



# Noncoding RNAs as therapeutic targets in early stage diabetic kidney disease

Mitsuo Kato

Beckman Research Institute of City of Hope, Duarte, CA, USA

Diabetic kidney disease (DKD) is a major renal complication of diabetes that leads to renal dysfunction and end-stage renal disease (ESRD). Major features of DKD include accumulation of extracellular matrix proteins and glomerular hypertrophy, especially in early stage. Transforming growth factor- $\beta$  plays key roles in regulation of pro-fibrotic genes and signal transducers such as Akt kinase and MAPK as well as endoplasmic reticulum stress, oxidant stress, and autophagy related to hypertrophy in diabetes. Many drugs targeting the pathogenic signaling in DKD (mostly through protein-coding genes) are under development. However, because of the limited number of protein-coding genes, noncoding RNAs (ncRNAs) including microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) are attracting more attention as potential new drug targets for human diseases. Some miRNAs and lncRNAs regulate each other (by hosting, enhancing transcription from the neighbor, hybridizing each other, and changing chromatin modifications) and create circuits and cascades enhancing the pathogenic signaling in DKD. In this short and focused review, the functional significance of ncRNAs (miRNAs and lncRNAs) in the early stages of DKD and their therapeutic potential are discussed.

**Keywords:** Diabetic nephropathies, Long noncoding RNA, MicroRNAs, Signal transduction, Untranslated RNA

## Introduction

The increasing incidence of both type 1 (T1D) and type 2 diabetes (T2D) is a worldwide concern that augments the rates of various micro- and macrovascular complications [1–3]. About 40% of diabetic patients develop diabetic kidney disease (DKD), which leads to chronic kidney disease (CKD) and end-stage renal disease (ESRD) [4–6]. Several biochemical and signal transduction

mechanisms leading to DKD have been studied over the years, but the increasing rates of the disease indicate that we need a better understanding of the underlying molecular mechanisms [7–10]. Since the number of protein-coding genes is limited [11,12], noncoding RNAs (ncRNAs) including microRNAs (miRNAs) and long non-coding RNA (lncRNA) have become attractive molecules for identifying drug targets for human diseases. Transcriptome (RNA) sequencing studies have implied that most of the genome could be transcribed into RNA, and many of transcripts are not protein-coding [13,14]. Most of the ncRNAs are lncRNAs (> 200 nucleotides), and there are also small ncRNAs, such as miRNAs [14,15]. lncRNAs have functions in biological processes, gene expression, cell-cycle control, differentiation, and immune responses [16,17]. lncRNAs regulate the expression of genes in cis (neighboring genes) and/or trans (genes genetically far away) locations by several mechanisms including histone-modifying complexes to change chromatin states

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Correspondence: Mitsuo Kato

Beckman Research Institute of the City of Hope, 1500 East Duarte Road, Duarte, CA 91010, USA. E-mail: mkato@coh.org  
ORCID: <https://orcid.org/0000-0002-1783-1084>

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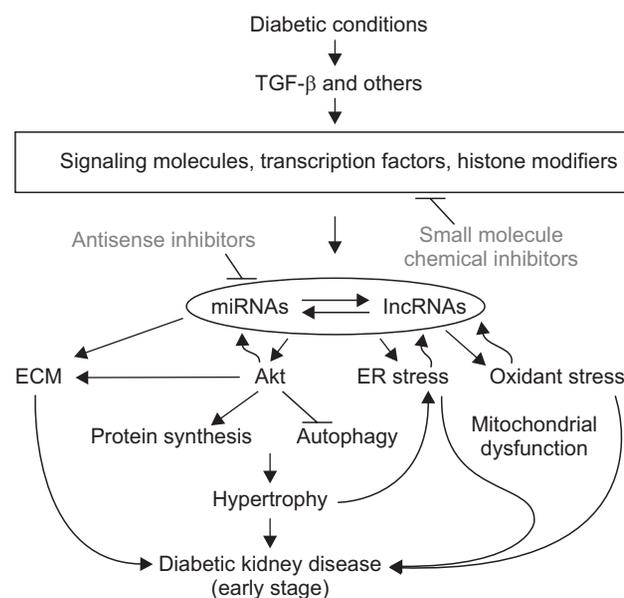
and modulate the transcription factors or hosting other small RNAs [16–20].

