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Therapeutic Landscape of Diabetic Nephropathy: Insights from Long Noncoding RNAs

ABSTRACT

Objective: Diabetic nephropathy (DN) is a major complication of diabetes mellitus and a leading cause of end-stage renal disease. Long noncoding RNAs (lncRNAs) have emerged as critical regulators in various biological processes, including those implicated in DN pathogenesis. This manuscript provides a comprehensive review of the therapeutic potential of lncRNAs in the context of DN, elucidating their roles as diagnostic markers, prognostic indicators, and therapeutic targets.

Materials and methods: A systematic review of current literature was conducted, focusing on studies investigating the involvement of lncRNAs in DN pathophysiology and therapeutic interventions. The literature search was performed in Medline, Scopus, WOS, and PubMed databases. Key findings related to the regulatory mechanisms of lncRNAs in DN progression and their modulation by pharmacological agents or gene therapy approaches were synthesized.

Results: This extensive analysis examines the many functions of lncRNAs in DN, including their participation in crucial physiological mechanisms. The analysis systematically examines the abnormal functioning of certain lncRNAs in the progression of DN, with a focus on their possible use as indicators for diagnosis and prognosis. Furthermore, we examine the molecular mechanisms by which lncRNAs regulate the course of DN.

Conclusions: Understanding the intricate roles of lncRNAs in DN pathogenesis opens avenues for the development of novel diagnostic tools and therapeutic interventions. Targeting dysregulated lncRNAs holds considerable promise in mitigating DN progression and improving clinical outcomes for patients with diabetic kidney disease. Further research efforts are warranted to validate the clinical utility of lncRNA-based therapeutics in DN management. (Clin Diabetol 2024; 13, 5: 307–318)

Keywords: biomarkers, diabetes, lncRNAs, kidney disease, treatment

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Introduction

One of the primary factors leading to the eventual emergence of end-stage renal disease (ESRD) is diabetic nephropathy (DN). This complication arises from consistently elevated blood glucose levels and the subsequent chronic allergic response [1–4]. Approximately

35–40% of individuals with diabetes develop DN, a condition that significantly impacts their quality of life (QoL) and substantially increases the risk of mortality [5, 6]. According to the 10th edition of the International Diabetes Federation (IDF) Diabetes Atlas, it is projected that by 2030, there will be a total of 643 million adults worldwide with type 2 diabetes, up from 537 million in 2021. Moreover, in 2021, diabetes-related disorders claimed the lives of more than 6.7 million individuals aged 20 to 79.

Prolonged hyperglycemia can cause significant damage to various organs, leading to debilitating and sometimes fatal consequences such as cardiovascular diseases, neuropathy, and nephropathy. DN, an early complication of diabetes, is characterized by clinical symptoms such as declining glomerular filtration rate (GFR) and increasing urine protein levels [7, 8]. Pathological features of DN include renal enlargement, thickening of the kidney's basement membrane, mesangial proliferation, and podocyte loss [9]. Despite the importance of controlling hypertension, blood glucose levels, and the renin-angiotensin pathway in reducing protein intolerance in type 2 diabetes, it has not completely prevented treatment-resistant proteinuria and ESRD [7, 10, 11]. Hence, it is imperative to delve into the underlying causes of diabetic complications and identify novel targets for effective DN prevention to enhance the QoL for individuals with diabetes.

Oxidative damage, the inflammatory response, and changes in metabolic rates induced by persistent hyperglycemia are among the factors contributing to the development of diabetic neuropathic pain [6, 12]. A growing body of research suggests that impaired autophagy, leading to the accumulation of damaged proteins and organelles, is associated with disruption in cellular homeostasis and the onset of DN [5, 12–15].

Long noncoding RNAs (lncRNAs) are garnering increasing recognition for their involvement in various biological processes, including kidney disease. Recent research indicates that lncRNAs may play a significant role in the development and progression of DN [16, 17]. Multiple studies have revealed differential expression of lncRNAs in DN patients, suggesting their potential as biomarkers for the condition [18–20]. Furthermore, it has been acknowledged that lncRNAs offer promising avenues for therapeutic intervention in DN [21, 22]. However, further research is necessary to fully elucidate the mechanisms by which lncRNAs operate in DN and to devise effective therapeutic strategies.

