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Review Article

The emerging role of MALAT1 lncRNA in diabetic nephropathy: based on the review of the literature and bioinformatic analysis

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ABSTRACT

Previous studies have found that the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) exerts its biological effects on the progression of diabetic nephropathy by sponging microRNAs and affecting the gene transcription of downstream molecules. In this study, the primary emphasis is placed on the functions that MALAT1 plays in relation to the pathophysiology of diabetic nephropathy as well as the processes that underlie these roles. In addition, the usage of this long noncoding RNA as a possible biomarker or therapeutic target for diabetic nephropathy will be discussed.

Keywords: long Noncoding RNA, MALAT1, MicroRNA, Diabetic Nephropathy

Abbreviations: AMPK: AMP-activated protein kinase; circRNAs: circular RNAs; ceRNA: competing endogenous RNAs; DKD: diabetic kidney disease; DN: Diabetic nephropathy; DM: diabetes mellitus; EMT: epidermal to melanin transition; ERSD; stage renal disease; FoxO: forkhead box O; GFR: glomerular filtration rate; HIF-1: hypoxia-inducible factor 1; NLRP3: NOD-like receptor protein 3; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; mTOR: mammalian target of rapamycin; ncRNA; noncoding RNA; lncRNAs; long noncoding RNAs; PI3K: hosphoinositide 3-kinase; Ras: rat sarcoma viral oncogene; TF: transcription factor; T2D; type 2 diabetes

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Introduction

Diabetic nephropathy (DN), also known as diabetic kidney disease (DKD), is regarded as one of the most serious microvascular consequences of diabetes mellitus (DM) (1). DN is the major cause of end-stage renal disease (ESRD) worldwide, which is related to higher morbidity and mortality in patients with diabetes (2). Patients with diabetes have a thirty to forty percent chance of developing DN (3). The overall prevalence of nephropathy in individuals with type 2 diabetes (T2D) in Iran was found to be 30.6%, according to a meta-analysis that included 18 papers and 6190 people ranging in age from 20 to 83 years (4). The increased excretion of albumin, hyperglycemia, hypertension, dyslipidemia, obesity, and smoking are some of the key risk factors that contribute to the development and progression of DN (5, 6).

The diagnosis of DN is made in the laboratory based

on the presence of albuminuria over a prolonged period of time and a gradual decline in glomerular filtration rate (GFR) (7). However, albuminuria has a number of drawbacks, such as a high degree of variability and a low degree of sensitivity, and the level of albuminuria sometimes cannot correctly reflect the particular situation of DN (8). In addition, the fall of GFR without albuminuria, also known as nonproteinuric diabetic kidney disease, has been increasingly identified, particularly in subjects with T2D (9, 10). As a result, a growing number of innovative biomarkers have surfaced with the purpose of identifying individuals who are at risk of developing DKD as well as early DKD in the hope of preventing the occurrence of ESRD (11).

In recent years, there has been an uptick in the amount of evidence suggesting that noncoding RNA (ncRNA), in particular long noncoding RNAs (lncRNAs), play an important part in the development and progression of DN (12-16). In addition, a large number of studies have shown that cell-free ncRNAs have been dysregulated in the serum, plasma, urine, and peripheral blood samples of patients with T2D (17-20). The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), also termed nuclear enriched abundant transcript 2 (NEAT2), is one of the ncRNAs in human disease that has received the most attention from researchers, especially in diabetes and diabetic-related complications (21, 22). In this study, the primary emphasis is placed on the functions that MALAT1 plays in relation to the pathophysiology of DN as well as the processes that underlie these roles. In addition, the discussion will be about the usage of this lncRNA as a possible biomarker or therapeutic target for DN.

Methods

In this narrative review, a systematic literature review was performed using PubMed, Google Scholar, and Web of Science for English up to 4 June 2023, using the terms "DN", "DKD", "diabetes", "lncRNA", and "MALAT1". To predict MALAT1-microRNA (miRNA) interactions, experimentally validated miRNA targets of MALAT-1 lncRNA were extracted from the NPInter.V4 database (23). Subsequently, a list of experimentally validated mRNA targets of miRNAs related to MALAT-1 was obtained from the miRTarBase database (24). The KEGG pathway enrichment analysis was carried out using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) and miEAA 2.0 databases to explore functional annotation and pathway enrichment of the extracted target mRNAs (25, 26).

