Review Article

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DIAGNOSTIC IMPORTANCE OF MIRNA IN DIABETIC RETINOPATHY

Sanchita Srivastava, Alina Zaidi, Sheeba Afreen, Ale Eba, Muneshwar, Syed Tasleem Raza

Department of Biochemistry

Era's Lucknow Medical College & Hospital, Sarfarazganj Lucknow, U.P., India-226003

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Address for correspondence

Dr. Syed Tasleem Raza
Department of Biochemistry
Era's Lucknow Medical College & Hospital, Lucknow-226003
Email: tasleem24@gmail.com
Contact no: +91-8707038841

ABSTRACT

Diabetes type II is an autoimmune disorder of multiple etiologies that is basically due to deregulation of blood glucose homeostatis, thus causing hyperglycemia accompanied by various other disturbances of carbohydrates, fat and protein metabolism. Broad classification of these diabetic complications involves two major groups - microvascular which includes retinopathy (leading to blindness), nephropathy (leading to renal failure) and neuropathy (leading to nerve damage) and macrovascular, including cardiovascular complexity and peripheral vascular disease. Diabetic retinopathy (DR) is a microangiopathy that induces optical complications in a diabetic subject that leads to acquired blindness in young adults due to high susceptibility of cellular components of retina towards the hyperglycemic environment. A large number of protein coding genes and some non-coding RNAs (ncRNAs) are reported to be involved, among which miRNAs are a small group of ncRNAs that are broadly studied to understand the pathology of the disease. Therefore, the functions and initiation of miRNAs could be regulated as their variation is allied with a broad array of functional defects, including incurable conditions. This review focuses on the molecular mechanisms of miRNA in response to DR.

KEYWORDS: Diabetes type II, Diabetic retinopathy, Micro RNA, Vascular endothelial growth factor (VEGF), NF-κB, Silent Information Regulator Protein 1 (SIRT1).

INTRODUCTION

Diabetes type II is an autoimmune disorder of multiple etiologies that is basically due to deregulation of blood glucose homeostasis, thus causing hyperglycemia accompanied by various other disturbances of carbohydrates, fat and protein metabolism (1-2). The prevalence of this disease worldwide is a serious threat as it has increased substantially since last 50 years and has been adjudged to adversely hit 592 million population by 2035 (3). The pathogenesis of this heterogeneous disease involves various factors such as genetic, epigenetic and environmental factors (4). The basic mechanism behind the development of this chronic disease is the disability of β cells to produce compensatory insulin which is a necessary step towards increased insulin resistance (5). The vascular complication of the prolonged sustainability of the disease is a serious and thus reduces the life expectancy of an individual (6). General signs and symptoms that mark the onset of the disease include blurred vision, polyurea, polydipsia, weight loss and polyphagia (7). It has therefore become crucial to develop improved therapeutic strategies for chronic conditions related to diabetic complications. Broad classification of these diabetic complications involves two major groups - microvascular which includes diabetic neuropathy, diabetic retinopathy and diabetic nephropathy and macrovascular, including cardiovascular complexity and peripheral vascular disorders (8).

Microvascular complications of diabetic retinopathy

DR is a microangiopathy that induces optical complications in a diabetic subject that leads to acquired blindness in young adults due to high susceptibility of cellular components of retina towards the hyperglycemic environment (9-10). The disease progresses with elevated vascular permeability, ocular hemorrhages, moderate or severe Non Proliferative Diabetic Retinopathy (NDPR) characterized by liquid discharge due to peripheral vascular closure, Proliferative Diabetic Retinopathy (PDR) abnormal neovascularization (NV) from the preexisting choroid beneath the retina and posterior vitreous surface (11). DR is predicated as a salient reason for vision impairment among working population (12-13).Meta analysis of population based studies estimated that the global thrust of this abrasive vision among population is attributable to DR (14) reporting 2.6 million consequences in 2015 which is projected to rise up to 3.2 million cases in 2020 (15). Although epidemiological studies suggest that improved therapies

