Long Noncoding RNAs in Diabetic Nephropathy: Emerging Regulators

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Abstract

Background: Diabetic nephropathy (DN) is a leading cause of end-stage renal disease worldwide, characterized by complex pathogenic mechanisms involving metabolic disturbances, hemodynamic alterations, inflammation, and fibrosis. Recent advances have highlighted the critical roles of long noncoding RNAs (lncRNAs), in regulating gene expression and cellular functions pertinent to DN progression. Evidence indicates that lncRNAs influence key pathogenic processes such as fibrosis, inflammation, oxidative stress, and apoptosis, thereby modulating disease development and severity. Their stability and presence in body fluids make them promising biomarkers for early detection and potential therapeutic targets. This review includes current understanding of lncRNAs in DN, focusing on their biogenesis, mechanisms of action, involvement in disease pathways, and clinical implications.

Keywords: *Long Noncoding RNAs, Diabetic Nephropath*

Introduction

Diabetic nephropathy is a significant microvascular complication of diabetes mellitus and the leading cause of end stage renal disease (ESRD) ***)Badal&Danesh, 2014(***. Almost 20 to 40% of T2DM patients progress to nephropathy and almost 40% of those will develop ESRD ***)Molitch et al., 2015(***. The incidence of diabetic nephropathy is a complex, still unclear, process influenced by duration of diabetes, glycemic control, presence of hypertension, and genetic predisposition ***(Bell et al., 2015)***.

Biomarkers were formerly considered that albuminuria preceded kidney function decline in diabetic kidney disease (DKD), but recent epidemiological studies revealed that a distinct group of patients presented kidney dysfunction without developing albuminuria ***(Sugahara et al., 2021).*** Additional biomarkers of glomerular and/or tubular injury have been proposed to uncover early renal dysfunction and structural lesions, even before microalbuminuria occurs ***(Papadopoulou et al., 2017)***, prompting the exploration of molecular markers such as long noncoding RNAs.

Biogenesis and Classification of lncRNAs

Long noncoding RNAs (LncRNAs) are a large class of 200-nt long noncoding transcripts that lack the ability of protein coding. LncRNAs biogenesis is quite complicated. LncRNAs share mRNAs in several characteristics especially in their transcriptional and processing steps, most of lncRNAs are transcribed by RNA polymerase II, the majority of them are spliced, polyadenylated and 5′-capped ***(Huarte.,2015).***

Based on their genomic positioning relative to protein-coding genes, lncRNAs are classified into several categories: antisense lncRNAs are transcribed from the opposite strand of protein-coding genes and often overlap with exons or introns, enabling them to regulate their sense counterparts; intergenic lncRNAs, are transcribed from regions between protein-coding genes and function independently to influence gene expression at distant loci; intronic lncRNAs originate within introns of protein-coding genes; bidirectional lncRNAs are transcribed from shared promoters but in opposite directions; and enhancer

RNAs (are produced from enhancer regions, modulating enhancer-promoter interactions ***(Dahariya et al., 2019)***.

These diverse classifications underpin their multifunctional mechanisms, which include epigenetic regulation via chromatin remodeling, acting as decoys or guides to influence transcription, serving as scaffolds assembling regulatory complexes, and functioning as posttranscriptional regulators by sequestering microRNAs or modulating mRNA stability ***(Ahmad et al., 2021).***

Mechanisms of Action of lncRNAs in Diabetic Nephropathy

LncRNA is an important regulator of various biological processes, including proliferation, differentiation, invasion and apoptosis ***(Ji et al., 2003).*** LncRNA are evolving as new biomarkers and therapeutic targets in several human diseases ***(Gutschner et al., 2013).***

Although the functional roles of lncRNAs in T2DM have only been revealed in recent years, accumulated evidence has demonstrated the biological or pathological roles of lncRNAs in the progression of diabetes and its complications. The mechanisms of lncRNA function in this disease involve pancreatic β cell homeostasis modification, lipid metabolic regulation and inflammatory responses ***(Chen et al., 2020).***

Diabetic nephropathy is associated with abnormal expression of specific lncRNAs, which are considered potential biomarkers for its diagnosis. Research has shown that these lncRNAs play a role in renal fibrosis and podocyte damage, ultimately impairing kidney function ***(Geng, et al., 2024)***.

