mechanisms of action are shown in Figure 1. miRs are first transcribed by RNA polymerase II as primary miRs (pri-miRs) in the nucleus through a complicated and multistep process. The pri-miRs are then processed further in the nucleus by Drosha into a 60~70 nt precursor miR (pre-miR), acting with its dsRBD partner, called DGCR8 (24-26). The nuclear export protein, exportin-5, carries the pre-miRs to the cytoplasm bound to Ran GTP, which can transport RNAs and proteins through the nuclear pores (27, 28). The

resulting pre-miRs have a hairpin structure. Dicer and its dsRBD partner protein cleave the pre-miRs to generate a duplex containing two strands in the cytoplasm (29). The duplex is recruited into an RNA-protein complex called RNA-induced silencing complex (RISC), which is dependent on Dicer, other RNA-binding domain proteins, and members of the Argonaute protein family (30, 31). And finally switching to mature forms--a single RNA filament of a 20-22nt. The mRNA targeting pathway by miRs involves recognition and binding between the miRs and mRNA (32). This miR-mRNA interaction happens with either complete or incomplete matching via a Watson-Crick base-paring mechanism (33, 34). Successive research has shown that each miR has the ability to silence hundreds of different target genes, estimating that miRs regulate gene expression of >60 % of the mRNAs. Moreover, one mRNA can be targeted by more than one miR, thus adding complexity to the regulatory networks (33-35).

4. MIRS IN VASCULAR DEVELOPMENT AND INJURY

In recent years, the importance of miR gene regulation for vascular development and function in patients with diabetes has been widely studied (36). Furthermore, Dicer silencing significantly impaired the angiogenesis capacities of endothelial cells (ECs) (37). Given that Dicer is an important regulator in the production of miRs, we can conclude that miRs play critical functional roles in vascular development. Chronic hyperglycemia leads to vascular disease, and several studies in patients, animal models and *in vitro* studies have revealed that hyperglycemia and AGEs alters endothelial metabolism and function, causing vascular injury (3). It has been proposed that diabetes alters the expression and function of many of the aforementioned miRs. Circulating miRs have emerged as novel biomarkers of diabetes (38). Many inflammatory processes are involved with miRs. For example, miR-126 was one of the first miRs found to have altered circulating concentrations in T2DM (21, 39). It is suggested that endothelial hypoxia-inducible factor (HIF)-1α promotes atherosclerosis inflammation, and the process is regulated by miR-19a (40). Moreover, miR-19a regulates lipopolysaccharide-induced endothelial cell apoptosis through modulating the expression of apoptosis signal-regulating kinase 1 (41). miR-21 is involved with fibrosis, and promotes renal fibrosis in diabetic nephropathy by targeting phosphatase and tensin homologue (PTEN) and mothers against decapentaplegic homolog (SMAD) 7 (42). Recently, a meta-analysis confirmed that 40 miRs are significantly dysregulated in T2DM. miR-29a, miR-34a, miR-375, miR-103, miR-107, miR-132, miR-142-3p and miR-144 are potential circulating biomarkers of T2DM (43). Down-regulation of miR-34a alleviates mesangial proliferation *in vitro* and glomerular hypertrophy in mice with early diabetic nephropathy by targeting growth Arrest Specific-1 (GAS1) (44). Chen *et al*. have demonstrated that miR-34a is an important regulator in vascular SMC (VSMC) function and neointima hyperplasia, suggesting its potential therapeutic application for vascular diseases (45). miR-34a may be further investigated as a therapeutic target to reduce β-cell death and dysfunction (46). miR-135a promotes renal fibrosis in diabetic nephropathy by regulating transient receptor potential-canonical 1 (TRPC1) (47). miR-135a targets insulin receptor substrate 2 (IRS2) levels by binding to its 3' untranslated region and this interaction regulates skeletal muscle insulin signaling, which provide more information about aberrant miRs-135a signatures associated with diabetes (48). miR-138 might promote proliferation and migration of smooth muscle cell (SMC) in db/db mice through suppressing the expression of silent mating-type information regulator 2 homolog 1 (SIRT1) (49). Khamaneh *et al*. suggest that changes in the expression of miR-155 may participate in the pathogenesis of diabetes-related complications (50). They showed that miR-155 expression was significantly decreased in diabetic kidney, heart, aorta, peripheral blood mononuclear cells, and sciatic nerve compared with the controls (50). Furthermore, Huang *et al*. found that high glucose levels induced over-expression of miR-155 and miR-146a in human renal glomerular endothelial cells, which in turn increased tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β1, and nuclear factor (NF)-κB expression (51). miR-346 regulates SMAD3/4 expression in renal tissue, which influences renal function and glomerular histology in DN mice (52). miRs are expressed abundantly in quiescent endothelial cells and can suppress abnormal endothelial activation through targeting multiple angiogenic signaling pathways specifically in the endothelium (53). Caporali *et al*. demonstrated that miR-503 regulates pericyte–endothelial cell crosstalk in microvascular diabetic complications (54). Knockdown of miR-378a increases expression of vimentin and β3 integrin, which accelerates fibroblast migration and differentiation *in vitro* and enhances wound healing *in vivo* (55). From all the above (Table 1), it is evident that miRs are associated with diabetic vascular alterations. However, this subject needs further investigation.