miRNAs are endogenous small ncRNAs (20–25 nucleotides) that usually silence the expression of target genes by hybridizing to the 3'-untranslated regions (3'UTR) of target mRNAs (translational repression and/or mRNA degradation) [21]. Sixty percent of the human protein-coding genes are potentially regulated by miRNAs [21]. miRNAs are expressed as relatively long primary transcripts (pri-miRNAs) transcribed by RNA polymerase II in the nucleus [21–23]. Pri-miRNA is processed to precursor miRNAs (pre-miRNAs, ~70 nucleotide stem-loop structures) by the Drosha/DGCR8 complex in the nucleus. The pre-miRNAs are transported to the cytoplasm by exportin-5 and are cut to mature miRNAs by Dicer in the cytoplasm [21–23]. One strand of mature miRNAs is recruited into the RNA-induced silencing complex (RISC), which contains the Argonaute (Ago) family of proteins that interacts with the 3'UTR of the target mRNAs and induces translational repression or target RNA degradation [21,22]. Although the miRNA targets were predicted by matching seed sequences and flanking sequences by *in-silico* study [21,24,25], more targets have been identified recently through direct interaction of miRNAs and target RNAs by immunoprecipitation of RISC components (such as Ago) and RNA sequencing strategy [26–28]. These new targets identified by the recent techniques also provide unexpected targets for human diseases. Genetic deletions of Dicer or Drosha in mice cause severe problems in cardiac and renal organs, suggesting the functional relevance of miRNAs in these diseases [29–36].

### ncRNAs in the early stage of DKD

The functions of individual miRNAs provide some hints regarding the mechanistic contribution to DKD progression. Earlier studies on miRNAs in DKD involved miRNAs enriched in kidney or cell-type specific expression in kidney tissues [37,38]. Several miRNAs (miR-192, miR-200b/c, miR-216a, and miR-217) in the kidney are increased in transforming growth factor (TGF)- $\beta$ 1-treated mouse mesangial cells (MMCs) and in renal glomeruli of mouse models of diabetes, streptozotocin (STZ)-injected T1D mice, and T2D *db/db* mice [39–45]. Those miRNAs play roles in extracellular matrix (ECM) accumulation and hypertrophy (Akt activation) through targeting E-box

repressors (ZEB1/2) and PTEN or YBX-1 [39,41,43–45]. Interestingly, some of these miRNAs are creating signal cascades and circuitries to enhance and accelerate the same signals and contribute to the pathogenesis of DKD (Fig. 1). This might be a mechanism of persistent expression of pathologic genes in DKD and other diabetic complications even after controlling hyperglycemia by insulin [1,8,41,43,45–51]. miR-192 is regulated by Smad, p53, and Ets-1 from the transcription factor binding sites in the miR-192 promoter [47,52,53]. The regulation involved epigenetic mechanism through increased histone acetylation by p300 activated by Akt at the miR-192 promoter region, suggesting a link from epigenetics to miRNAs [8,47]. These initial studies have pointed to miR-192 as a master regulator in TGF- $\beta$ 1 response to initiate miRNA cascades and increase expression of ECM genes



**Figure 1.** A proposed model of diabetic kidney disease (DKD) mediated by ncRNAs and potential targets for prevention and treatment. Several ncRNAs (miRNAs and lncRNAs) are involved in the progression of DKD by targeting genes related to ECM accumulation, hypertrophy, ER stress, inflammation, oxidative stress, and signal transduction, especially in the early stages. Some of these key RNAs and signaling molecules create amplifying cascades and circuitries that activate each other and accelerate the same signals. The miRNAs and lncRNAs are direct or indirect potential targets for prevention of DKD. Direct upstream factors that control ncRNA expression can also be alternative targets (see main text for details). ECM, extracellular matrix; ER, endoplasmic reticulum; lncRNA, long noncoding RNA; miRNA, micro RNA; ncRNA, noncoding RNA; TGF, transforming growth factor.