Exploring the therapeutic landscape of DN through the lens of lncRNAs holds promising prospects for innovative treatment approaches to combat this severe complication of hyperglycemia. DN plays a significant role worldwide in the progression to ESRD, yet available treatment options are often limited and insufficient in halting disease progression. lncRNAs are intricately linked to the onset of DN and play crucial roles in regulating gene activity and cellular processes. Understanding the specific roles of these lncRNAs in the development of DN enhances our grasp of the fundamental molecular mechanisms underlying kidney injury. This study aims to identify potential therapy targets by investigating the complex interplay between lncRNAs and key pathways implicated in DN. Leveraging the therapeutic potential of lncRNAs has the potential to revolutionize DN care, offering novel avenues for personalized and tailored therapies to improve patient outcomes and QoL. By thoroughly analyzing and integrating existing treatment options for DN alongside a focus on the roles of lncRNAs, this research endeavors to shed light on how lncRNAs could be utilized for diagnosis, prognostication, and treatment of DN.

The goal of this article is to synthesize current research findings to gain a deeper understanding of how lncRNAs might be harnessed for diagnosing, predicting outcomes, and treating DN. This study seeks to provide valuable insights into the therapeutic landscape of DN, highlighting the potential of lncRNAs as promising candidates for novel diagnostic and therapeutic approaches in managing this devastating consequence of diabetes mellitus.

LncRNAs: an overview

LncRNAs constitute a class of RNA molecules with transcripts exceeding 200 nucleic acids in length. Despite their inability to encode proteins, they are widespread in eukaryotic genomes [23–25]. The majority of lncRNAs are transcribed from a single strand within protein-coding gene loci and are located within the nuclear or cytoplasmic compartments of cells [26, 27]. In recent years, there has been significant interest in lncRNAs due to growing recognition of their roles in biology. However, despite their involvement in various developmental stages and diseases, the fundamental biological processes of lncRNAs remain poorly understood. Previous research on lncRNAs has yielded conflicting findings, and the activities associated with many lncRNAs remain largely unknown. Nevertheless, discoveries regarding lncRNAs have provided substantial insights into their functions in maintaining physiological homeostasis [28–31].

LncRNAs play crucial roles in the regulation of epigenetic modifications (Fig. 1). They exert control over epigenetic gene expression by influencing chro-