5. MIRS REGULATING EPC FUNCTION AND VASCULAR REPAIR

Endothelial dysfunction depends on the extent of the injury, as well as the capacity for repair (56). The endothelium has a weak capacity for self-repair, because it is formed mostly of terminally differentiated cells with low proliferative capacity (35). Bone-marrow-derived mononuclear cells that are capable of regeneration circulate in the peripheral blood (57). As a group, these different cell populations were initially classified as EPCs, which have the capacity to differentiate to endothelial cells (19). EPCs play an important role in vascular homeostasis and repair in patients with T2DM (19, 58). EPCs migrate toward injured endothelial regions, where

Table 1. miRs expressed in vascular development and injury

miRs	Up/Down regulation	Targets	Function regulated	References
miR-19a	Up	CXCL1	Monocyte adhesion	(40)
miR-21	Down	SMAD7/PTEN	Glomerulosclerosis	(42)
miR-34a	Down	Notch1	VSMC proliferation/neointima formation	(45)
miR-135	Down	TRPC1	Renal fibrosis	(47)
miR-138	Down	SIRT1	VSMC proliferation	(49)
miR-155/146	Down	---	Migration, angiogenesis	(51)
miR-503	Down	CXCR4, DLL4, FZD4	Inflammation-mediated glomerular endothelial injury	(54)
miR-346	Down	SMAD3/4	Ocular neovascularization	(53)
miR-378a	Down	Vimentin and β3 integrin	Matrix accumulation, glomerular hypertrophy and mesangial cell proliferation	(55)

Table 2. miRs expressed in EPCs related to vascular repair

miRs	Up/Down regulation	Targets	Function regulated	References
miR-21	Down	WWP1	Proliferation	(68)
miR-22	Down	AKT3	Senescence	(69)
miR-31	Down	TBXA2R	Angiogenesis/vasculogenesis	(23)
miR-126	Up	Spred-1	Migration, apoptosis, proliferation, angiogenesis	(12, 17)
	Down	PIK3R2	Inhibit EMT	(71)
miR-130a	Down	Runx3	Proliferation, migration, differentiation, apoptosis, colony and tubule formation	(21)
	Down	MAP3K12	Apoptosis	(70)
miR-150	Down	c-Myb	Migration, tube formation, homing, thrombus recanalization and resolution	(72)
miR-206	Down	VEGF-A	Migration, Tube Formation	(73)
miRs-221	Up	c-kit	Neovasculogenesis	(74)
miR-720	Down	VASH1	Migration and tubule formation	(23)

