MicroRNAs: Potential Targets in Diabetic Retinopathy

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ABSTRACT

Diabetic retinopathy (DR), a serious microvascular complication of diabetes, is a leading cause of blindness in adults. The pathogenesis of DR involves a variety of tissues and complex mechanisms, such as inflammation, oxidative stress, optic neurodegeneration, and autophagy. Nowadays, microRNAs (miRNAs), a novel group of non-coding small RNAs, have been extensively studied and recognized to play a key role in the pathogenesis of DR through aforementioned pathways. Furthermore, some miRNAs have been proposed as biomarkers that may be utilized to screen for DR. Also, miRNAs are a new therapy for DR. In this review, we summarize several miRNAs and, their roles in the pathogenesis of DR. miRNAs, as potential pharmacological targets for the diabetic retinopathy, may provide new insights for the treatment of DR.

Introduction

miRNAs are single-stranded non-coding small RNAs (19–22 nucleotides) generated from a well-organized RNA processing event, and they also belong to highly conserved endogenous RNA sequences. Thus far, approximately 2000 miRNAs across the human genome have been identified and play an important role in physiology and pathophysiology [1]. miRNAs are found to express in all human cell-types and are involved in the major biological processes including cell growth, differentiation, and apoptosis [2]. In the last decade, miRNAs have received substantial attention as potential players involved in microvascular complications of diabetes, affecting the kidney, retina, and peripheral neurons. Compelling evidence indicates that abnormally expressed miRNAs have pivotal roles in key pathogenic processes of microvascular complications [3], such as oxidative stress, apoptosis, inflammation, and angiogenesis. miRNAs have become one of the hot issues after siRNA in recent years.

Circulating miRNAs as Biomakers in DR

Although miRNAs are not involved in gene coding, they play a regulatory role in Eukaryotic gene expression, cell and individual de-velopment. Upregulation of miRNA can be used to identify functional phenotype, and the inhibition or downregulation can be investigated for functional deletion phenotypes. The combination of upregulation and downregulation can be used to identify the gene regulated by a specific miRNA, as well as cell process affected by the specific miRNA. It is speculated that miRNA regulates one third of the human genes [4]. Meanwhile, some breakthrough study in 2016 [5] demonstrated that miRNAs are also extracellular, being present in a cell-free circulating form in the serum, plasma, saliva, tears, aqueous and vitreous humor, and urine [6, 7], which could be called circulating miRNAs.

Zampetaki et al. [8] found that miR-27b and miR-320a are being significantly and independently associated with higher risk of DR. It is an important advance in the field of miRNAs biomarkers that has implications in the areas of DR pathogenesis, prognostication, monitoring, and therapeutics. Compared to tissue-derived miRNAs, circulating miRNAs are more stable. Cells release miRNAs into the circulation, where they have a long-life span (approximately 2 weeks); their stability in plasma/serum/urine on freeze-thawing, efficient recovery, and availability of quantitative detection methods enhance their use as a biomarker as well as a potential media-

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tor of physiological and pathological processes [9]. Therefore, miR-NAs are very feasible as novel biomarkers for certain diseases, such as DR.

As biomarkers in DR, miRNAs not only expressed in serum, but also occur in vitreous humor. Notably, in the same individuals, only a few circulating miRNAs were detected in vitreous compared with serum [10]. In ▶Table 1, we have summarized miR-126 [11, 12], miR-211 [13], miR-93[14–16], miR-122 [17], miR-221 [18], miR-27b and miR-320a [8], miR-150–5p, miR-21–3p and miR-30b-5p [19] as biomarkers in DR over the past 5 years. At the same time, we have focused on miRNAs in vitreous humor (VH) of DR, such as miR-126 [20], miR-19a and 27a [21], miR-29a [22, 23], miR-93 and 20a [21], and miR-200b [24] in ▶Table 2.

miRNAs and Diabetic Retinopathy (DR)

DR is a progressive disease, which is duration-dependent and develops in stages of growing severity, with oxidative stress, inflammation, and angiogenesis etc. leading to microvascular alterations. Xiong et al. [25] found that miRNAs perform critical regulatory functions during the early stages of DR evolution, including development, differentiation, proliferation and stress responses in DR pathogenesis [26]. Generally, there are two major DR stages – non-proliferative (NPDR) and proliferative (PDR) retinopathy. In NPDR, thickening of the basement membrane and pericytes/endothelial cell loss result in increased vascular permeability and development of microvascular abnormalities, such as dilated vessels, capillary microaneurysms, shunts, and vascular occlusion. In PDR, both leaking and breaking of immature and fragile new vessels can cause vitreous hemorrhages, macula edema, fibrosis, retinal detachment, and possibly sight loss [3]. Here, we present a summary and discuss the possibility of targeting miRNAs in potential treatment of DR, providing new ideas for prevention and treatment of DR.