Results and Discussion

LncRNA and miRNA interactions: miRNA Sponge

ncRNA refers to the portion of an RNA molecule that does not get translated into a protein (27). There are various subclasses of ncRNA, including miRNA, circular RNAs (circRNAs), pseudogenes, tsRNAs, and piRNAs (28). The association of ncRNA with a variety of disorders, including cancer, inflammatory diseases, and metabolic diseases, has been the subject of a significant number of research studies (29, 30). miRNA is a type of single-stranded (ss) RNA transcript that has the function of post-transcriptional control and RNA silencing (31). RNA polymerase II and RNA Pol III (for some of them) are the enzymes responsible for the transcription of key miRNAs (32). The process of transcription results in the production of pri-miRNA molecules, which have changes similar to those found in mRNA, such as 5' capping and 3' polyadenylation, and have a hairpin structure that covers the mature miRNA sequence (29). miRNAs interact with short complementary sequences in the 3′ untranslated regions and govern cell cycle progression, apoptosis, and cellular development (33).

LncRNAs are single-stranded (ss) RNA with a length of 200 nucleotides. These RNAs are unable to encode proteins (34). Through the control of genomic expression, epigenetic alteration, and post-transcriptional regulation in cis or trans, lncRNAs play a significant role in a variety of physiological and pathological cellular functions (35). Additional important roles played by lncRNAs include genetic imprinting, genomic rearrangement, regulation of the cell cycle, and splicing (36, 37). The interaction between microRNAs and long noncoding RNAs, known as miRNA sponge or competing endogenous RNAs (ceRNA), can diminish the inhibitory effects of miRNAs on mRNAs or sponge them (38). Indeed, lncRNAs have the potential to behave as a sponge, soaking up a greater proportion of the miRNAs that are available to the target mRNA, thereby preventing the target gene repression (39) (**Figure 1**).

The prediction of MALAT1-miRNA interactions in DM

The MALAT1 gene is located within human chromosome 11q13 and was initially discovered in a screen for transcripts associated with metastasis and patient survival in non-small cell lung cancer (40, 41). The major mechanisms of post-transcriptional regulation of MALAT1 include alternative splicing, promoting trimethylation of histone H3 at lysine 27, and facilitating transcription factor (TF) binding to the promoter of target genes and ceRNAs (42, 43).

The bioinformatics analysis revealed that ninety-two experimentally validated miRNA targets for MALAT-1 were identified by the NPInter database. The enrichments of the miRNAs in KEGG pathway categories were performed using miEAA 2.0 databases. The significant KEGG pathway categories and correlated miRNAs were presented in the heatmap generated in DIANA-miRPath. Moreover, enrichment analysis revealed that the 32 miRNA targets of MALAT-1 were enriched in diabetes-related pathways including hypoxia-inducible factor

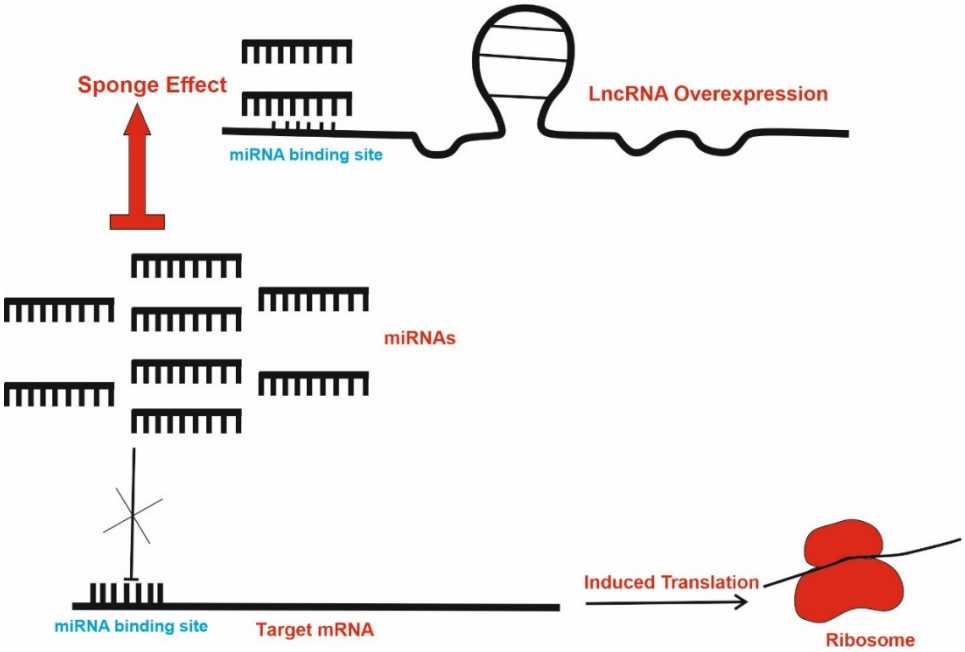

Figure 1. Schematic overview of the interaction between lncRNA and miRNAs. miRNA sponge or competing endogenous RNAs (ceRNA) could diminish the inhibitory effects of miRNAs on mRNAs or sponge them.