chemokine signals are released, such as stromal cell-derived factor (SDF)-1α (59), intercellular adhesion molecule (ICAM)-1 (60), and vascular cell adhesion molecule (VCAM)-1 (61). Homing to the injured sites takes place through interactions axes such as SDF-1α/chemokine CXC receptor (CXCR)4 (62), ICAM-1/CD18 (60), and VCAM-1/integrin α (61). Once embedded in the injured site, EPCs are involved in endothelial repair either by proliferation or forming new endothelial cells (63). Increasing research suggests that diabetes and other chronic metabolic disease affect the number and function of EPCs (64). The differences in miRs in EPCs between patients with and without diabetes have been verified by other researchers (64-67). Zuo *et al.* suggested that miR-21 suppresses EPC proliferation by activating the TGF-β signaling pathway via downregulation of WW domain-containing E3 ubiquitin protein ligase 1 (WWP1) (68). EPCs also play an important role in postnatal neovascularization, and the process is also regulated by miRs. Zheng *et al*. indicate that miR-22 induces EPC senescence by downregulating AKT expression, providing a potential novel target for the reversal of EPC dysfunction in angiogenesis (69). Moreover, our previous study proved that downregulation of miR-130a contributes to EPC dysfunction in patients with diabetes via runt-related transcription factor 3 (Runx3) (21). Downregulation of miR-130a may underlie endothelial dysfunction in diabetes through the activation of the c-Jun N-terminal kinase signaling pathway (70). Zhang *et al*. showed that miR-126 targets PI3K regulatory subunit p85 beta (PIK3R2) to inhibit endothelial-to-mesenchymal transition (EMT) in EPCs, and this process involves regulation of the PI3K/Akt signaling pathway (71). miRs have the potential to be used as biomarkers for early diagnosis of intimal hyperplasia in cardiovascular disease, and as therapeutic tools for cardiovascular diseases mediated by the EMT process (71). Other miRs, such as miR-31, miR-126, miR-206, miR-221 and miR-720, play an important role in regulating EPC migration, proliferation and apoptosis (12, 23, 72-74). We summarized the content about miRs regulating EPC functions and vascular repair in Table 2.

6. MIRS IN PLATELET FUNCTION AND INFLAMMATION IN DIABETES

DM can be regarded as a metabolic syndrome, containing complex risk factors such as dyslipidemia, elevated blood pressure, and raised plasma glucose, representing prothrombotic and proinflammatory states (75). Platelets are the core component of the prothrombotic process. Although platelets are anuclear, they are capable of protein synthesis and contain different mRNAs and miRs (76-79). Platelets contain large amounts of miRs that are altered by disease, in particular, DM (80, 81). Platelet-derived miRs can regulate platelet protein expression (76). Elgheznawy *et al* indicated that β1 integrin and FXIII-A were downregulated by platelet miR-223 (80). This was confirmed by other studies (82-84). Hyperglycemia activates platelet function through miR-144 and miR-223, which downregulates IRS-1 and upregulates P2Y receptor 12 (P2Y12) expression in the platelets of patients with T2DM, through the IRS-1/PI3K/Akt signaling pathway (85). Cystatin expression is downregulated by platelet-derived miR-92a in patients with T2DM and lower limb ischemia (86). However, Stratz *et al*. did not find any differences in platelet miRNA profiles between patients with and without diabetes (87). In Stratz *et al*. study, drugs used to treat coronary artery disease may have influenced the results. Some studies have a found marked reduction of miRs after anti-platelet therapy (88-92). It is suggested that circulating miRs can be novel biomarkers for platelet activation (93), and platelet-derived miRs have been shown to be novel biomarkers the early diagnosis of T2DM (94).

miRs are associated with inflammatory status in patients with T2DM. Recent studies have suggested that miR-146 inhibits the inflammation associated with diabetic retinopathy. miR-146 inhibits NF-κB activation and subsequent inflammatory responses in human retinal endothelial cells (95). Fulzele *et al*. found that ectopic expression of miR-146 suppressed adenosine deaminase-2 (ADA2) expression and activity, and TNF-α release in amadori-glycated albumin (AGA)-treated human macrophages related to retinal inflammation (96). Decreased serum level of miR-146a is a sign of chronic inflammation in patients with T2DM (97). Circulating angiogenic cells from patients with T2DM and major cardiovascular events have high levels of miR-21, which demonstrates that circulating miR -21 is a biomarker of systemic inflammatory status (98). Figure 2 shows the mechanism of inflammation and platelet hyperactivity in T2DM, showing the possible targeting sites for miRs.

