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MINI REVIEW

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The effects of expression of different microRNAs on insulin secretion and diabetic nephropathy progression

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MicroRNAs (miRNAs) have recently become well-known efficacious biomarkers for the diagnosis of diabetic nephropathy (DN). MiRNAs, short noncoding RNAs, are posttranscriptional regulators of gene expression, which regulate several biological cell functions, including insulin production and secretion, as well as insulin resistance in tissues. Today, the focus of the medical world is centered on the role of miRNAs as mediators for different diseases, such as DN and end-stage renal diseases (ESRD). MiRNAs are stable and detectable in human biological fluids, so their detection for early diagnosis of different diseases is highly sensitive and specific. Previous reports have shown that the alteration of miRNA profiles significantly correlates with specific stages of DN, kidney fibrosis, and renal dysfunction. This review was aimed at assessing the pathway of different miRNA expressions responsible for insulin secretion disorder and DN progression.

KEYWORDS
diabetic nephropathy (DN), microRNAs (miRNA), renal dysfunction

1 | DIABETIC NEPHROPATHY

Diabetic nephropathy (DN), one of the microvascular long-term outcomes of type 1 and type 2 diabetes mellitus, has shown a skyrocketing rate of incidence recently. More than 40% of diabetic patients have end-stage renal disease (ESRD), requiring painful and expensive regular dialysis though the mortality rate is still high. DN is characterized by glomerular hyperfiltration, nephron enlargement, and mesangial cell hypertrophy, later progressing to glomerulosclerosis (Bherwani, Saumya, Sandhya, Patel, & Ghotekar, 2016). Despite the existing published evidence on the association between circulating microRNAs (miRNAs) and diabetes or its complications (Guay & Regazzi, 2016; Sebastiani et al., 2017), there are discrepant results regarding the different subsets of miRNAs and studies on the precise molecular mechanisms still remain inconclusive. This review is focused on the promising role of microRNAs, new mechanistic mediators in DN.

2 | MicroRNAs

MicroRNAs are small (~21–22 nucleotides), single-stranded, noncoding RNAs that can regulate gene expression at the posttranscriptional level through blocking translation or promoting the cleavage of their target mRNA, leading to its suppression (Gusev, Schmittgen, Lerner, Postier, & Brackett, 2007; Huang et al., 2011). They can bind to the sequences of the 3′-untranslated region (3′-UTR) in the target mRNA and interfere with its translation, and yet not disrupt the mRNA. Thirty percent of human protein-coding genes have been shown to be regulated by miRNA, which emphasizes its crucial role in controlling both biological and pathological functions, including metabolism, cellular differentiation, proliferation, apoptosis, carcinogenesis, and tissue development (Lucas & Raikhel, 2013; Shi, Wei, Zhang, & She, 2014). Some of the major functions of miRNA are regulating insulin synthesis, secretion and sensitivity, differentiating pancreas islet β-cells, glucose and lipid metabolism, and insulin resistance (Calderari, Diawara, Garaud, & Gauguier, 2017; Hennessy, Clynes, Jeppesen, &

O'Driscoll, 2010). The current advanced technology in detecting kidney miRNAs including microarrays and quantitative PCRs followed by generation sequencing has helped researchers in developing miRNAs as a therapeutic target and a reliable potential biomarker. A cluster of miRNAs is highly expressed in the kidney, so its role in the pathogenesis and progression of DN is promising (A. C. Chung, Yu, & Lan, 2013; Wonnacott, Bowen, & Fraser, 2017).