miRNAs, Oxidative Stress, and DR

Hyperglycemic, a known instigator in DR, could provoke oxidative stress and the studies show that changes in miRNAs expression levels may be associated with the onset and progression of DR. After consulting the literature, we found that miR-7, 15a, 27b, 100, 145, 195, 200b, 365, 383, and miR-455–5p are associated with oxidative stress in DR. Next, we will elaborate on the role of these miRNAs in DR.

miR-7

Hypoxia is associated with an increment in oxidative stress [27] and the disruption of endothelial adhesion molecules [28, 29], resulting in increased endothelial permeability [30] and impairment of vasodilation [31]. The study of Garcia-Morales et al. [32] showed that hypoxia in DR increases the expression of miR-7, which in turn reduces the protein availability of EPAC-1; the loss of EPAC-1 in endothelial cells causes endothelial junctional instability and concurrently hyperpermeability, resulting in oxidative stress. Combined, hyperpermeability and oxidative stress might further reduce the oxygen transport creating a feed-forward mechanism that aggravates DR. These results suggest that miR-7 could take part in DR by oxidative stress pathway.

▶Table 1 miRNAs as biomarkers in DR and their changes.

miRNAs	Changes in DR	Targets
miR-126	↑	VEGF/IRS-1
miR-211	↑	Sirtuin1
miR-93	↓	VEGF
miR-122	↑ / ↓	–
miR-221	↑	–
miR-27b	↓	Antiangiogenic
miR-320a	↑	Thrombospondin-1
miR-150–5p	↓	–
miR-21–3p	↑	–
miR-30b-5p	↑	–

▶Table 2 miRNAs in vitreous humor (VH) of DR.

miRNAs	Change in VH	Significance
miR-126	↑	miR-126 is closely related to the pathogenesis and progression of PDR, and the miR-126 expression level rises with the increase of severity of PDR
miR-19a miR-27a	↑	miR-19a and miR-27a combined are putative diagnostic biomarkers for PDR
miR-29a	↓	miRNA-29a has been shown to be a negative regulator of DR and its decrease in expression levels is associated with exacerbation of PDR
miR-93 miR-20a	↑	miRNA-20a and miRNA-93 could suggest a prognostic biomarker potential for sight-threatening PDR complications such as recurrent vitreous hemorrhage (RVH)
miR-200b	↑	Both miRNA-200b and VEGF are increased in the vitreous of patients with PDR but in a noncorrelated pattern. miRNA-200b may be involved in the pathogenesis of PDR but through VEGF-independent mechanisms
		Further studies are needed to identify the miRNA-200b targeted genes that are involved in PDR pathogenesis and to examine the potential role of miRNA-200b as a target for PDR treatment

miR-15a, miR-27b, miR-145, miR-383

Many studies have shown that reactive oxygen species (ROS) is a major causative factor involved in the development of DR [33]. Based on the study of Kamalden et al. [34], miR-15a, produced in pancreatic β-cells, can enter the bloodstream and contribute to retinal injury. They found that miR-15a overexpression results in oxidative stress by targeting Akt3 and by inhibiting PI-3 kinase path-

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way to induce ROS accumulation, which lead to apoptotic cell death. In other words, miR-15a is correlated with diabetes severity and may contribute to the development of DR.

Li, Hui, Kang et al. [35] found that miR-27b reduces the generation of ROS and downregulates the P13K/AKT/mTOR signaling pathway by inhibition of Nox2. Hui and Yin [36] found miR-145 overexpression reduced the intracellular ROS production and malondialdehyde level, whereas it increased the activity of superoxide dismutase. Therefore, miR-145 can reduce high-glucose induced oxidative stress and apoptosis in retinal endothelial cells. In addition, PRDX3 is a target of miRNA-383, which can play a role in cell survival by decreasing the ROS [37, 38]. Meanwhile, miR-383 mediates high glucose-induced oxidative stress and apoptosis in retinal pigment epithelial (RPE) cells by repressing peroxiredoxin 3 (PRDX3) [39]. These miRNAs may have an impact on the treatment or prevention of DR.