in DKD [39,41,43–45,47,49,52,53]. miR-192 and miR-215 induce phenotype transition of mesangial cells (MCs) by targeting  $\beta$ -catenin-interacting protein 1 in TGF- $\beta$ 1-treated glomerular MCs and glomeruli from diabetic *db/db* mice, suggesting multiple functions in DKD [54]. miR-192 expression is also increased in STZ-injected type 1 diabetic mice fed a high-fat diet [42]. Although some reports showed decreased expression of miR-192 in very late stage [55,56], a decrease of this miRNA might be the result, but not the cause of DKD, because miR-192 KO mice did not show any kidney problems and were even protected from DKD [8,51,53]. miR-21 is one of the well-studied miRNAs in DKD, is upregulated in several animal models of DKD and human patients, and targets PTEN, mTOR, matrix metalloproteinases, Smad7, Cdc25a, and Cdk6 [57–60]. More severe renal injuries have been observed in miR-21 KO mice crossed with TGF- $\beta$ 1 transgenic mice [61], and upregulation of miR-21 is protective against renal ischemia–reperfusion injury [62]. miR-93 is a key miRNA (targeting vascular endothelial growth factor-A) that is downregulated in the glomeruli of diabetic *db/db* mice in renal podocytes and microvascular endothelial cells treated with high glucose condition [63]. Interestingly, miR-93 also targets MSK2, a member of the ribosomal S6 kinase family of serine/threonine kinases, and regulates histone H3 Ser10 phosphorylation (H3S10P) [64,65]. Decreased miR-93 causes an increase in H3S10P and enhances the expression of pathogenic genes through nucleosomal remodeling in DKD [65]. miR-29c was initially identified as an upregulated miRNA under diabetic conditions and activated Rho kinase by targeting Spry-1, related to ECM accumulation and podocyte apoptosis [66]. In cardiac fibrosis, miR-29 targeting collagen was reported [67], and a significant decrease of miR-29 family members and increased collagens were observed in kidney cells from diabetic mice and cells treated with TGF- $\beta$ 1 [68–70]. Interestingly, the anti-diabetic drug linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, upregulates miR-29 and prevents fibrosis in a mouse model of DKD [71].

Let-7 family members are downregulated in several cancers and also in renal cells treated with TGF- $\beta$ 1, which induces fibrosis through TGF- $\beta$ 1 receptor and collagens [72,73]. Interestingly, the processing of let-7 family members is downregulated by lin28b and upregulated in MMC treated with high glucose or TGF- $\beta$ 1 and in glomeruli

from STZ-injected diabetic mice through Smad2/3 activation [74,75]. miR-135a is increased in serum and renal tissue from patients with DKD and *db/db* mice and promotes ECM accumulation by targeting transient receptor potential cation channel, subfamily C, member 1 (TRPC1) [76]. TGF- $\beta$ 1 decreases miR-130b but upregulates TGF- $\beta$ 1 receptor 1 through unique mechanisms including Ybx1/NFYC targeted by miR-216a, implying another miRNA-mediated amplifying cascade [77]. miR-30 family members are decreased in DKD, and their target connective tissue growth factor (CTGF) is upregulated [78]. miR-22 regulates bone morphogenetic protein-6 (BMP-6) and BMP-7 and further increases TGF- $\beta$ 1 signaling [79]. miR-433 increases TGF- $\beta$ 1 signaling and fibrosis by targeting antizyme inhibitor 1, a regulator of polyamine synthesis through a miRNA-mediated circuit [80]. miR-26a is upregulated by high glucose, activates mTORC1, and enhances hypertrophy and ECM accumulation [81], while the same miRNA is downregulated in DKD patients and also by TGF- $\beta$ 1 in cultured podocytes, leading to an increase of its target CTGF [82]. miR-23b alleviates fibrosis and albuminuria in DKD by targeting Ras GTPase-activating protein SH3 domain-binding protein 2 [83]. miR-146a KO mice showed enhanced proteinuria, renal macrophage infiltration, glomerular hypertrophy, and fibrosis through accelerated inflammation [84] and also showed accelerated glomerular injury and albuminuria in STZ-induced diabetes and podocyte injury through increased ErbB4 and Notch-1, implying that ErbB4/EGFR is a practical target for therapeutics, because several pan-ErbB inhibitors are available [85].

On the other hand, hypertrophy–related miRNAs have been identified. As mentioned above, in the miRNA cascade, miR-216a and miR-217 activate Akt related to hypertrophy by targeting PTEN in the mouse model of DKD and MMC treated with TGF- $\beta$ 1 [41]. The miR-200 family also activates Akt by targeting PI3K inhibitor FOG2 [44]. miR-21 also targets PTEN and activates Akt [86–88]. miR-451 is decreased in early DKD in *db/db* type 2 diabetic mice and induces hypertrophy through Ywhaz, a protein related to activation of MAPK [89]. miR-214 is also upregulated by high glucose and induces hypertrophy and matrix expansion by targeting PTEN in renal glomerular mesangial and proximal tubular epithelial cells [90]. miRNA-181a downregulates DEPTOR (mTOR inhibitor) and activates mTORC2, which activates Akt in TGF- $\beta$ -induced