3 | BIOGENESIS OF miRNA

The process of miRNA biogenesis occurs in both nucleus and cytoplasm (Oliveto, Mancino, Manfrini, & Biffo, 2017). Initially, miRNA genes are transcripted by RNA polymerase II; then, primary transcripts (pri-miRNAs) are capped and polyadenylated (X. Chen, Li, Guo, Zhang, & Zeng, 2017; Olejniczak, Kotowska-Zimmer, & Krzyzosiak, 2018). The pri-miRNAs with several hairpin-like structures form the stem-loop precursor of miRNAs (~70 nucleotides long), which is modified by the ribonuclease III (Drosha) in a microprocessor complex or by DiGeorge syndrome critical region gene 8 (DGCR8). Subsequently, Ran-GTP/exportin 5 complex transfers pre-miRNAs from the nucleus to the cytoplasm (Kato, Castro, & Natarajan, 2013). In the cytoplasm, more cleavage might occur in the pri-miRNA stem-loop structure by Dicer, another RNase III enzyme, and its cofactor, TAR RNA-binding protein. Finally, the duplex miRNAs with approximately 22 base pair double-strand RNAs are generated. The next step will be loading the miRNA strand (guide strand) into the RNA-induced silencing complex (RISC), while the other strand is rapidly degraded. The RISC complex is a multiprotein complex including the Argonaute (Ago) family and the mature miRNA, which is necessary for miRNA-mediated gene silencing. The miRNA-RISC can be the specified binding sites within the 3′-UTR of the target mRNA, depending on the degree of complementarily between the miRNA and the target mRNA transcript; so miRNAs can help with translational repression, protein synthesis inhibition, and accelerated transcript degradation through uncapping and deadenylation or mRNA cleavage (Kato & Natarajan, 2015; McClelland & Kantharidis, 2014; Natarajan, Putta, & Kato, 2012) (Figure 1).

4 | DIABETES AND miRNAs

The family of miRNAs has been found to have a major contribution in alteration of gene expression and is involved in β-cells dysfunction and insulin resistance. Current evidence show that miRNAs can play a role in regulating glucose hemostasis, through modifying the β-cell insulin-producing function, insulin secretion and signaling pathways of insulin functions in peripheral tissues such as liver, muscle, and adipose tissue (LaPierre & Stoffel, 2017; Shi, Zhao et al., 2014). Initially, the beneficial impacts of miRNAs were identified for different cancers. However, recently there has been a huge interest toward their application in other diseases, including diabetes (Sebastiani et al., 2017). Moreover, miRNA-30d (miR-30d), one of the miRNAs, may be upregulated by glucose, which induces insulin gene expression in β-cells. Also, overexpression of miR-30d protects β-cells against tumor necrosis factor (TNF) suppressing function in both insulin gene expression and insulin secretion (L. Liu, Lin, Zhang, Cao, & Liu, 2016; Tang, Muniappan, Tang, & Ozcan, 2009).

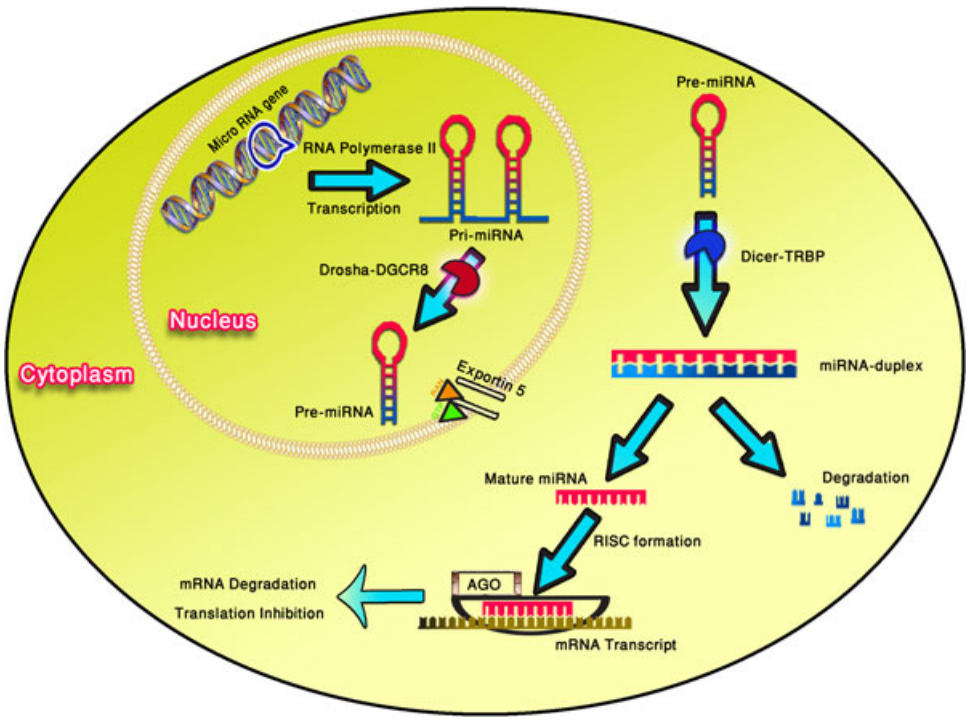

FIGURE 1 Biogenesis of miRNA [Color figure can be viewed at wileyonlinelibrary.com]