miR-100

miR-100, a member of miR-99 family (including miR-99a, miR-99b, miR-100), is a key apoptotic regulator in various cell types [40, 41]. Recently, it has been discovered that oxidative stress can upregulate miR-100 in retinal ganglion cells (RGCs), and hydrogen peroxide can induce apoptosis by increasing miR-100 expression. Conversely, diminished miR-100 expression is associated with activation of the AKT pathway, extracellular-signal-regulated kinase (ERK) pathway, and tropomyosin receptor kinase B (TrkB) pathway [42]. And a study in 2014 [43] has found IGF1R (IGF-1 receptor) was directly regulated by miR-100 in RGC-5 cells, and siRNA-mediated IGF1R knockdown activated AKT protein through phosphorylation; downregulated miR-100, thus exerted a protective effect on RGC-5 apoptosis. Therefore, reducing miR-100 expression can be an applied therapeutic method to protect oxidative stress-induced apoptosis.

miR-195

There is an established association between miR-195 and oxidative stress/diabetes-induced retinal endothelial cell injury because of miR-195 acting as a regulator for mitofusin-2 (MFN2), which is known to be involved in oxidative stress and diabetes associated complications [42]. Based on the luciferase report assay, miR-195 binds to the 3'-UTR of MFN2 mRNA and its overexpression can result in the downexpression of MFN2 protein leading to tube formation and an increase in blood-retinal barrier permeability [44], thus leads to DR. Therefore, miR-195 could be a potential therapeutic target for intervention of DR in future [45].

miR-200b

miR-200b is one of the well-known miRNAs, which could affect DR by affecting oxidative stress. Although bioinformatic analyses identified a number of potential target genes of miR-200b, we focus on oxidation resistance 1 (Oxr1) as a downstream target gene regulated by miR-200b. A study represented that miR-200 can downregulate Oxr1 expression in the retina of diabetic rats as increasing the expression of Oxr1 induces oxidative stress and apoptosis [46]. These results suggested that miR-200b-regulated Oxr1 potentially has a protective role in DR.

miR-365 and miR-455–5p

In the retina, miR-365 was mainly expressed in the INL (inner nuclear layer), PR layer, and RPE (retinal pigment epithelial) layer, especially in Müller cells. Based on a study by Wang et al.[47], Timp3 is a target of miR-365 and is negatively regulated by miR-365. They demonstrated that the increase of miR-365 in retinal Müller cells participated in the pathogenesis of DR through oxidative stress, and miR-365 inhibits Timp3 to increase oxidative stress. In other words, miR-365/Timp3 could be a potential therapeutic target for treating DR.

Suppressor of cytokine signaling 3 (SOCS3) is a direct target gene of miR-455–5p and negatively regulated by miR-455–5p. The study showed that augmentation of miR-455–5p remarkably alleviated HG-triggered oxidative stress injury as reflected by decreased the production of intracellular ROS and malondialdehyde (MDA) content as well as NADPH oxidase 4 expression, concomitant with enhanced the activities of superoxide dismutase, catalase, and GPX [48]. That is to say, miR-455–5p has antioxidant activity and could be as a new potential therapeutic agent for DR treatment.

miRNAs, Inflammation, and DR

Hyperglycemia stimulates inflammation and promotes vascular dysfunction of the retina, leading to increased capillary permeability and vascular leakage. Therefore, inflammation signaling pathways play a major role in DR. miRNAs can interact with mRNA on miRNA response element that is found in the UTR of the mRNA target. With that, miRNAs regulate almost every cellular and developmental process, including the regulation of instinct immune responses and inflammation [49]. Herein we could summarize the role of miRNAs in inflammation pathways of DR. After consulting the literature, we found that miR-15a, 145, 146 are associated with inflammation in DR.

miR-15a, miR-15a/16, and miR-145

miR-15a is a key regulator of both pro-inflammatory and pro-angiogenic pathways and is downregulated in diabetic retina. Based on a study conducted by Wang et al. [50], miR-15a was identified as a miRNA that provides inhibition to both ASM and VEGF-A activation. They previously found that acid sphingomyelinase (ASM), the enzyme converting sphingomyelin into pro-inflammatory and pro-apoptotic ceramide, is highly activated by diabetes in the retina [51]. Endothelial cells, which represent a major source of ASM, had the highest level of activation of ASM in diabetic retina. Therefore, they provide an entirely new mechanism for the pathogenesis of DR based on diabetes-induced downregulation of miR-15a expression leading to pro-inflammatory and pro-angiogenic changes in the diabetic retina due to unopposed activation of miR-15a target genes, ASM and VEGF-A [50].