glomerular MC hypertrophy and ECM protein expression [91]. Autophagy inhibition by the miR-192 cascade induces hypertrophy through Akt activation and FoxO3a phosphorylation [92]. About 40 miRNAs are included in the miR-379 cluster, which is regulated by endoplasmic reticulum (ER) stress in DKD [19]. Because miR-379 targets EDEM3 (inhibitor of ER stress) and miR494 targets Atf3 (repressor of CHOP), upregulation of this miRNA cluster augments ER stress in DKD [19]. ER stress also induces ECM accumulation (fibrosis) and hypertrophy in renal cells (Fig. 1). Interestingly, the miRNA cluster is hosted by an lncRNA (lncMGC, megacluster), which controls expression of the whole cluster [19]. This ER stress-regulated lncMGC is also involved in fibrosis and hypertrophy by regulating the miR-379 miRNA cluster. LncRNA LINC01619 regulates miR-27a/FoxO1 and ER stress-mediated podocyte injury in DKD [93]. LncRNAs (Hyperlnc) regulated by hypoxia-induced ER stress are identified in pericytes [94]. Therefore, ER-stress-regulated lncRNAs may have important functions in pathogenesis of kidney diseases. miR-216a and miR-217 were induced by TGF- $\beta$ 1 alone with their host lncRNA, RP23-298H6.1-001 [41].

miR-192 is co-regulated in MCs with its host lncRNA CJ241444, which is induced by TGF- $\beta$ 1 through the promoter Smad binding sites and epigenetic regulation via transcription factor Ets-1 and histone acetylation [47]. Plasmacytoma variant translocation 1 (PVT1), which was identified in a potential locus for diabetic ESRD in a genome-wide single-nucleotide polymorphism genotyping study, increases expression of plasminogen activator inhibitor 1, TGF- $\beta$ 1, and ECM genes in MCs treated with high glucose conditions [95,96]. Five miRNAs (miR-1204, miR-1205, miR-1206, miR-1207, and miR-1208) mapped to the PVT1 locus are also upregulated by high glucose in human MCs and modulate expression of ECM [97,98]. Therefore, those lncRNAs function as host RNAs for small RNAs such as miRNAs [8,51]. LncRNA CYP4B1-PS1-001 is significantly decreased in the early stage in diabetic *db/db* mouse, and overexpression of the lncRNA inhibits proliferation and fibrosis of MCs [99]. LncRNA MALAT1 (metastasis-associated lung adenocarcinoma transcript) is upregulated in a mouse model of DKD and involved in podocyte injury through  $\beta$ -catenin [100]. Comprehensive screening identified 21 lncRNAs upregulated in two models of renal fibrosis but downregulated in Smad3-knockout mice [101]. Another comprehensive screening

of noncoding RNAs by RNA-sequencing has been done in association with early development of DKD [102]. LncRNA *Tug1* regulates mitochondrial bioenergetics in diabetic nephropathy through PGC-1 $\alpha$  [103]. LncRNA *ErbB4-IR* promotes diabetic kidney injury by targeting miR-29b, which regulates collagen genes and ECM accumulation [104]. LncRNA 1700020I14Rik alleviates cell proliferation and fibrosis in DKD through miR-34a-5p/Sirt1/HIF-1 $\alpha$  signaling [105]. LncRNA MALAT1 regulates renal tubular epithelial pyroptosis by modulating miR-23c targeting embryonic lethal abnormal vision (ELAVL) 1 in DKD [106]. Those reports also suggest crosstalk between lncRNAs and miRNAs and circuitry mediated by miRNAs and lncRNAs related to fibrotic events, inflammation, and mitochondrial bioenergetics associated with DKD [9,19,41,103,107,108]. Therefore, two major modes of regulation of miRNAs by lncRNAs have been proposed in DKD. First, lncRNAs enhance the expression of miRNAs by hosting miRNAs or neighboring miRNAs. Second, lncRNAs inhibit the function of miRNAs by hybridizing to miRNAs (sponge function) [109].