5 | MiRNAs AND INSULIN SECRETION

Some miRNAs can target genes involved in pancreas development, β-cell proliferation, insulin secretion, and, eventually, insulin exocytose (Lu, Fei, Yang, Xu, & Li, 2015). For example, microRNA-30d (miR-30d), one of the miRNAs upregulated by glucose, can induce insulin gene expression in pancreatic cells. Therefore, high expression of miR-30d protects β-cells against the suppressing effects of TNF. It effects on both insulin transcription and insulin secretion, through downregulating mitogen-activated protein kinase 4 (MAP4K4) (Tang et al., 2009; Xie et al., 2011). Previous studies have shown that in the islets of diabetic db/db mice, in which the MAP4K4 expression level is elevated, the miR-30d expression is decreased (Zhao, Mohan, Ozcan, & Tang, 2012). Hence, miRNA expression is crucial for accurate pancreatic islet development. For example, the expression of miR-375, one of the most abundant miRNAs in islet cells, is managed by pancreatic and duodenal homeobox 1 (Pdx-1) and neurogenic differentiation factor-1 and transcription factors for the development of the endocrine pancreas (Avnit-Sagi, Vana, & Walker, 2012). The inhibition of miR-375 has been shown to induce major defects in pancreatic islet development. So, it has a negative regulatory role in glucose-induced insulin secretion. Further, the high expression of miR-375 does not affect ATP production or intracellular calcium, increased by glucose though it influences the late step in the insulin secretory pathway (Eliasson, 2017; X. Li, 2014). MiR-375 has been implicated to reduce myotrophin expression, a route involved in insulin granule fusion, and control insulin gene expression (Jafarian et al., 2015). MiR-375 also contributes to several features of β-cells, including insulin expression and secretion, β-cell proliferation, and adaptation to insulin resistance (Y. Li et al., 2010). MiR-375 is expressed in β-cells and non-β-cells islets, where it might affect glucose homeostasis by inhibiting insulin secretion (Kloosterman, Lagendijk, Ketting, Moulton, & Plasterk, 2007). In addition, miR-375 can regulate the expression of phosphoinositide-dependent protein kinase-1 (PDK1), which relates the PI3 kinase signaling pathway with the functions of the β-cell regulator. Therefore, reduced expression of PDK1 mediated by miR-375 decreases insulin gene expression and its secretion (X. Li, 2014; Yan, Lin, & He, 2014).

6 | OTHER miRNAs INVOLVED IN INSULIN SECRETION

MiR-96 has an inhibitory effect on the expression of Granuphilin, an essential component involved in docking of insulin-containing vesicles to the plasma membrane. So, it negatively regulates insulin exocytosis, by targeting the transcription factor Onecut 2 gene (W. M. Yang, Min, & Lee, 2016). On the other hand, miR-96 decreases the expression of the Noc2 gene (Nucleolar complex protein 2), a Rab GTPase effector that is necessary for insulin exocytosis (Jeong, Park, Yang, & Lee, 2013). Excess miR-124a expression can control several elements of the exocytose pathways directly or indirectly. Subsequently, it increases the basal insulin release and decreases the insulin exocytosis pathway. Previous studies have shown that miR-124a can suppress Foxa2 (Forkhead box protein A2) target genes such as the ATP-sensitive K1 channel and the transcription factor Pdx-1. Therefore miR-124a can be involved in the regulation of insulin secretion (Jing et al., 2014).