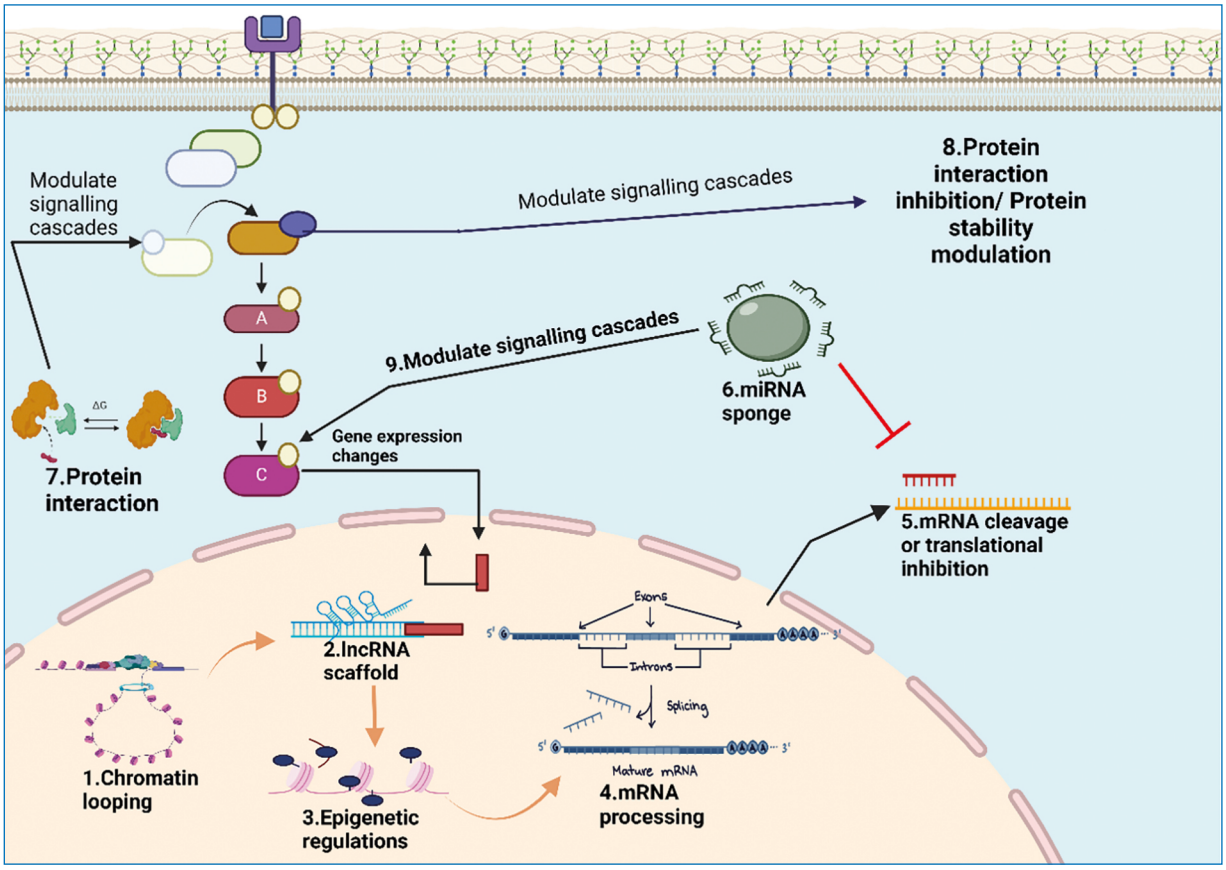

Figure 1. The Regulatory Processes Governing LncRNA Function
The subcellular positioning of lncRNA is usually a reliable indicator of its activity since it includes associations with RNA, proteins, and chromatin. LncRNAs have two main functions: they may either cause chromosomal cycling or act as a scaffold, attracting various molecules that regulate a gene activator and can either increase or reduce gene production. LncRNAs may bind to gene promoters to start methylation modifications that regulate gene expression (3). Furthermore, lncRNAs can attract regulatory proteins to mRNAs, so exerting influence on mRNA processing (4). MiRNAs have been linked to mRNAs that promote mRNA degradation or obstruct the process of translation to decrease mRNA function following the exchange of mitochondrial assets to interpretation (5). When cytoplasmic lncRNAs selectively bind to miRNAs, they function as miRNA sponges, therefore reducing the inhibitory effect on mRNA (6). In addition, cytoplasmic lncRNAs have a role in stabilizing and regulating protein interactions, which in turn influence signaling cascades and subsequent alterations in gene activity. MiRNA splashing has the potential to modify signaling pathways by impacting the performance underlying mRNA (9)
lncRNA — long noncoding RNAs; mRNA — messenger RNA; miRNA — microRNAs

matin structure [32–34], histone modification [35, 36], alternative transcription [37], X-chromosome inactivation [38], and dosage compensation [39]. Despite their inability to encode protein molecules, lncRNAs can modulate transcription by regulating transcription factors, enhancers, and promoters [40–43]. Additionally, lncRNAs contribute to post-transcriptional modifications by stabilizing messenger RNAs (mRNAs) and serving as precursors for short RNAs [44–46]. In the context of interacting with transcriptional regulatory networks, lncRNAs and microRNAs (miRNAs) engage in competitive relationships [47–52].

LncRNAs exert control over gene expression through various mechanisms, both during transcription and post-transcription [42, 53]. They often regulate transcription by modulating chromatin [54], targeting specific DNA locations through interactions with various chromatin-modifying components. A notable example is the close association between *HOTAIR* (HOX transcript antisense RNA) and the Polycomb repressive complex 2 (PRC2) and Lys-specific demethylase 1 (LSD1). These complexes play a role in removing active demethylation of lysine 4 residue on histone 3 (H3K4me2) [55]. Another example is *GATA-AS* (*GATA* antisense), another lncRNA, which regulates endothelial cell proliferation