Some miRNAs have been implicated in oxidative stress, a major player in DKD pathogenesis. Nox4, a key player in DKD [110–112], was identified as a miR-25 target, suggesting that decreased miR-25 expression upregulates Nox4 to promote oxidative stress and renal dysfunction in rats [113]. Another recent discovery is that the form of MeCP2 phosphorylated by HIPK2, which is known to repress transcription by binding to methylated cytosine, also binds to DGCR8 and inhibits processing of pri-miRNAs [114]. HIPK2 is a key regulator of kidney fibrosis [115], significantly inhibits miR-25 processing (miR-25 reduction and NOX4 increase) through phosphorylation of MeCP2, and was detected in diabetic kidney and MMC treated with TGF- $\beta$ 1. Therefore, the connection from HIPK2 to MeCP2 through miRNA processing is a potential mechanism underlying early stage DKD [116]. Nox4 was also identified as a target of miR-146a, which was downregulated in high-glucose-treated endothelial cells [117]. miR-205 expression downregulates production of reactive oxygen species through decreases in heme oxygenase and superoxide dismutase (SOD) 1 and 2 [118]. miR-377 was identified as upregulated miRNA by high glucose or TGF- $\beta$ 1 in MCs and increased fibronectin expression and oxidant stress by repression of manganese SOD (Mn-SOD/SOD2) and p21-activated kinase [40]. The miRNA

cascade (miR-192, miR-216a, and miR-217) activates Akt and inhibits FoxO3a/SOD2 signaling, leading to oxidative stress in MC [41,119]. Aldose reductase downregulates miR-200a-3p and miR-141-3p, which target Keap1-Nrf2, TGF- $\beta$ 1/TGF- $\beta$ 2, and Zeb1/Zeb2 signaling in MCs and kidneys of diabetic mice [120]. These reports suggest that ncRNAs regulating oxidant stress have critical functions in DKD.

### ncRNAs as biomarkers

Comprehensive studies of miRNAs in biofluids and tissues provide clues about biomarkers and diagnostics in clinical translational research. Early detection of DKD is extremely useful to prevent progression to renal failure. Several biomarkers, such as peptides, growth factors, and cytokines, of DKD progression have been reported [121]. However, miRNAs are gaining interest as sensitive, noninvasive, and quantitative diagnostic biomarkers for DKD, because of their relatively higher stability in biofluids (urine and plasma and in exosomes) and recent development of detection and quantification methods [122]. Several reports have profiled miRNAs in urine, urinary sediment, urinary exosomes, and in blood or sera of patients with many types of kidney diseases and showed significant correlation with kidney diseases and also with specific stages, fibrosis, renal function (glomerular filtration rate) decline, albuminuria, rapid progression to ESRD, or tissues [8,108,123–138]. lncRNAs can be biomarkers for some human diseases [139]; however, the utility of lncRNAs as biomarkers is not conclusive in DKD. In addition to the above-mentioned publications, more reports showing correlation of ncRNA with kidney diseases and their stages will provide more precise diagnosis of patients by ncRNA profiling.

### Targeting ncRNAs for prevention and treatment of DKD

Many drugs targeting TGF- $\beta$  or angiotensin II signaling are already under development for treatment of DKD [140,141]. Several reports have shown that miRNAs and lncRNAs are dysregulated in DKD, so targeting them is a potential therapeutic intervention, and some are currently being assessed in trials for preclinical stages [112,129]. miRNA levels can be controlled with miRNA mimics or

antisense miRNAs (inhibitor), and stable nuclease-resistant oligonucleotides have been developed for miRNA and lncRNA inhibitors. Locked nucleic acid (LNA) is one of the most potent modifications for inhibiting miRNA activity specifically [41,142,143], and there are LNAs currently in clinical trials [144]. LNA-modified anti-miR-192 specifically and effectively inhibited miR-192, as well as downstream miRNAs (miR-216a, miR-217, and miR-200 family) and p53 in the renal cortex of diabetic mice, and reduced key features of DKD [41,45,53,143]. miR-21 inhibitors also prevented DKD in mouse models [57–60,145]. 2'-O-methyl antisense oligonucleotides targeting miR-29c showed reduced rates of DKD in *db/db* mice [66]. Targeting lncRNAs is another potential treatment for human diseases [146]. As mentioned above, lncMGC is a hosting ncRNA of the miR-379 cluster. Targeting this lncRNA by LNA-modified antisense oligonucleotides through RNaseH-mediated RNA cleavage (sometimes called GapmeR) [147–149] effectively reduces the expression of lncMGC and cluster miRNAs and attenuates the early features of DKD in a mouse model [19]. MALAT1 siRNA partially restores podocyte function and prohibits  $\beta$ -catenin nuclear accumulation in mouse models of DKD [100]. Therefore, the strategy to inhibit miRNAs and lncRNAs by antisense inhibitors is an encouraging therapeutic approach (Fig. 1).