Hyperglycemia can induce hyperexpression of miR-124a in pancreatic β-cells, which impairs insulin secretion after glucose stimulation. The alterations of miR-124a expression may contribute to β-cell dysfunction (de Siqueira et al., 2017). MiRNA-375 directly regulates insulin secretion through suppressing glucose-induced insulin secretion. It targets myotrophin mRNA, which contributes to adhesion of insulin secretory granules with the plasma membrane through depolymerization of actin filaments (Marchand et al., 2016). MiR-375 can regulate the pathway of insulin secretion in the pancreatic β-cells, which is further modulated by the effects of miR-124a and miR-96 on the components of exocytosis pathways (Chakraborty, Doss, Bandyopadhyay, & Agoramoorthy, 2014; Ofori, Malm, Mollet, Eliasson, & Esguerra, 2017). There is evidence showing that miR-375 knockout may intensify α cells in pancreatic islets and gluconeogenesis, leading to elevated plasma glucagon levels and hepatic glucose output, whereas overexpression of miR-375 reduces the expression of its targets myotrophin and phosphoinositide-dependent protein kinase-1. Overall, miR-375 is an essential miRNA for glucose homeostasis, β-cell proliferation, and α- and β-cell turnover (Arvidsson et al., 2018; Kloosterman et al., 2007).

7 | IMPORTANT miRNAs IN TISSUES

There are different miRNAs in peripheral tissue that help improve insulin functions. Previous research has shown that deregulation of miRNA expression in the liver may influence glucose homeostasis and promote progression of diabetes (van de Bunt et al., 2013).

8 | MiRNAs IN LIVER TISSUE

High levels of miR-122, miR-192, miR-148a, and miR-194 in the liver are downregulated in hepatocytes, which explains their possible role in regulating the glucose and metabolism of lipids. One of the most abundant miRNAs in the liver is miR-122, which affects hepatocytes functions (Raitoharju et al., 2014; Thakral & Ghoshal, 2015).

9 | MiRNAs IN ADIPOCYTE TISSUE

On the other hand, miR-143 is upregulated during human pre-adipocyte differentiation. It plays an important role in adipocyte differentiation, lipid metabolism, and adipogenesis (T. Wang et al., 2011).

10 | MiRNAs IN MUSCLE TISSUE

Insulin may downregulate 39 different miRNAs in muscle tissue, such as miR-1, miR-206, and miR-133a/b, which are well-known miRNAs for their role in muscle development and growth. Also, miR-29a and miR-29c are highly enriched in insulin-sensitive tissues (Chien et al., 2015; Koutsoulidou, Mastroyiannopoulos, Furling, Uney, & Phylactou, 2011). Evidence has shown that miR-1 and miR-133a, nearly 25% of the total miRNA expression in skeletal muscle, regulate glucose homeostasis, whereas miR-133a/b decreases glucose transporter type 4 expression, leading to a reduction in insulin-induced glucose uptake in cardiomyocytes (Katta et al., 2013; W. Liu et al., 2013). In diabetic cases, miR-133a/b expression levels are severely reduced in skeletal muscle, which is associated with higher fasting glucose levels. Glucose exposure increases miR-1 and miR-133a/b expression levels, which suppress insulin-like growth factor-1 (IGF-1). IGF-1 and IGF-1 receptors are important determinants of insulin sensitivity in muscle tissues (de Gonzalo-Calvo et al., 2017; Katta et al., 2013). In addition, miR-24 and miR-144 are involved in insulin sensitivity in muscles, as miR-24 levels decrease in diabetic patients. On the other hand, miR-208a/b and miR-499 are expressed in both the heart and the skeletal muscles, excluding miR-208a, which is cardiac specific, and miR-206, which is found only in skeletal muscle. In the impaired glycemic homeostasis, the miR-133a expression alters in the skeletal muscle of diabetic patients (Caporali, Miscianinov, Saif, & Emanueli, 2016; L. Liu et al., 2018).