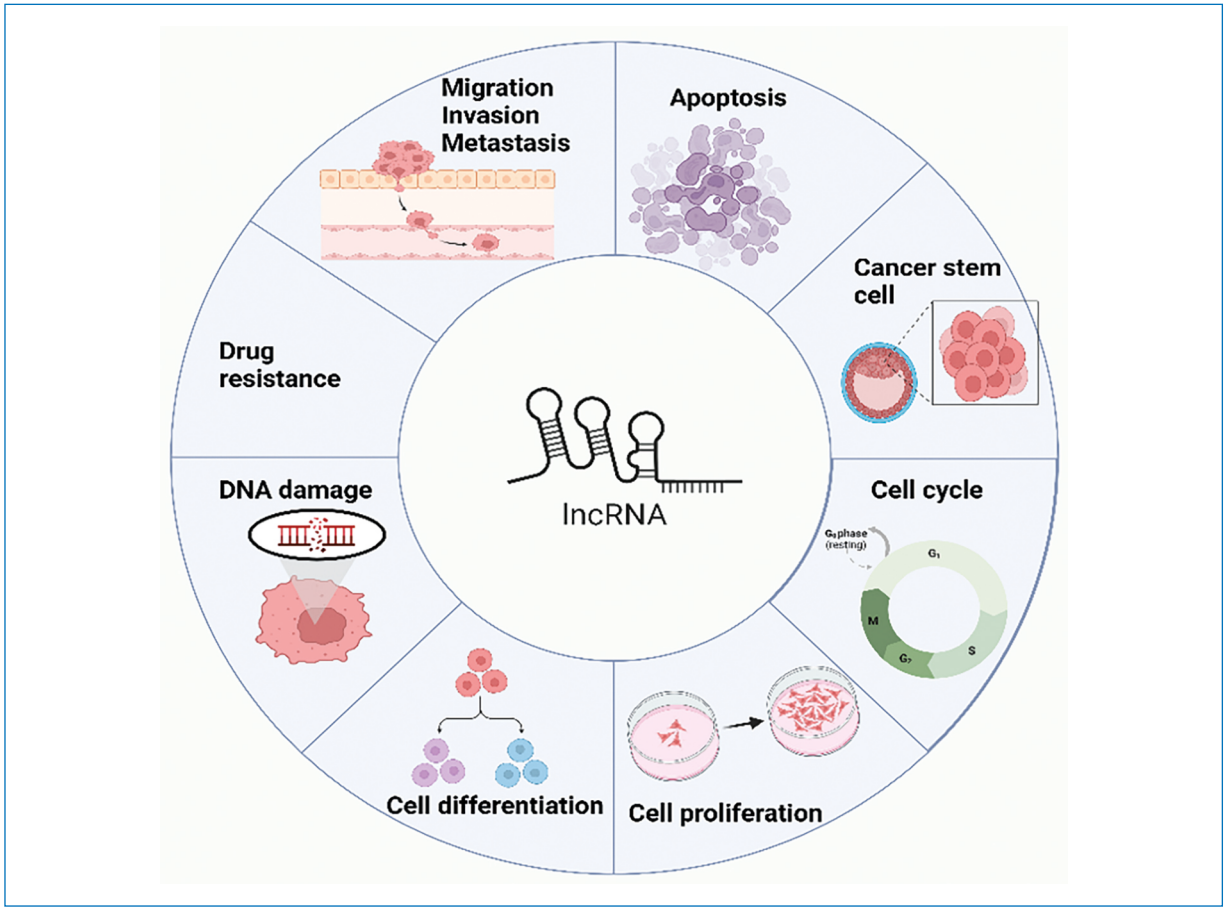

Figure 2. LncRNAs Play a Crucial Function in the Control of Cell Functions
DNA — deoxyribonucleic acid; lncRNA — long noncoding RNAs

by interacting with lysyl oxidase-like 2 (*LOX2*), an epigenetic regulator, to modify H3K4me3 [56]. LncRNAs participate in various biological activities, including cell division, by regulating gene transcription and post-translational expression (44) (Fig. 2).

Imbalances of lncRNAs in insulin resistance and DN

LncRNAs have been linked to the abnormal regulation observed in diabetes and DN. Numerous investigations have emphasized the part lncRNAs play in the emergence of numerous illnesses. An example of this is a review paper that examines the dysregulation of lncRNAs and miRNAs in diabetes. The study highlights their role in controlling the behavior of genes and the mechanisms that cause disorder, in addition to their potential as indicators for predicting outcomes and candidates for therapeutic interventions [57]. Furthermore, some lncRNAs, including *GM5524*, *GM15645*, *SNHG16*, and metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*), are disrupted in the setting of DN. This has significant consequences for the disease's underlying mechanisms and suggests that these lncRNAs might serve as prospective options for therapeutic interventions [58–60]. Additionally, researchers have examined the significance of non-invasive indicators, for instance miRNA-21 and lncRNA growth arrest-specific 5 (*GAS5*) in the initial stages of DN and hyperglycemia. This investigation has provided insights into their diagnostic usefulness and their involvement in the development of these illnesses [61]. The results highlight the critical part that lncRNAs play in the dysregulation associated with hyperglycemia and DN, suggesting potential benefits aimed at the advancement of detection and treatment options.