7. MIRS AS POTENTIAL PROGNOSTIC BIOMAKERS AND THERAPEUTIC TARGETS IN DIABETIC VASCULOPATHY

Our understanding of how these miRs function in cellular networks provides new molecular targets for therapy of diabetic vasculopathy, and the first examples of miR-based therapy in animal models are well underway. Zampetaki *et al*. identified two angiogenicmiRs, miR-320a and miR-27b, as potential biomarkers for diabetic retinopathy (38). Liu *et al*. presented direct evidence suggesting that miRs are intrinsic suppressors of pathological ocular angiogenesis in endothelial cells (53). Suppression of endogenous miRs in pathological neovascularization may induce endothelial activation to trigger pathological angiogenesis. miRs as endothelium-specific intrinsic inhibitors of pathological ocular angiogenesis suggest the potential of modulating miRs for the treatment of neovascular eye diseases and potentially other vascular diseases (53). García *et al*. suggested that patients with diabetic retinopathy had higher expression of miR-221 than those without retinopathy, and identification of biomarkers of diabetic complications might be useful for monitoring disease progression and potential therapeutic targets (65). DM is a high risk factor for stroke and leads to more severe vascular and white-matter injury than stroke alone. Cheng *et al*. provided evidence for epigenetic regulation of gene expression and function in chronic experimental diabetic neuropathy (99). They also showed that miR-126 may contribute to human umbilical cord blood cells (HUCBC)-induced neurorestorative effects in T2DM mice (100). Yousefzadeh *et al*. found that deregulation of miR-146a may be involved in the pathogenesis of diabetic neuropathy (101), which suggests that miR-146a is a potential biomarker in diabetic retinopathy. Another serious microvascular complication is diabetic nephropathy. Liu *et al*. suggested that urinary miR-126 was significantly higher in patients with T2DM with diabetic nephropathy (102). Successful treatment significantly reduced urinary miR-126 in patients with T2DM with diabetic nephropathy (102). So, miR-126 could be used as a biomarker of diabetic nephropathy and to monitor the treatment response (102). Other current studies have proved that EPCs are biological markers of peripheral arterial disease (103). And now studies have proved that endothelial progenitor cells as a biological marker of peripheral artery disease (104). Riches *et al*. suggested that increased expression of miR-143/5 in saphenous vein SMCs from patients with T2DM induces persistent changes in phenotype and function, indicating that miR-143/5 play an important role in diabetic peripheral vascular disease (105, 106).

miR-21 overexpression enhances TGF-β1-induced EMT by targeting SMAD7, which aggravates renal damage in diabetic nephropathy (107). miR-34a alleviates mesangial proliferation *in vitro* and glomerular hypertrophy (44), and miR-135a promotes renal fibrosis in diabetic nephropathy (47). miR-346 attenuates SMAD3/4 expression in renal tissue and ameliorates renal function and glomerular histology in mice with diabetic nephropathy, which paves the way for clinical studies of miR-346 in diabetic nephropathy (52). Bhatwadekar *et al*. used