11 | MiRNAs IN KIDNEY TISSUE

One of the miRNA family obtained through K-means clustering is the kidney-specific miRNA cluster, which includes miR-192, miR-194, miR-204, miR-215, and miR-216. There were higher levels of these miRNAs in the renal glomeruli of diabetic rats (Khella et al., 2013; Warren & Cowan, 2015). MiR-21 increases in fibrotic kidneys and the enhanced expression of miR-21 can upregulate the transforming growth factor beta 1 (TGF-β1) or TNF-α in human renal tubular epithelial cells (Loboda, Sobczak, Jozkowicz, & Dulak, 2016). MiR-192 mediates TGF-β function and plays a major role in kidney development and the pathogenesis of DN. On the other hand, TGF-β1 upregulates miR-192 expression in cultured glomerular mesangial cells. In diabetic mice glomeruli, miR-192 increases the collagen expression and alters the expression of other renal miRNAs. So, reducing renal miR-192 expression decreases renal fibrosis and improves proteinuria. This supports the possibility of an anti-miRNA-based translational approach for the treatment of DN (A. C. K. Chung, Huang, Meng, & Lan, 2010; Kato, Dang et al., 2013). MiR-192 and miR-205 are proprietarily expressed in the renal cortex and closely associated with the pathophysiology of DN. Also, miR-200c, miR-141, miR-205, and miR-192 are intimately correlated with disease severity and progression in patients with IgA nephropathy. Evidence has shown that miR-192 and miR-205 are elevated in the renal tissues of patients with hypertensive glomerulosclerosis (G. Wang, Kwan, Lai, Choi et al., 2010; G. Wang, Kwan, Lai, Chow et al., 2010). Moreover, miR-377, one of the most abundant miRNAs in DN patients, has shown to reduce the expressions of p21-activated kinase-1 and superoxide dismutase 1, 2, which enhance fibronectin production. Consequently, overexpression of miR-377 in DN indirectly induces increasing fibronectin production with a critical role in the pathophysiology of DN (Peng et al., 2017; Q. Wang et al., 2008). High glucose levels can induce overexpression of miR-377 in human mesangial cells, which increases the expression of the matrix fibronectin protein that causes the progression of DN. Further, miR-377 increases the susceptibility to oxidative stress and accumulation of the extracellular matrix protein in the mesangial cell in response to high glucose levels (Duan et al., 2017). There are findings showing that TGF-β can upregulate miR-200 and miR-216 and enhance the accumulation of ECM proteins, such as collagen, in mouse mesangial cells, which explains its role in the pathogenesis of DN. On the other hand, TGF-β upregulates miR-200b/c and subsequently downregulates FOG2, which activates the PI3K-Akt pathway, responsible for glomerular mesangial hypertrophy (Kato et al., 2011; Lan, 2012). One of the miRNAs involved in fibrotic disorders is miR-21, which regulates fibronectin production by a transcriptional mechanism in response to high glucose in mesangial cells. MiR-21 increases glucose-induced CREB-regulated transcription coactivator 1 (CRTC1) activity, which results in renal cell hypertrophy and fibronectin gene expression. On the other hand, high glucose has a direct impact on phosphatase and tensin homolog protein (PTEN) downregulation, leading to Akt activation. Thus, miR-21 regulates PTEN levels and Akt/CRTC1 activity, which mediates the pathologic features of diabetic kidney disease (Chau et al., 2012; Kolling et al., 2017; McClelland et al., 2015). Some studies show an inverse correlation between miR-21 expression and PTEN affluence in type 1 diabetic kidney followed by increased expression of fibronectin in mesangial cells (Seeger, Fischer, Muhly-Reinholz, Zeiher, & Dimmeler, 2014).

12 | MiRNAs AND DN

Recently, a unique class of naturally occurring short noncoding RNA, called miRNA, has been introduced as important posttranscriptional regulators of gene expression, which can regulate different biological functions. Significant attention has also been paid towards the role of miRNAs as mediators or diagnostic biomarkers for different diseases, such as DN. MiR-21 is a central mediator of signal transduction pathways activating PTEN, Akt, and CRTC1, which is involved in the pathogenesis of DN; thus targeting miR-21 can be beneficial for treating diabetic renal dysfunction (Z. Zhang et al., 2009). There is evidence suggesting that hyperglycemia induces miR-21 gene expression followed by reducing Smad7 abundance and increasing nuclear factor-κB (NF-κB)-mediated inflammation (Zhong et al., 2013). On the other hand, miR-29b plays a protective role in diabetic kidney diseases and may have therapeutic potential for DN complications as well (Sun et al., 2017). MiR-29b has been shown