Table 1: KEGG pathways enrichment analysis for genes regulated by MALAT1-miRNAs axis

Subcategory	Enrichment	P-value	P-adjusted	Observed	genes
HIF-1 signaling pathway	depleted	4.57e-6	1.33e-4	9	29
FoxO signaling pathway	depleted	3.85e-5	4.62e-4	10	37
PI3K-Akt signaling pathway	depleted	3.04e-5	4.62e-4	12	69
MAPK signaling pathway	depleted	5.84e-5	6.42e-4	7	54
Rap1 signaling pathway	depleted	2.36e-4	0.001353	7	38
Ras signaling pathway	depleted	2.36e-4	0.001353	7	40
mTOR signaling pathway	depleted	1.77e-4	0.001353	4	22
TGF-beta signaling pathway	depleted	8.43e-4	0.0042801	6	23
Wnt signaling pathway	depleted	0.0013139	0.005527	3	21
Toll-like receptor signaling pathway	depleted	0.0017519	0.0068014	3	24
Jak-STAT signaling pathway	depleted	0.0096295	0.0249234	6	26

1 (HIF-1) signaling pathway, forkhead box O (FoxO) signaling pathway, phosphoinositide 3-kinase (PI3K)-Akt signaling pathway, rat sarcoma viral oncogene (Ras) signaling pathway and mammalian target of rapamycin (mTOR) signaling pathway (**Table 1**).

The role of MALAT1-miRNA interactions in DN

Previous studies have found that MALAT1 exerts its biological effects on the progression of DN by sponging miRNAs, interacting with miRNAs, and affecting the gene transcription of downstream molecules (Figure 2). The focus here is on the potential function of MALAT1 as a miRNA sponge in DN.

MALAT1 facilitates high glucose-induced endothelial-to-mesenchymal transition and renal fibrosis

Renal fibrosis is an important stage in the progression of DN into ESRD (44). This pathological event takes place as a result of an abnormally high level of extracellular matrix being deposited in the kidney tissue as a result of hyperglycemia, inflammation, and oxidative stress (45, 46). In recent years, it has been reported that ncRNA is involved in both epithelial-to-mesenchymal transition

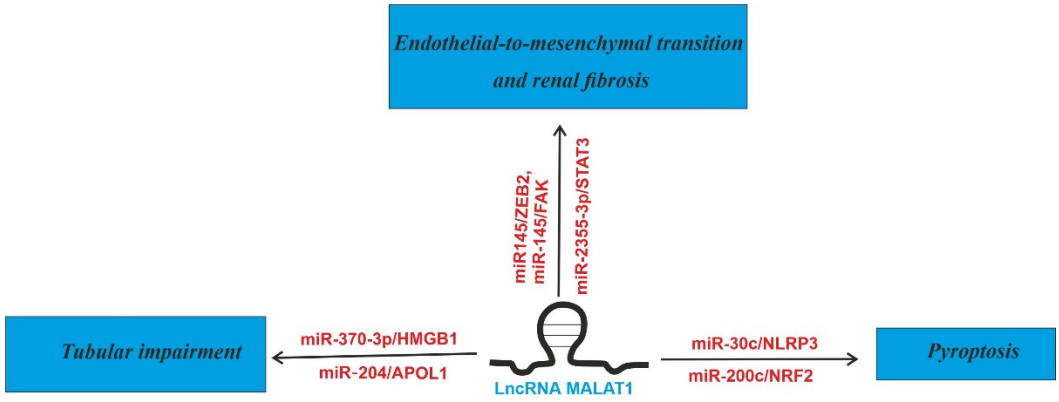

Figure 2. Schematic representation of MALAT1 function in DN. Sponging effect of MALAT1 on the miRNAs could induce endothelial-to-mesenchymal transition and renal fibrosis, pyroptosis and tubular impairment in breast DN.

and the damage of tubular cells (47). MALAT1 is one of the ncRNAs whose role in endothelial-to-mesenchymal transition and renal fibrosis has been explored. It has been demonstrated that MALAT1 is capable of acting as a sponge RNA for miR-145, which allows it to control the expression of the target gene ZEB2 and, as a result, induce epidermal to melanin transition (EMT) as well as fibrosis (48). Upregulation of MALAT1 in response to high glucose treatment has been shown to induce EMT in HK-2 cells by activating the Wnt/-catenin pathway (49). Huang et al. demonstrated that MALAT1 expression levels are increased in renal tissues of diabetic rats and high glucose-treated cells. This was associated with an increase in protein levels of collagen I and IV, fibronectin, and laminin in HK-2 cells. They also found that MALAT1 overexpression caused the level of miR-2355-3p to decrease, which led to the induction of cell damage, renal fibrosis, and kidney tissue destruction via the miR-2355-3p/IL6ST/STAT3 signaling pathway (50). Furthermore, it has been shown that the expression levels of MALAT1 were upregulated in renal fibrotic tissues in diabetic patients and this lncRNA could worsen renal fibrogenesis in obstructive nephropathy through the miR-145/FAK pathway (51).