Some lncRNAs are well-conserved from human to mouse, but other lncRNAs are not. Based on the function of lncRNAs (enhancing miRNA expression or inhibiting miRNA function), even if some lncRNA sequences are not conserved between species, their secondary structures or positions in the genomes are sometimes very similar, and they might have the same functions. In this situation, we need to design species-specific antisense inhibitors against lncRNAs. It might be necessary to redesign human-specific inhibitors to treat patients even if some lncRNA inhibitors work in animal models of DKD.

Optionally, the direct upstream mechanisms controlling the expression/transcription of miRNAs and lncRNAs are another therapeutic target (Fig. 1). miR-192 is epigenetically regulated through Ets-1 and histone acetylation, which can be activated by Akt and inhibitors, such as MK-2206, and inhibits miR-192 expression and early features of DKD in mouse models [47]. Several reports have shown Akt activation in animal models of diabetic complication including DKD [119,150–152],

and a pharmacological inhibitor of Akt (AS101) showed renoprotection in rat models of diabetes [153]. The anticancer agent paclitaxel decreases miR-192 expression and decreases fibrotic damage in the remnant kidney model [154]. Approaches to upregulate functional miRNAs are more challenging than inhibition because stable and active molecules are required, although *in-vivo* delivery methods including adeno-associated virus vectors [129] and bacteriophage MS2 virus-like particles have been tested for overexpressing miRNAs [155]. Targeting negative regulators of miRNAs, such as lin28 (inhibitor of let-7 processing) [72–75] or HIPK2 (inhibitor of miR-25 processing) [114–116,156,157] by siRNA, antisense inhibitors, or chemical inhibitors might be possible (Fig. 1). In fact, small molecule chemical inhibitors of lin28 or HIPK2 (BT173) have been screened and tested to treat cancers or diabetic complications [158–160]. Again, the anti-diabetic drug linagliptin, a DPP-4 inhibitor, upregulates miR-29 and prevents fibrosis in a mouse model of DKD [71].

On the other hand, CRISPR-Cas9 genome editing (and alternatives to Cas9) [161–164] has recently advanced our ability to control genetic and epigenetic changes. The CRISPR-Cas9 system is based on the immune systems in bacteria, which produces degradation in the DNA of invaders such as phages. Using this method in mammalian systems, it is getting easier and faster to introduce site-specific mutations, large deletions, and replacements even in mammalian cells and to create mutant animals. The method can also introduce point mutations or correct mutations in wild-type sequences [165–168]. Another advantage of the system is locus-specific control of gene activation or repression using a protein fusion of Cas9 with transcriptional activators or repressors [169–171]. More interestingly, using a fusion protein of Cas9 with DNA methyltransferase, histone modifying enzymes, or other DNA or histone modifying enzymes, it is possible to change the epigenetic marks, DNA methylation, histone acetylation, or methylation in the locus-specific manner [172–176]. Because epigenetic changes near disease-related genes are critical for DKD and persistent expression of disease genes, site-specific epigenetic modification must be more effective for use in patient treatment since known epigenetic modifying drugs usually have genome-wide (nonspecific) effects, which may cause side effects.

In conclusion, miRNAs and lncRNAs are involved in progression of DKD by targeting genes related to fibrosis, hypertrophy, ER stress, inflammation, oxidant stress, and signal transduction [8,49,112]. An interesting fact is that molecular events in the early stages of disease, such as ECM, hypertrophy, ER stress, and oxidative stress, are frequently observed before later features such as proteinuria in mouse models, and targeting the ncRNAs (early molecules) is effective at reducing the occurrence of such late features [8,19,51,53,143]. Therefore, early detection and treatment of patients before physiological changes such as proteinuria might be necessary to prevent DKD. Because molecular pathogenesis sometimes varies from patient to patient, patient-specific treatments targeting specific ncRNAs (precision medicine) must be considered in treatment of DKD patients [8,70,108]. Some of these RNAs create amplifying cascades and circuits. Therefore, targeting a single miRNA may not be sufficient for DKD treatment. A combination of multiple ncRNAs might be necessary for future treatment of DKD, especially in the early stage, although further study of the expression and functions of those RNAs is necessary.

### Conflicts of interest

The author has no conflicts of interest to declare.

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