to be upregulated in endothelial cells and podocytes under high glucose conditions. It also might be regulated through the activation of both TGF-β/Smad3 and NF-κB signaling pathways. Improvement of miR-29b levels in kidney tissue via gene therapy might block TGF-β/Smad3-mediated kidney fibrosis and NF-κB renal inflammation and subsequently inhibit DN (Y. Liu et al., 2010; Sun et al., 2017; Y. Zhang et al., 2014). MiR-29b can also regulate inflammatory process through cytokine expression by T cells mediated through the Sp1/NF-κB/miR-29b regulatory system (H. Y. Chen et al., 2014) (Figure 2). The majority of miRNAs shown to be beneficial in nephropathy are regulated through the activation of profibrotic cytokine TGF-β (Lee & Choi, 2015). Because of these properties, miRNAs have been recently considered as diagnostic biomarkers of DN (Campion, Sanchez-Ferras, & Batchu, 2017).

13 | GENE THERAPEUTIC IMPACT OF miRNAs

MiRNAs act at several points in the distinct pathways inducing insulin secretion or resistance, so they could be potential therapeutic targets for diabetes (Mirra et al., 2015). Several miRNAs have been identified in the pathology of DN, and these small molecules have presented a new possibility for therapeutic intervention (Sethupathy, 2016). Some researchers have attempted to downregulate or upregulate specific miRNAs using one of several delivery approaches in animal models of DN. The tendency to control the expression of miRNAs levels using chemically modified, stable, nuclease-resistant oligonucleotides (miRNA inhibitors and mimics) could be developed for the treatment of patients in the future (Jackson & Linsley, 2010; Szeto et al., 2012; Y. Zhang et al., 2015). For example, miR-192 can control several kidney miRNAs related to DN, so it is a good candidate target to be evaluated for DN treatment (X. Yang & Liu, 2017). Recently, efficient reduction of miR-192 was observed in vivo in normal mice injected with locked nucleic acid (LNA)-modified anti-miR-192 (Y. Putta et al., 2012).

14 | IMPORTANCE OF miRNAs FOR CLINICAL PRACTICE

MiRNAs can be considered as potential therapeutic targets for diabetes, because they are involved in different pathways leading to insulin secretion or resistance (Hashimoto & Tanaka, 2017). The recent advances in the technology of miRNA detection and quantification, including the introduction of microarrays, quantitative PCRs and next-generation sequencing, have directed a huge interest towards developing miRNAs as therapeutic targets and potential biomarkers for different human diseases. Circulating miRNAs in blood are found to be sensitive biomarkers for cancer, tissue injury and heart failure. High levels of miRNAs in urinary sediment have been reported in patients with IgA nephropathy (Putta et al., 2012). MiR-192 is a good target to be considered for the treatment of DN because it can control other renal miRNAs involved in the pathogenesis of DN. After the injection of LNA-modified antimiR-192, there was a remarkable reduction in miR-192 in normal mice in in vivo conditions (Putta et al., 2012). Different miRNAs have been recognized to be involved in the pathology of DN, which can be potentially used for therapeutic intervention in diabetic patients. The majority of therapeutic studies for miRNAs have looked into their beneficial impacts on cancer. MiRNAs, which regulate oncogene