have been introduced in developed countries which have counterbalanced the increasing trend of the disease and reduced the incidence of vision threats (16-19). The pathogenesis and complexity of DR involves cascades of mechanisms such as imbalanced radicals and anti-oxidants through excess reactive oxygen species (ROS) due to elevated blood glucose levels in the retina thus activating the four canonical pathways that cause disruption of retinal architecture (20). Stimulated secretion of pro-inflammatory cytokines inflicts systemic inflammatory environment for retina that ultimately leads to retinal microvascular abnormalities (21-22). Neuronal degeneration is also depicted with the progression of the disease via altered metabolism which leads to programmed cell death of retinal ganglion cells (RGC) and malfunctioning of glial cells (23) These metabolic modulations of DR also affect the hereditary modifications in gene (DNA methylation, histone modifications, and miRNAs regulation) thereby aggravating the progression of the disease in spite of controlled glucose levels (24-25). Post translational modifications along with epigenetic changes interact closely leading to pathological alterations in retina.

A multiple number of protein coding genes such as vascular endothelial growth factor (VEGF) (26), pigment epithelium derived factor (PEDF) (27), angiopoietin (28), and bone morphogenetic protein (BMP) (29) related to the pathways involved in the pathogenetic mechanism of DR play crucial role in vascular changes. In addition to these protein coding genes, some non-coding RNAs (ncRNAs) are reported to be involved, among which miRNAs are a small group of ncRNAs that are broadly studied to understand the pathology of the disease (30-33).

Emerging role of microRNA in disease progression

Micro RNAs (approx. 21–23 nts long) are highly conserved sequences of endogenous small non coding RNAs present in the form of cell free structures n blood circulation (10) that modulate gene expression at post-transcriptional level by binding to complementary 3' UTR of the target mRNA and thereby restraining protein synthesis (34-35). Major signaling pathways could be adversely affected if associated miRNA are dysregulated and hence they are meant to control gene regulatory functions (36). A particular miRNA can regulate the expression of numerous other mRNAs; on the contrary, more than 60% of mRNAs allow concomitant interaction with multiple miRNAs through predicted binding sites. (37). Therefore, the functions and initiation of miRNAs could be regulated as their variation is allied with a broad array of functional defects, including incurable conditions Indeed, these circulatory miRNAs are also involved in various physiological mechanisms such as cell expansion, differentiation, apoptotic pathway and metabolism of the cellular components hence, they are employed in various pathologies in the form of diagnostic, prognostic and predictive biomarkers as they can be easily be extracted through non- invasive procedures (38-39).

miRNAs have been discovered to be involved in modulating DR-related NV. An elevated level of glucose in blood is the prime origin of type 2 DM and its associated complications. DR is a persistent ocular complexity associated with DM, presenting microvascular and macrovascular complications. The adverse consequences of high glucose (HG) cause impairment to the components of blood-retinal barrier (BRB) that basically include human retinal ECs (HRECs) and retinal pigment epithelial (RPE) cells thus inducing dysfunction of BRB leading to DR progression (40-43) and hence used for numerous investigations to pacify their role in miRNAs. The first impending role of miRNAs in DR was observed through their altered expression levels in retina and RECs of a diabetic induced rat model, 3 months after the onset of diabetes. It was depicted via miRNAs array profiling that 80 miRNAs showed significantly high expression levels and 6 were less expressive in retina of diabetic rat in comparison to control model. Whereas, RECs of diabetic rats showed up-regulated levels of 16 miRNAs ($P<0.01$) and down-regulated levels for 104 miRNAs compared with those in controls ($P<0.01$) (44). Xiong et al. also diagnosed the retinas of STZ-induced DM rats in which he found 17 dysregulated miRNAs, 10 weeks after the onset of DM (45). Diverse expression levels of some retinal miRNAs coincides the track of DR, signifying a strong correlation between miRNA dysregulation and DR development.