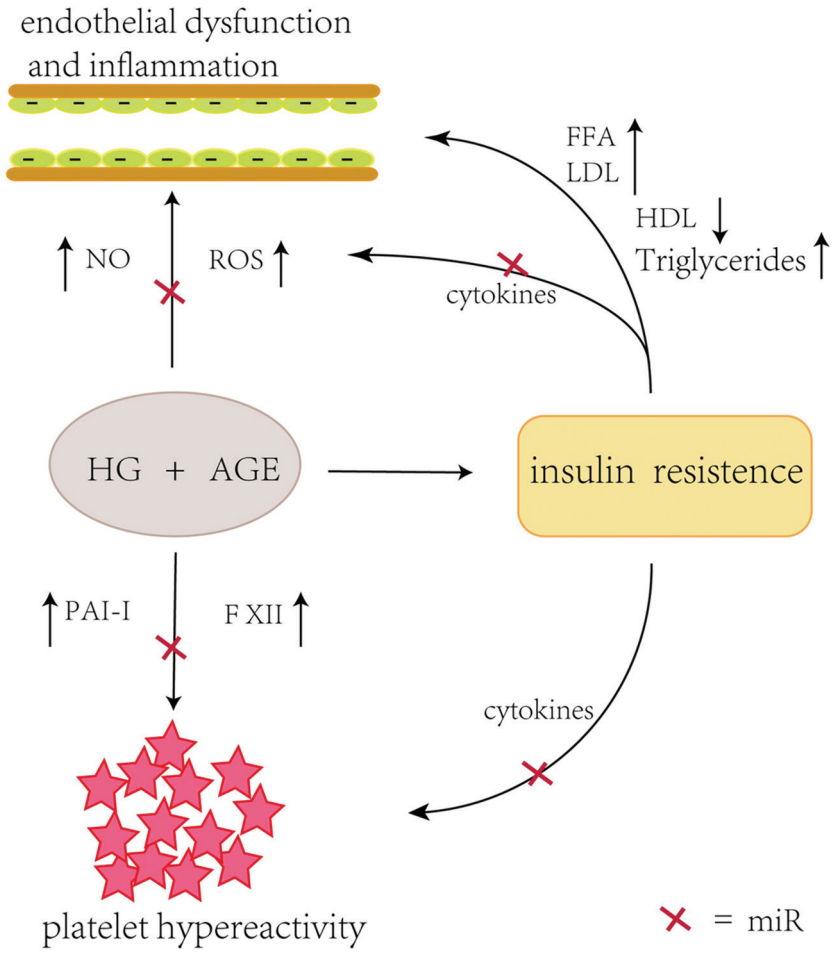

Figure 2. Biological processes of platelet functions and inflammatory status in diabetes. AGE = advanced glycated end-products; FFA = free fatty acid; FXII = factor XII; HDL = high-density lipoprotein; HG = hyperglucose; LDL = low-density lipoprotein; PAI-1 = plasminogen activator inhibitor-1; ROS = reactive oxygen species.

autologous CD34+ cells for vascular repair in spatients with diabetic microvascular disease, and restoring levels of miR-92a enhanced the usefulness of CD34+ cells in autologous cell therapy (106). Endothelial HIF-1α promotes atherosclerosis by triggering miR-19a-mediated CXC ligand (CXCL)1 expression and monocyte adhesion, indicating that inhibition of the endothelial HIF-1α/miR-19a pathway is a therapeutic option againstatherosclerosis (40). So, as in animal experiments, miR-98 upregulated TRB2 in targeting way, which plays important roles in the pathogenesis of diabetic complications (108). Thus, miR-98 may be regarded as a novel therapeutic strategy for early large artery defects in T2DM. In summary, experiments *in vitro* and *in vivo* indicate that miRs are potential prognostic biomakers and therapeutic targets in diabetes.

8. CONCLUSIONS AND PERSPECTIVES

miRs are involved in vascular injury and repair, and fibrosis, and have many pathological effects in diabetes. One single miR can possibly modulate dozens of target genes simultaneously, and one gene can be targeted by multiple miRs, thus, it is necessary to understand better the integration of miRs within gene regulatory networks. Although researchers have made a lot of progress, there is a need to learn how to prevent or delay T2DM vasculopathy with molecular-based therapies. There is a need to find miR-based biomarkers and diagnostic strategies useful for the early detection of these complications in asymptomatic patients.

9. ACKNOWLEDGEMENTS

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Abbreviations: miRs: microRNAs; T2DM: type 2 diabetes mellitus; SMCs: smooth muscular cells; AGEs: advanced glycation end products; EPCs: endothelial progenitor cells; pri-miRs: primary miRs; PBMCs: peripheral blood mononuclear cells; EndMT: endothelial-to-mesenchymal transition; DR: diabetic retinopathy; DN: diabetic neuropathy; RISC: RNA-induced silencing complex; CAD: coronary artery disease; Ago: Argonaute;TRBP: the HIV-1 TAR RNA binding protein; dsRBP: a

double strand RNA binding protein; DGCR8: dsRBD domain binding partner protein; PTEN: phosphatase and tensin homologue; SMAD: decapentaplegic homolog; GAS1: growth Arrest Specific-1; TRPC1: transient receptor potential-canonical 1; IRS2: insulin receptor substrate 2;SIRT1: silent mating-type information regulator 2 homolog 1;SDF-1α: stromal cell-derived factor -1α; ICAM-1: intercellular adhesion molecule-1;CXCR4: chemokine CXC receptor4;WWP1: WW domain-containing E3 ubiquitin protein ligase 1; Runx3: runt-related transcription factor 3; PIK3R2: PI3K regulatory subunit p85 beta; EMT: endothelial-to-mesenchymal transition; HUCBC: human umbilical cord blood cells;ADA2: adenosine deaminase-2; AGA: amadori-glycated albumin.

Key Words: Diabetic Vasculopathy, MicroRNAs, Signaling Pathway, Review

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