Evidence has shown that lncRNAs are associated with TGF-β/Smad3-mediated renal inflammation and fibrosis and might be functionally important in modulating renal responses to hyperglycaemia and the progression of diabetic nephropathy ***(Alvarez & DiStefano, 2013).***

Specific lncRNAs Implicated in Diabetic Nephropathy LncRNA NEAT1

Nuclear enriched abundant transcript 1 (NEAT1) is consistently upregulated in various diabetic models. Its expression is elevated in the renal tissues of DN patients ***(Liao et al., 2021)*** and in the renal tissues of diabetic mice and rats (***Huang et al., 2019).*** NEAT1 is also highly expressed in mouse mesangial cells treated with high glucose. This lncRNA plays a pro-fibrotic role, promoting cellular proliferation, epithelial-to-mesenchymal transition, and the deposition of extracellular matrix. Its mechanism involves targeting miR-27b-3p/ZEB1, miR-23c, and the Akt/mTOR pathway ***(Wang et al., 2019).***

LncRNA ANRIL

Antisense non-coding RNA in the INK4 locus (**ANRIL**) is also found to be upregulated in diabetic conditions. It shows increased expression in the renal tissues, peripheral whole blood, and serum of DN patients ***(Chang et al., 2020 & Zhu et al., 2022).*** In high glucose-treated human renal mesangial cells, ANRIL is upregulated and contributes to the proliferation of cells and the deposition of ECM. ANRIL exerts its effects by targeting miR-15b-5p/WNT2B and miR-98b-5p/NOTCH2 ***(Chang et al., 2020 & Li et al., 2020 b).***

LncRNA TUG1

Taurine upregulated gene 1 (TUG1) shows a more complex expression pattern. It is downregulated in the renal tissues of DN patients ***(Shen et al., 2019).*** The role of TUG1 appears to be protective; it helps inhibit endoplasmic reticulum stress and maintains mitochondrial function. It achieves this by targeting CHOP/PGC-1a and coregulators enriched at its promoter ***(Shen et al., 2019; Long et al., 2020 & Li et al., 2021).*** In podocytes, hyperglycemia decreases Tug1 lncRNA, which decreases the autoregulation of PGC-1a of itself and thereby decreases mitochondrial bioenergetics. ***(Leung&Natarajan, 2018)***

LncRNA MALAT1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is upregulated in the peripheral whole blood and serum of DN patients ***(Zhou et al., 2020 & Petrica et al., 2021).*** It is also highly expressed in the serum of patients with diabetes-related end-stage renal disease ***(Fawzy et al., 2020).*** In high glucose-treated mouse podocytes, MALAT1 is upregulated and promotes oxidative stress, pyroptosis, and the detachment of podocytes from the glomerular basement membrane. This is mediated

through the Wnt/b-catenin and miR-200c/Nrf2 pathways ***(Hu et al., 2017 & Zuo et al., 2021).*** In human proximal tubular epithelial cells, high glucose also upregulates MALAT1, which promotes EMT via the Wnt/b-catenin pathway ***(Zhang et al., 2019).***

LncRNA PVT1

Plasmacytoma variant translocation 1 (PVT1) is a pro-apoptotic lncRNA that is consistently upregulated in the context of diabetic nephropathy. Its expression is elevated in the serum of DN patients ***(Zhong et al., 2020)*** and in the renal tissues of diabetic mice ***(Liu et al., 2019).*** In a cellular context, PVT1 expression is also increased in high glucose treated mouse podocytes, where it promotes apoptosis by targeting the EZH2/FOXA1 axis ***(Liu et al., 2019).***

LncRNA ARAP1-AS2

ARAP1 antisense RNA 2 (**ARAP1-AS2**) is a lncRNA associated with promoting cellular proliferation and epithelial-to-mesenchymal transition in DN. Its expression is elevated in the serum of DN patients ***(Yang et al., 2019).*** This lncRNA is also found to be upregulated in high glucose-treated human proximal tubular epithelial cells, where it targets ARAP1 to exert its pro-fibrotic and proliferative effects ***(Li et al., 2020 a).***