Function of lncRNAs in the progression of renal disorders

The worldwide incidence of chronic kidney disease (CKD) is rising quickly, making it an important issue in international public health. Hence, it is essential to ascertain new therapeutic targets linked to the develop-

ment and the progression of kidney disease. There is a growing amount of research suggesting that lncRNAs may have significant regulatory functions in several renal diseases, including the progression and onset of CKD, renal cell carcinoma (RCC) with acute kidney injury (AKI). The presence of RCC indicates a strong likelihood that lncRNAs might serve as effective and innovative targets for future therapies and diagnostic methods in kidney diseases. Advocating for a pivotal position regarding lncRNAs in kidney diseases, nuclear paraspeckle assembly transcript 1 (*NEAT1*), a lncRNA, which is essential to the body's own immune response, was found clear evidence of a correlation between the seriousness of AKI in shock. Its harmful activity is attributed to its role in irritation along with cell death, both of which are regulated through *NEAT1*, an essential protein. More specifically, pro-inflammatory cytokines and reactive oxygen species are produced at higher levels when *NEAT1* is upregulated. *NEAT1* further increases expression of Bax and caspases 3 and 9, leading to improved apoptosis, a biological process that involves programmed cell death [62–64]. A primate-specific long non-coding RNA (*PRINS*), lncRNA induced by hypoxia-inducible factor 1 alpha (HIF-1α), is another significant lncRNA involved in the development of AKI, after oxygen deprivation. *PRINS* engages with controlled normal T-cell releases and secretes pro-inflammatory cytokines, contributing to the development of ischemia-reperfusion damage. Moreover, as a well-known apoptotic controller, *PRINS* increases cell mortality more when ischemia-reperfusion damage is present [65]. Glomerulosclerosis and renal fibrogenesis are crucial factors linked to the advancement of CKD and its development into ESRD. Emerging data indicate that the lncRNA known as TGF-β/Smad3-interacting long noncoding RNA (*lnc-TSI*) suppresses a crucial mechanism that leads to the development of fibrosis. By binding with Smad3, lnc-TSI stops transforming growth factor beta 1 (TGF-β1) from being phosphorylated. In order to offer additional proof of the impact on TGF-β1, human participants were added. Renal fibrosis was gradually induced by administering lnc-TSI. A unilateral ureteral obstruction paradigm was employed to investigate expansion of renal fibrosis (RF). Additionally, lnc-TSI has the potential to function as a biomarker, as evidenced by the discovery that patients having IgA-associated nephropathy that originally had lower levels of lnc-TSI activity in their renal biopsy results additionally experienced faster development of RF [66]. Another significant lncRNA, known as *HOTAIR*, recently shown to serve a significant effect in the development of RCC via chromatin remodeling. Evidence was presented that the inhibition of *HOTAIR* with the use of small interfering RNA markedly decreased the extent of split cells along with the RCC cellular propensity to proliferate and penetrate neighboring tissues through the reduction of enhancer of zeste homolog 2 (*EZH2*) expression, both in vivo and in vitro, and the hiring procedure Lys-27 in histone 3 (*H3K27me3*). Moreover, significant cellular development and multiplicity indicators comprise p16, p21, and p53. *HOTAIR* knockout animals demonstrated dysregulation of several genes, which may be caused by the absence of chromatin-remodeling recruitment. The *HOTAIR* gene is responsible for a complicated process that results in the release of p53 from repression. *H3K27me3* and *EZH2* control the gene activity of p16 and p21 [67]. The progression of RCC is also considerably aided by FoxO3-induced lncRNA 1 (*FILNC1*), which suppresses the c-Myc-regulated conversion of energy. The expression of *FILNC1* is decreased in RCC both in laboratory cell cultures and in living organisms, resulting in the prevention of glucose-induced cell death and the stimulation of growth in conditions of low glucose concentration circumstances. From a mechanistic standpoint, *FILNC1* functions as a decoy to AUF1, a protein that binds to AU-rich elements in RNA. It causes the intake of glucose to decrease via binding to c-Myc mRNA. Mice lacking *FILNC1* exhibited larger tumor growth and weight in contrast to the control group. Significantly, there was a definite association observed among an elevated level of *FILNC1* and the medical conditions that RCC patients experienced, indicating that *FILNC1* plays a major role in RCC [68]. Recently, Wu and colleagues conducted a study on lncRNA expression in RCC. There were 141 patients in this study; 71 of them had clear cell RCC (ccRCC), and the remaining 62 were controls. The set of training and testing samples derived from patient serums revealed and validated a signature made up of five lncRNAs: *lncRNA-LET*, *PANDAR*, *PVT1*, *linc00963*, and phosphatase and tensin homolog pseudogene 1 (*PTENP1*). This finding highlights the substantial potential of lncRNA for clinical use [69].