Molecular mechanisms of specific miRNA in response to DR

miR200b

The most studied miRNA firstly discovered in association with DR was miR200b.The expression level of miR 200b were observed to be curtailed in the high glucose (HG) subjected endothelial cells and the retina of streptozotocin (STZ) treated diabetic rat after 1 month of diabetic onset whereas, its approved target, VEGF was found elevated at mRNA as well as protein levels (46). VEGF expressions are regulated by the overexpression of miR200b in the retinas of diabetic rats thereby preventing glucose induced endothelial hyperpermeability and retinal angiogenesis in human umbilical vein ECs (HUVECs). Contrawise, an antagonist of miR200b can boost VEGF production further elaborating the mechanisms of miRNA in DR

pathogenesis. A separate study conducted on a genetical construct of (Akita 8 month old diabetic mice) suffering from type I diabetes revealed significant increased expression levels of miR200b in comparison to control (47). It is particularized through various findings that miR200b deregulates the apoptosis and oxidative stress mechanism by inhibiting expression of the gene oxidative resistance1 (Oxr1) involved in the process. Moreover, miR200b is responsible for delaying DR by regulating the proliferation of HRECs through altered VEGF and TGF β1 expressions (48). While investigating the sera of DR patients, decreased expression levels of miR200b and increased levels of VEGFA was seen as compared to control patients (49). Another study revealed elevated expressions of miR200b in vitreous samples of eyes with PDR compared to control ($P<0.001$) and higher vitreous VEGF expression significantly higher in PDR group than in control group ($P<0.001$) and no significant correlation between miR200b and VEGF (50). Various conclusions are drawn from the above stated experiments that miR200b is downregulated HG treated ECs in the retina of STZ induced rat models and sera of DR patients whereas, it is unregulated in the retina of Akita mice and vitreous of PDR patients. Through these observations it was presumed that the variability in the results could be due to the differences in the duration of the diabetes. It was also deduced that the pathological changes synchronized with DR progressions may pose distinct effects on miRNA regulation at distinct stages of DR.

miR146

miR146 possess the ability to modulate NF-κB inflammatory cells through which, it was firstly explored in association with DR. NF-κB is a inducible proinflammatory transcription factor that plays a prominent role in modulating cellular inflammatory response at early stages of DR via miR146. The increased level of miR146 poses a negative feedback on NF-κB (51) and hence it plays a key role as negative regulator in multiple pathways of NF-κB activation which is completely affirmed by experiments conducted by various investigators for example Cowan et al illustrated a negative feedback mechanism which mediates activation of NF-κB by miR146 through thrombin induced G-protein coupled receptor (GPCR) (52). Ye et al ascertained that overexpression of miR-146a condensed the levels of NF-κB cells under hyperglycemic conditions (53).These empirical results imply that miR146a negatively regulates the pace of multiple inflammatory responses through NF-κB activation. Fibronectin (FN) is an extracellular protein (ECM) which characterizes chronic complications in diabetes if its levels are inflated. It is regulated by miR146 and is considered as a chief component for enhanced synthesis of ECM proteins in diabetes (54). miR146 also prevents Human Retinal ECs (Human Retinal ECs) from HG induced apoptosis by inhibiting STAT3/VEGF pathway via IL5 signaling (55). Along with miR146a, miR146b also has a vital role in inflammation procedure. In a study pursued by Fulzele et al it was observed that miR146b-3p has an association with HRECs by increasing its permeability and prevents the BRBs functioning in DR (56).

miR126

Observations fetched from oxygen induced retinopathy (OIR ice) unveiled down regulation of miR126. A dramatic vision loss is confronted due to pathological alteration in retinal NV mediated by various angiogenic factors such as IGF, hypoxia inducible factor-1 α (HIF-α) and VEGF, and hence under marked conditions restoration of miR 126 controls the levels of these factors thereby, reducing retinal NV. Declined levels of miR 126 stimulate p38 and ERK pathways and enhance the expression of these angiogenic factors downstream (57). Downregulation of miR126 is found in diabetic mice and approved by Ye et al. Angiogenesis is promoted through maintenance of extracellular vesicles (EVs) derivative of mesenchymal stem cells (MSCs) under diabetic conditions through paracrine signaling pathway. Under, hypoxic conditions expression levels of angiogenic factors VEGF and HIF 1 α are elevated due to down regulation of miR 126 in pericytes via MSc derived EV (58). Clinically the serum expression of miR126 is significantly decreased in diabetic patients in comparison to subjects without evident complications. Hence, serum experiments analysis of miR126 is a good diagnostic marker to monitor the outcome of disease. (59). A large cohort of type 1diabetes patients displayed significantly lower levels of miR126 than in control and were limited to the vascular complexities of diabetes with proliferative retinopathy in patients (60).