LncRNA CASC2

Cancer susceptibility candidate 2 (CASC2) is a lncRNA with a protective role in DN. Unlike the previously mentioned lncRNAs, CASC2 is downregulated in high glucose-treated human renal mesangial cells. It acts to inhibit proliferation, inflammation, and fibrosis by targeting the miR-135a5p/TIMP3 axis ***(Zhu et al., 2021).***

LncRNA Gm4419

Gm4419 is a lncRNA that promotes inflammation and fibrosis in diabetic conditions. It is upregulated in high glucose-treated mouse mesangial cells, and its mechanism involves targeting NF-kB to exert its pathological effects ***(Yi et al., 2017).***

LncRNA-MGC

LncRNA-MGC which hosts a mega cluster of miRNAs, including miR-379. Increase in miRNA activity from this cluster increases Extracellular matrix accumulation as well as hypertrophy associated with early stages of diabetic nephropathy ***(Leung&Natarajan, 2018)***.

Clinical Implications of lncRNAs in Diabetic Nephropathy diagnostic and therapeutic target The stability and detectability of lncRNAs in body fluids such as blood and urine make them attractive candidates for non-invasive biomarkers. Promising evidence has revealed that lncRNAs could serve as potential biomarkers for early diagnosis of diabetes and its complications ***(Alipoor et al., 2021)***.

MALAT1 expression is significantly higher in DN patients compared to those with type 2 diabetes mellitus alone, making it a potential diagnostic biomarker when combined with other indicators such as ACR, creatinine, and 1-microglobulin ***(Fawzy et al., 2020***). MALAT1 is directly correlated with biomarkers of podocyte damage, including synaptopodin and podocalyxin, and exerts detrimental effects on podocyte integrity **(*Petrica et al., 2021)***. Diabetic nephropathy tissues have considerably higher MALAT1 expression levels than normal tissues ***(Yang et al., 2022).***

MALAT1 expression levels were higher in diabetics with ESRD than those of the diabetics without ESRD ***(Fawzy et al., 2020).*** MALAT1 expression is higher in the diabetic micro-albuminuria group than in the diabetic normoalbuminuria group. This suggests that MALAT1 may be a useful biomarker for the early diagnosis of DN ***(Shoeib et al., 2023).***

Diabetic kidney disease patients had higher MALAT1 expression profiles in peripheral blood mononuclear cells compared to control groups ***(Zhou et al., 2020).*** Recent research has demonstrated that individuals with type1 diabetes who also have diabetic renal disease had higher MALAT1 expression levels in their urine samples***(Dieter et al., 2023).***

CASC2 might be explored as a potential biomarker for diabetes management and prognosis, particularly regarding its effects on renal function in diabetic patients ***(Chen et al.,2020).*** **Future prospective**

Looking forward, further research employing high-throughput sequencing and bioinformatics will continue to identify novel lncRNAs involved in DN, although many remain uncharacterized mechanistically ***(Salido-Guadarrama et al., 2023).*** Developing precise delivery systems capable of targeting renal tissues is critical for translating these findings into clinical therapies. Combining lncRNA modulation with existing treatments could provide synergistic benefits, potentially reversing or halting disease progression. Integrating lncRNA profiling into personalized medicine approaches holds promise for improving outcomes in patients with DN ***(Wang et al., 2025).***

Conclusion

Long noncoding RNAs have emerged as vital regulators in the pathogenesis of diabetic nephropathy. Molecules such as MALAT1 and CASC2 exemplify the diverse roles of lncRNAs; some promoting fibrosis, inflammation, and podocyte injury, others exerting protective effects. Their capacity to influence key signaling pathways, coupled with their stability and detectability in biological fluids, positions them as promising biomarkers and therapeutic targets. Despite current challenges, ongoing research continues to uncover their therapeutic potential, offering hope for more effective early diagnosis and personalized treatments for DN

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