Role of lncRNA in diabetic nephropathy

Diabetic nephropathy stands as the primary contributor to CKD and ESRD, prevailing globally [70, 71]. Numerous published studies underscore the significant role of lncRNAs in the initiation and progression of DN [72–75]. Notably, several lncRNAs have been linked to mitochondrial functions, underscoring the importance of mitochondrial activity, as evidenced in studies [75, 76]. One dysregulated lncRNA implicated in DN progression is lncRNA *Erbb4-IR*. This specific lncRNA notably contributes to DN onset via the TGF-β/Smad3 signaling pathway, contingent upon an additional component

[77]. *Erbb4-IR* expression is enhanced in the presence of high-quality glycosylation end products. In the well-established mouse model of type 2 diabetes (T2D), db/db mice with diabetes, suppression of *Erbb4-IR* conferred protection. Therapeutic intervention for T2D aims to mitigate proteinuria and RF, where there is an increase in collagen I and IV synthesis in tubular and mesangial cells. Individuals with diabetes with *Erbb4* knockdown showed reduced *Erbb4-IR* expression, potentially affecting collagen I and IV formation in mesangial and tubular tissues. Mechanistically, *Erbb4-IR* acts as an intermediary for miR-29b suppression, exacerbating renal inflammation [78]. These findings suggest potential for targeted *Erbb4-IR* interventions to attenuate DN progression [79]. Another pivotal lncRNA implicated in DN development is *MEG3* (maternally expressed 3) [80]. Functional investigations indicate *MEG3's* antiproliferative role, with implications in various malignancies [81, 82]. Additionally, *MEG3* is associated with glucose resistance and premature aging in individuals with T2D [83]. Mechanistically, *MEG3*, overexpressed in hyperglycemia, serves as a decoy to counteract miR-145, resulting in reduced collagen IV synthesis and fibronectin release. This leads to diminished mesangial fibrosis and notable improvements in key DN characteristics within kidney cells and plasma. Furthermore, *MEG3* may sequester miR-181a, contributing to damage and inflammation through the Egr-1/TLR4 signaling pathway [84]. These findings underscore *MEG3's* role in inducing inflammation, leading to detrimental effects on DNA and fibrosis.

GAS5 is another lncRNA implicated in the pathogenesis of DN [85]. It acts as a decoy for miRNAs to safeguard renal function by inhibiting fibrosis and mesangial cell proliferation. Studies observed lower *GAS5* levels in 58 DN patients. *GAS5* operates as a reservoir for miR-221, a miRNA that directly interacts with sirtuin-1 (SIRT1), a renoprotective factor in diabetes complications, promoting fibrous component production in mesangial cells [86]. *GAS5* also directly boosts SIRT1 expression, enhancing its ability to mitigate damage to tubular, podocyte, and mesangial cells in DN [85]. Moreover, *GAS5* can recruit *EZH2* to inhibit matrix metalloproteinase 9 (MMP9) production, resulting in reduced fibrous component levels, including collagens I, III, and TGF-β1. This leads to improvements in DN-associated biological markers, such as serum BUN and creatinine, along with 24-hour urine protein levels [87].

X-inactive specific transcript (*XIST*), originally known for its involvement in X chromosome inactivation, is also linked to DN onset. In individuals with diabetes, *XIST* expression increases, and its inhibition prevents interstitial inflammation [88]. Mechanistically, *XIST* acts as a sponge for miR-93-5p, which targets MSK2 and VEGFA and has been associated with DN progression [89, 90]. *XIST* also facilitates *CDKN1A* gene expression, leading to kidney damage and fibrosis by inhibiting miR-93-5p suppression [90]. Kato and colleagues identified host lncRNAs, including *lncMGC*, as potentially crucial in DN development. Elevated glucose or TGF-β1 levels were found to increase *lncMGC* levels, thereby controlling miR-379 cluster transcription. This upregulation of miRNAs within the cluster promotes extracellular matrix production, contributing to DN fibrosis [91].

Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (*PGC-1α*), a key regulator of mitochondrial activity in DN, is reported to be diminished in the condition [92–94]. Recent research suggests that taurine can enhance *PGC-1α* activity. The *lncRNA TUG1* (taurine up-regulated 1), located on chromosome 22q12, regulates *PGC-1α* expression [72, 94, 95]. *TUG1* exhibits protective effects in DN by upregulating *PGC1α* expression, enhancing mitochondrial bioenergetics, and reducing podocyte apoptosis. Genetic modification-induced *TUG1* expression improved glomerular basement membrane thickness and reduced podocyte apoptosis, thereby improving the relationship between albuminuria and DN progression [76]. Abnormal *TUG1* expression is associated with decreased estimated GFR in human patients and contributes to podocyte apoptosis by suppressing the transcriptional regulator C/EBP identical protein (CHOP), thus reducing cytotoxicity [96]. Additionally, *TUG1* can sequester *miR27a-3p*, mitigating its pro-fibrotic and pro-inflammatory effects [96, 97].

MALAT1 lncRNA expression correlates with podocyte apoptosis under high glucose conditions. *MALAT1* interacts with serine/arginine splicing factor 1 and β-catenin, leading to podocyte damage. *MALAT1* disruption reduces podocyte apoptosis [98]. Furthermore, Li et al. demonstrated increased *MALAT1* expression in tubular cells from mice with diabetes exposed to high glucose levels. *MALAT1* upregulation inhibits miR-23c, relieving suppression of ELAV Like RNA Binding Protein 1 (ELAVL1), which targets the pro-inflammatory gene *NLRP3*, thus preventing cell death [99].

NEAT1 lncRNA stimulates the Akt/mTOR signaling pathway, contributing to renal fibrosis in DN. *NEAT1* suppression decreases TGF-β1, fibronectin, and collagen IV mRNA expression, inhibits mesangial cell secretion, and reduces ECM protein content, even under high glucose conditions. *NEAT1* may promote ECM formation and mesenchymal-epithelial transition by targeting *ZEB1* and *miR-27b3p* [100–103]. Suppression of *NEAT1* reduces kidney damage in DN mice,

Table 1. LncRNAs in Diabetic Nephropathy

lncRNAs	Mechanism	References
Erbb4-IR	Decoy	[77]
GAS5	Decoy	[85]
Gm6135	Decoy	[119]
H2k2	Decoy	[120]
HOTAIR	Decoy	[121]
MEG3	Decoy	[80, 83, 84]
XIST	Decoy	[88]
CYP4B1-PS1-001	Guide	[122, 123]
ENSMUST00000147869	Guide	[124]
LRNA9884	Guide	[125]
MALAT1	Guide	[98]
NEAT1	Guide	[101, 103]
NONHSAG053901	Guide	[126]
Rpph1	Guide	[127]
SPAG5-AS1	Guide	[128]
TUG1	Guide	[72, 80, 96]
lnc-MGC	Scaffold	[91]
ZEB1-AS1	Signal	[123]

CYP4B1-PS1-001 — cytochrome P450 family 4 subfamily B member 1-phosphate synthase 1; *Erbb4-IR* — erb-b2 receptor tyrosine kinase 4-IR; *GAS5* — growth arrest-specific 5; *HOTAIR* — HOX transcript antisense RNA; *MEG3* — maternally expressed 3; lncRNA — long noncoding RNAs; *MALAT1* — metastasis-associated lung adenocarcinoma transcript 1; *NEAT1* — nuclear paraspeckle assembly transcript 1; *Rpph1* — ribonuclease P RNA component H1; *SPAG5-AS1* — sperm associated antigen 5 antisense RNA 1; *TUG1* — taurine up-regulated 1*XIST* — X-inactive specific transcript; *ZEB1-AS1* —zinc finger E-box binding homeobox 1 antisense RNA 1

highlighting its significant role in disease progression and fibrogenesis [103].

Treatment for diabetic nephropathy with miRNA and lncRNAs

Genes associated with diseases can be regulated by miRNAs, making miRNA-based therapies a potential alternative treatment option. Chemically modified oligonucleotides, such as miRNA mimics or antagomiRs, have been developed to mimic or suppress miRNAs, ensuring the effectiveness of miRNA-based therapy. One example of this approach is the use of locked nucleic acid (LNA) structural antagonists to suppress the synthesis or function of specific miRNAs [104, 105]. Interestingly, LNA-miR-192 has shown promise as a treatment for DN by reducing miR-192 production. This reduction in miR-192 transcription, in response to *TGFB*, leads to lower levels of the subsequent miRNA and diminishes the activity of key genes involved in fibrosis formation in a mouse model [106]. The primary objective of miRNA-based intervention is to prevent renal fibrosis, which aligns with the goals of most current medications for DN patients. Administration of antagomiR-miR-21 via subcutaneous injection effectively inhibited renal fibrosis development in CKD mice by reducing damage to both glomerular and tubular cells [107]. In another study, reintroducing miR-29b expression in mice with DN led to decreased collagen matrix accumulation, reduced fibrosis, and inhibition of the TGF-β/Smad3 pathway [108]. These findings suggest that miRNA--based therapy could be a potential option for treating DN in the future.