miR29 a/b

miR29 b is also associated with the DR. It is located in the Retinal Ganglion Cells (RGCs) and the Inner Nuclear Layer (INL) of the retina of both normal and STZ induced mice. Upregulation of this miR was seen after diabetic onset of 35 days in the retina of diabetic induced rat. miR29b also indirectly regulates proapoptopic RNA dependent protein kinase (PKR) and associated protein (RAX) localized in RGCs of retina (61). It is found that miR29b renders a protective effect against RGCs and INL cells in the early stages of STZ induced diabetic mice via proapoptopic PKR

pathway. Lin et al observed in an in vitro study that miR29 if upregulated also suspends HG induced apoptosis through reduced synthesis of caspase 7 in RPE cells and direct targeting of phosphatase and tensin homolog (PTEN) (61). miR 29a is also associated with AGT which is a rennin angiotensin system found in various organs and prevalent in variety of disease progression along with diabetes (62).In diabetic retina miR29a is decreased along with overexpressed angiotensionogen (AGT) and upregulation of miR29a regulates the vascular density, tortuosity and EC nuclei by inhibiting high levels of AGT (63). Thus DR development can be blocked by miR29a via down regulation of AGT witnessed in a rat model.

miR-195

Mortuza et al uncovered through his findings that up-regulation of *miR-195* in HG treated HRECs cells and retinal cells of diabetic mouse coincides with the down regulation of Silent Information Regulator Protein 1 (SIRT1). Alterations of SIRTs mediate some metabolic processes such as rapid aging in retina and ECs via increased oxidative stress by high glucose. Hence a plausible role of *miR-195*-SIRT1 signaling is ascertained in the modification of REC function as the neutralization of *miR-195* rescues SIRT1 expression and constrains tissue damage in DR. (64). Depending upon these previous findings, glucose induced oxidative stress that facilitates the over expression of miR 195 promotes two pathogenic modifications associated with DR ie; tube formation and enhanced permeability of retinal BRB. This process is additionally supported by a multifunctional mitochondrial protein found in the retinal cells of diabetic subject and HRECs (62, 63). Since miR195 is associated with the molecules related to oxidative stress leading to disease progression of DR, it can be used a potential therapeutic target.

Other miRNAs and their therapeutic roles in DR

Another miR associated with the SIRT1 signaling pathway is miR23b-3p which regulates HR induced cellular metabolic mechanism of DR. miR23b-3p expression is found elevated in HG treated HRECs. Whereas, reduced expression of miR23b-3p suppresses the expression of acetylated NF-κb by arresting the expression of SIRT1 thereby relieving the effects of metabolic changes induced by HG in HRECs (64).

Findings discovered by Kovacs et al revealed that the level of miR-34 family is found to be increased in the RECs of diabetic mice (65) whereas it is down regulated in a subset of ARECs cell which is confirmed by Hou et al. RPE cells show a proliferative and migratory tendency under pathological conditions such as DR. This characteristic feature of RPE cells is inhibited by miR34 a by inhibiting its target c-Met and other molecules of cell cycle such as CD2,4,6 and E2F1 and p-cdc2 (66). Up-regulation of miR34a also controls this tendency of RPE cells by down regulating the leucine rich repeat containing GPCR 4 expression and reduced expression levels of above mentioned cell cycle mediators (67).