In addition, the evidence showed that hyperglycemia can induce downregulation of miR-15a and miR-16, while overexpression of miR-15a and miR-16 can decrease pro-inflammatory signaling pathways of IL-1β, TNF-α, and NF-κB under conditions of hyperglycemia. Also, decrease of miR-15a and miR-16 induce retinal leukocytosis and increase CD45 levels, followed by upregulated levels of IL-1β, TNF-α, and NF-κB pathways [52]. Consequently, miR-15a

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and miR-16 can play essential roles in reducing retinal leukocytosis, probably through inhibition of inflammatory cellular signaling pathways [53].

Based on a study by Hui and Yin [36], miR-145 attenuates high glucose-induced oxidative stress and inflammation in retinal endothelial cells through regulating TLR4/NF-κB signaling. However, other mechanisms by which miR-145 affects the DR inflammatory pathway remain to be investigated.

miR-146

miR-146a is a well-known modulator of both the innate and adaptive immune response, which has been implicated to function in inflammation, innate immunity, and cancer. miR-146a has also been shown to regulate mitochondrial functions such as inflammation-aging [54–56]. A previous study showed miR-146a expression in different types of retinal cells, including retinal endothelial cells, Müller cells, and RPE cells [57]. One of the most important miRNAs in retinal endothelial cells is miR-146a, which is transactivated by NF-κB pathways for the upregulation of this expression. The increase of miR-146a expression levels also exerts negative feedback on IL-1R/TLR-mediated NF-κB activation by targeting IL-1 receptor-associated kinase 1 (IRAK1) and TNF-α receptor-associated factor-6. Thus, miR-146a can play a negative regulatory function in NF-κB activation pathways, which are related to inflammatory processes in DR [58].

In addition, a previous study showed an increase of ADA2 (AdenosineDeaminase-2) in macrophage-rich tissues during inflammatory [59, 60] and ADA2 activity is elevated significantly in pleural fluids of patients from patients with diabetes [61]. Then, it was found that ADA2 is a direct target of miR-146b-3p and decreased miR-146b-3p is associated with increased ADA2 activity. Ectopic expression of miR-146b-3p suppressed ADA2 expression, activity, and TNF-release in the AGA-treated human macrophages. These results suggest a regulatory role of miR-146b-3p in diabetes related retinal inflammation by suppressing ADA2 [62].

Finally, miR-146 may be an alternative therapeutic target for the treatment of diabetic retinopathy through inhibition of NF-κB signaling pathways. [63]. All in all, it is evident that miR-146 plays an important role in the inflammatory pathways that occur in DR. Thus, there is more work to be done in the future.

miRNAs, Angiogenesis, and DR

Angiogenesis is the process through which new blood vessels arise from the pre-existing post-capillary venule, which is usually the end result of DR, especially as a maker for distinguishing NPDR and PDR. A breakthrough experiment in 2006 first revealed the involvement of miRNAs in angiogenesis [64]. Regulation of angiogenesis is very complex and, the addition of latest dimension of miRNA-based regulation, have made it more complicated [65]. The term angio-miRNAs (angio-miRs) were proposed to miRNAs that regulate angiogenesis [66]. As we all know, a wide range of regulators and signaling molecules, including vascular endothelial growth factor-A (VEGF-A), fibroblast growth factor (FGF), epidermal growth factor (EGF), interferon, matrix metalloproteinase-1/9 (MMP-1/9) are associated with angiogenesis [67–69]. Herein, we have summarized some miRNAs that have impacts on DR by VEGF and FGF.

miRNAs can be divided in two types, one is pro-angiogenic and the other is anti-angiogenic. miR-126, miR-17–92 cluster, let-7b, 7f, miR-130, miR210, miR-378, and miR-296 are reported as pro-angiomiRs and miR-221/222, miR-328, miR-15b/miR-16, and miR-20a/20b function as anti-angiomiRs [70].