While miRNA-based therapy holds promise, the challenge lies in developing an effective delivery strategy for administering this treatment. Most miRNAs have been found to simultaneously regulate multiple target genes [109, 110]. Therefore, systemic or in vivo administration of these miRNAs may inadvertently affect unrelated pathways. Consequently, current research on miRNA-based treatments is primarily focused on enhancing delivery effectiveness and safety. To achieve this, vectors such as lipid or viral particles are utilized to target specific pathways and regions, ensuring that the therapy has a localized impact on particular cellular tissues and areas [111–113]. Additionally, the size of the therapeutic agent must be carefully considered to ensure it is small enough to cross the endothelial barrier and reach the intended organ or region without being filtered out by the renal system. However, in the case of treating DN, this filtration issue may actually

benefit miRNA-based medical treatment, as tubule epithelial cells tend to reabsorb components from the ultrafiltrate, minimizing loss [104]. Hence, there is potential for using miRNA-based therapies in treating DN patients. Nevertheless, further research, including clinical investigations involving humans, is necessary to validate these findings.

Several miRNA-based treatments have progressed to human clinical trials; however, none have been specifically designed to alleviate diabetic neuropathic pain. Miravirsen, a miR-122 inhibitor (LNA-antisense oligonucleotide), has advanced to phase II trials for treating HCV infections. Injections of miravirsen under the skin resulted in decreased HCV RNA levels, with the effect dependent on the dosage, and no signs of viral resistance were observed [114]. Additionally, RG-101, another miR-122 inhibitor for HCV-infected individuals, has successfully completed a phase I study [115]. Several other miRNA-based therapies are being developed for clinical trials targeting various human diseases. Consequently, investigating miRNA-based treatment for DN has emerged as a promising area of interest for researchers.

Another potential therapeutic approach involves using lncRNAs for DN treatment. Targeting lncRNA expression is preferred over miRNAs because lncRNAs are expressed differently across the body, act as transcription regulators, and show dysregulation in various cell types and diseases. Modified antisense oligonucleotides (ASOs) have been used to precisely target and silence lncRNAs, primarily located in the nucleus, by initiating their degradation via RNase H action. Modifications such as 2′-OMe RNA and LNA alterations at the 3′ and 5′ ends have been described [116]. The main challenge lies in ensuring precise ASO binding to the targeted spot on the lncRNA, as the complex structures of lncRNAs may obstruct this process [117]. Thus, the most practical approach is to provide or develop customized ASOs designed to target specific lncRNAs, albeit at a high cost per ASO. Furthermore, practical implementation of lncRNA-based therapy in living organisms presents challenges similar to miRNA therapies, including effective administration and treatment efficacy. Another obstacle stems from the diverse composition and non-conserved intron sequences of lncRNAs [118]. Consequently, specific inhibitor sequences may need to be developed for each individual lncRNA, particularly those derived from experimental animals. Hence, further research is needed to determine whether miRNA/lncRNA-based therapeutics can serve as a future therapeutic approach to slow the progression of DN.

Conclusions

In recent decades, lncRNAs have garnered significant attention in research. Now, our focus is shifting towards understanding their regulatory functions and interconnected roles in the development of DN. Previous studies have outlined various patterns of lncRNA expression throughout the progression of DN. However, further research is needed to fully comprehend the critical mechanisms through which lncRNAs influence epigenetic changes. The discovery of lncRNAs represents the emergence of a new field in molecular medicine for diseases related to DN. These findings are expected to provide novel insights into the intricate origins of DN and may eventually be incorporated into therapeutic strategies.

Article information

Author contributions

Md Sadique Hussain: software, supervision, writing — original draft, writing — review and editing; Mudasir Maqbool: formal analysis, visualization, writing — original draft; Nusrat K. Shaikh: formal analysis, validation, writing — original draft; Mohit Agrawal: supervision, validation, visualization; Ayesha Sultana: software, supervision, visualization.

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Conflict of interest

The authors declare no conflict of interest.

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