MiR 15 b and miR 16 show downregulation under hyperglycemic conditions and play a significant role in inhibiting insulin resistance and preventing the apoptosis under such conditions rendering protection to HRECs (68). In addition to their regulatory roles regarding insulin resistance, these mRNA also possess inhibitory roles in proinflammatory signaling hence preventing retinal leukostatis in DR that is illustrated by Ye et al. Some inferences drawn by various conclusions state that proinflammatory signals such as IL-1β, TNFα and NFκB in HRECs cells under HG conditions are significantly reduced by overexpression of miR15 a and miR16 (69). Wang et al elucidated dual action of miR15 in DR that is anti-inflammatory and anti angiogenic (70). Overwxpressed miR16 in a mouse model also brings ASM and VEGFA to non diabetic levels and prevents diabetic induced retinal permeability (70).

Up-regulation of some other miRs such as miR21 miR135 is also found NFκB sensitive in RECs and retinal cells of diabetic mice (65). Studies conducted on miR21 stated that its over expression constrains the expression of proapoptotic mediator, death domain associated protein (DAXX), on the other hand, silencing of the later reverses the inhibitory effect of the associated miR 21 in HG induced endothelial apoptotic process that indicate miR 21 can seize apoptosis of ECs by inhibiting the expression of DAXX (71).

Some of the symptoms of the DR such as Proliferative Vitreoretinopathy (PVR) and PDR are associated with the increased levels of miR21 in the vitreous of eye. There is a direct correlation between miR21 and disease progression as it is noticed that levels of miR21 in HG treated RPE cells are enhanced under the influence of TGF-β. Collectively it is clearly concluded from gain and loss of function studies that miR21 is a potent disease modifying miRNA and promotes development of retinal fibrosis (72)

An important role of miR155 is fetched from several studies suggesting it as a pathogenic element of DR (73). Its expression is negatively correlated with the Treg cells and TGFβ cells that are significantly reduced as the levels of miR155 is significantly increased in the peripheral blood of PDR patients. Hence, miR155 is

also considered as a immunomodulator in signaling pathway (74).

Essential therapeutic implications have been drawn from the relationship between miR106a and VEGF and HIF1 α (directly involved in DR progression) as these factors are significantly decreased with the up regulation of this miRNA thus preventing HG induced permeability (75). Some of the regulators of angiogenesis such as VEGF and Ang-2 are significantly reduced by the over expression of miR351 in hypoxic RF6A cells and rats retinas. This cross-talk is the mircovascular response that is seen under hypoxic conditions (76). Overexpression of miR20b in STZ induced diabetic rats prevents the HG induced transendothelial permeability and tube formation by decrease in the levels of VEGF through AKT3 silencing (77)

miR18 b directly targets IGF1 factor in HG induced HRECs and promotes cell proliferation and enhanced VEGF production. This miR attenuates the expression of VEGF by suppressing IGF1 signaling pathways clearly depicting its clinical significance (78).

CONCLUSION

Inspite of advancement in the treatment for glucose, blood pressure, vascular and neurological problems the incidence of diabetes is increasing globally at an alarming rate beyond expectation. Diabetic retinopathy is one of the common consequences of diabetes. Early renal damage along with diabetes increases the risk of DR leading to micro and macrovascular complications. It is difficult for many people to envisage the clinical track of the disease and is not well aware of the primary and secondary treatments, risk factors, control etc. Hence, the strategy should be towards the development of newer treatments that are highly sensitive and cost effective. Therefore, micro RNA can be used for this clinical practice as they act as important biomarkers in the field of disease pathogenesis, monitoring and therapeutics. miRNAs are found as effective biomarkers since they show stability even after vigorous processing steps and availability of quantitative detection enhances their importance in therapeutics. Through, this review it is clearly depicted that pro-inflammatory signaling is a basic pathological response of DR which leads to endothelial indisposition. Pro-inflammatory cytokines such as IL1β and TNFα are found elevated with the progression in DR pathogenesis which drives the disease to later stages. Current paradigms in the field of diabetes through the use of mouse models emanate many unanswered questions regarding the regulation of signaling pathways. Among different miRNAs miR-200b, miR-146a, and miR-126 are the most focused miRNAs for emerging delivery platforms for studying inflammatory pathways, oxidative stress and angiogenesis.

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