miR-126 is an endothelial specific miRNA, which plays a pivotal role in maintaining endothelial homeostasis and vascular integrity [71]. In response to VEGF and bFGF, it suppresses the negative regulators of angiogenesis such as sprout-related protein (SPRED-1) and PI3 kinase regulatory subunit 2 (PIK3R2), and promotes angiogenesis [11]. miR-200b is a cluster of miR-200 family, which are highly associated with epithelial-mesenchymal transition (EMT). VEGF-a gene is a direct target gene of miR-200b and its overexpression can reduce the growth level of retinal micro-vessel density (MVD) so as to reverse the occurrence of retinal lesions and can also reduce the number of vascular endothelial cells and inhibit the formation of retinal neovascularization buds [72]. Recently, miR-15a has been identified as a key regulator of pro-angiogenic pathway through direct binding to VEGF-a (but not VEGF-b, c and d) 3'UTR [73]. Based on the study of Wang et al. [50], miR-15a negatively regulates the expression level of VEGF-a. And VEGF-a and FGF2, by miR-15a is important in maintaining the delicate balance. Disruption of this balance could favor pathological angiogenesis, such as seen in DR. In addition, miR-15b and miR-16 have VEGF-a as their predicted target, which they are down regulated with hypoxia induction and promote VEGF-a expression which ultimately facilitates angiogenesis [74].

Finally, we introduce one of the family of miR-21, miR-21–5p. miR-21 is highly expressed in a variety of cancers [75–77] and diabetes-related diseases [78]. However, the effect of miR-21 on retinal angiogenesis is still not clear. In the present study, human retinal microvascular endothelial cells (HRMECs) were employed to investigate the effect of miR-21–5p on high glucose-induced angiogenesis and the underlying mechanisms. They found inhibition of miR-21–5p suppresses high glucose-induced proliferation and angiogenesis of human retinal microvascular endothelial cells by the regulation of AKT and ERK pathways via maspin [79], which is a target gene of miR-21–5p that involved in angiogenesis [80]. In conclusion, there are a great deal of miRNAs associated with angiogenesis, but angio-miRNAs in DR are still studied.

miRNAs and Therapy

Nowadays, targeting miRNAs is becoming a novel therapeutic approach. Developing miRNAs-based therapeutics has two major approaches: antagonists to inhibit endogenously present miRNA that has lethal gain of function and miRNA mimics, which can restore useful miRNAs, with the loss of function [81]. miRNA mimics are small, chemically modified, double stranded RNA molecules that can mimic endogenous mature miRNA molecules [82]. Both miRNA mimics and inhibitors have been delivered at the target tissues by use of numerous conjugate molecules in the experimental setting [83].

A study by Zhang, Cui, and Xu [84] found that FGF5 is a target gene of miR-145–5p and FGF5 knockdown could partially reverse the protective effects of miR-145–5p on RGC-5 cells. And miR-145–5p inhibitor decreased pro-inflammatory cytokines, including

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tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) levels, elevated cell viability and proliferation, as well as suppressed cell apoptosis. In other words, miR-145–5p inhibitor might be a neuroprotective target for DR. A new study found that miR-183 inhibitor suppressed the proliferation and angiogenesis of vascular endothelial cells by inactivating the PI3K/Akt/VEGF signaling pathway via the downregulation of BTG1, which may be a new therapeutic target for DR [85].

In addition, the study of Chen, Zhao, and Gu et al. [86] found FGF16 is a target gene of miR-144–3p and miR-144–3p inhibited high glucose-induced cell proliferation through suppressing FGF16 and MAPK signaling pathway, suggesting it may be novel targets for DR prevention. Also the current study supports that miR-384–3p inhibits the proliferation of RMECs through downregulating HK2 (hexokinase 2) and provides inhibition of retinal neovascularization in DR, which provides significant guidance for further exploring the therapeutic methods for DR [87].

In the future, miRNA mimics and inhibitors may be an effective way to treat DR, and studying the mechanism of miRNAs in DR may provide a new idea for DR therapy.

Conclusion and Perspective

In conclusion, miRNAs are involved in the pathogenesis of DR in various ways, including inflammation, oxidative stress, and angiogenesis. Studying their roles in DR could lead to a more detailed understanding of the development of the disease and its effective treatment. With the discovery of more miRNAs, miRNAs as biomarkers in DR has become a research hotspot. In addition to miR-27b and miR-320a, miR-150–5p and others have been found to act as biomarkers. Changes in miRNAs levels can be detected in diabetics at present, however, in the future we may find changes in miRNAs levels could distinguish the stages of DR or the type of diabetes. It is promising to use miRNAs to treat DR, but the specific pathophysiological processes of miRNAs and their target genes in DR still need to be fully studied and verified. miRNA mimics or inhibitors are now widely used in animal studies and may one day be a new way to treat DR. In order to reduce the risk of blindness in diabetic patients, we should further study the target of miRNAs and their effect on DR.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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