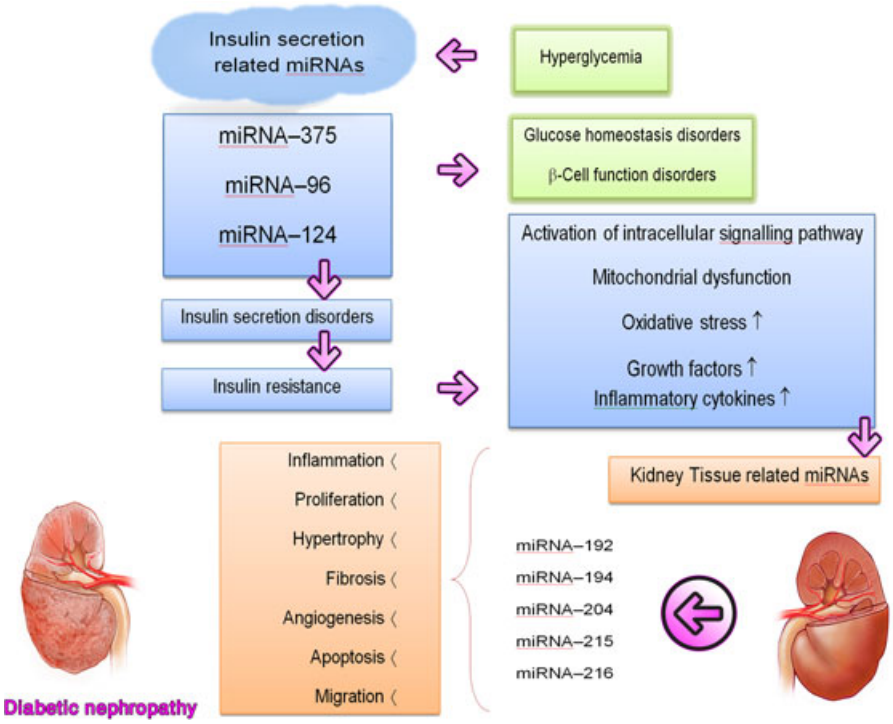

FIGURE 2 MiRNA, and insulin secretion and diabetic nephropathy progression [Color figure can be viewed at wileyonlinelibrary.com]

expression in cancerous cells, are often called oncomiRs. Because of the complexity of carcinogens, therapies aimed at the suppression of single oncogenes have shown limited therapeutic response. The same can be seen in other multifactorial diseases such as DN (Simpson, Wonnacott, Fraser, & Bowen, 2016). Despite a lot of efforts to develop more effective drugs to treat DN, not many of these treatments have met practical requirements. There are ongoing attempts to address existing gaps including targeting TGF-β1 or developing improved protocols for renin-angiotensin blockade. Still, new concepts should be investigated to design the most novel and practical therapies. There is no definite cure for DN; therefore, novel therapeutic targets are required for preventive and curative purposes. Dysregulation of miRNA expression has been shown to contribute to the development of different diseases, including DN; so, miRNAs are considered feasible targets for therapeutic interventions. Currently, there are three major strategies available for inactivating miRNAs whose expression is increased in a particular disease like DN: individual miRNA knockout, sponge miRNA, and antisense oligonucleotide (DiStefano, Taila, & Alvarez, 2013).

15 | MiRNA AD CANCER

Circulating miRNAs have emerged as excellent candidates for cancer biomarkers. Several recent studies have highlighted the potential use of saliva for the identification of miRNAs as novel biomarkers, which represents a great opportunity to improve diagnosis and monitor general health and disease. MiRNAs (miRNAs or miRs) constitute one of the most abundant classes of gene regulatory molecules. Different mechanisms have been miRNAs deregulation in cancer (Rapado-Gonzalez et al., 2018). MiRNAs play a role in cellular functions, including proliferation, cell cycle control, and programmed cell death, differentiation, invasiveness, and tissue-specific functions, such as immune responses, hormone secretions, and angiogenesis. Genome-wide analysis has shown the role of miRNAs expression in cancer types through mechanisms including defects in the miRNA biogenesis machinery, amplification/deletion of the region encompassing the miRNA, or aberrant transcriptional control (Ramassone, Pagotto, Veronese, & Visone, 2018). The miRNAs play a role in a variety of biological functions such as cell proliferation, differentiation, apoptosis, survival, invasion, and migration. Several studies have demonstrated mutations in miRNA-encoding genes or expression of miRNAs human diseases, including cancers (Lou et al., 2017).

16 | CONCLUSIONS

MiRNAs can play a role in regulating glucose hemostasis, through modifying β-cell insulin-producing function, insulin secretion and signaling pathways of insulin functions in peripheral tissues such as the liver, muscle, and adipose tissue. On the other hand, miRNA can suppress effects of TNF; therefore, the accurate recognition of miRNAs profiles can help to treat DN, kidney fibrosis, and renal dysfunction.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interests.

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