The interplay between lncRNA-MALAT1 and pyroptosis

It has been suggested that pyroptosis and further inflammatory response play a critical role in the DN pathogenesis (52). Pyroptosis is an inflammatory programmed cell death that is mediated by the activation of caspase-1 following the formation of the NOD-like receptor protein 3 (NLRP3) inflammasome complex (53). A number of studies have reported the influence of lncRNAs/miRNAs interaction in pyroptosis. In this regard, it has been reported that downregulation of MALAT1 could induce cell pyroptosis by inhibiting miR-30c targeting for NLRP3 in the high glucose-treated HK-2 cells (51). Moreover, Li et al. reported that lncRNA MALAT1 could moderate renal tubular epithelial pyroptosis by modulating the miR-23c-ELAVL1 axis in high-glucose-treated HK-2 cells (54). The findings of a recent study showed that knocking down of the MALAT1 protects MPC-5, a mouse podocyte cell line, against pyroptosis and oxidative stress caused by HG. This protection was achieved by the modulation of miR-200c and the expression of its target genes (55).

MALAT1 mediates tubular impairment induced by hyperglycemia and inflammation

One of the most important factors that contributes to the development of DN is tubular impairment, which can be caused by hyperglycemia (9). MALAT1 could activate the AMP-activated protein kinase (AMPK)/mTOR signaling by interacting with LIN28A and Nox4/AMPK/mTOR signaling axis, thereby worsening high glucose-induced renal tubular injury (56). It has also been suggested that downregulation of MALAT1 attenuates HK-2 cell viability inhibition, apoptosis, and inflammation induced by hyperglycemia by targeting miR-15b-5p (57). Interestingly, XU et al. revealed that paclitaxel could protect against LPS-induced acute kidney injury via the modulation of MALAT1/miR-370-3p/HMGB1 axis and the expression of TNF-α, IL-6 and IL-1β (58). A recent study investigated the involvement of MALAT1 lncRNA in the progression of cellular inflammation and renal tubular epithelial cell injury. The results revealed that the downregulation of MALAT1 may be able to reduce the severity of acute kidney injury by acting as a mediator of the miR-204/APOL1 pathway (59).

MALAT1 as a therapeutic target in DN

The evidence indicates that MALAT1 could act as a potential therapeutic target for the diagnosis and treatment of diabetes-related complications including DN (60). QiHuangYiShen, a traditional Chinese herbal

medicine formula, attenuates epithelial-mesenchymal transition in the kidney of diabetic nephropathy rats by the downregulation of MALAT1 lncRNA (61). Zuo et al. suggested that Atorvastatin exerts its protective effect on the kidney through the regulation of MALAT1 expression and reduction of oxidative stress. Indeed, they reported that Atorvastatin protects podocyte cells via the MALAT1/miR-200c/NRF2 signal pathway from pyroptosis and oxidative stress induced by high glucose treatment (55). Resveratrol (3,4′,5-trihydroxystilbene) is a polyphenol anti-toxin that can prevent a wide range of human diseases, including diabetes (62-64). Resveratrol reduced the expression levels of MALAT1 and thereby alleviated sepsis-induced acute kidney injury in cecal ligation and puncture (CLP)-induced septic model rats by deactivating the lncRNA MALAT1/MiR-205 axis (65).

Diagnostic role of MALAT1 as in DN

Promising evidence has revealed that lncRNAs could serve as potential biomarkers for early diagnosis of diabetes and its complications (17, 37). In this regard, it has been demonstrated that MALAT1 is significantly upregulated in DN tissues compared with normal (57). Fawzy et al. reported that serum levels of MALAT1 were elevated in the ESRD group compared to diabetics without ESRD. They also revealed that MALAT1 expression levels were correlated with higher levels of total triglyceride (66). In line with this finding, it has been shown that MALAT1 expression is increased in the micro-albuminuria diabetic group compared with the diabetic normoalbuminuria group and could act as a potential biomarker for early detection of DN (67). Furthermore, MALAT1 serum level has recently been recognized as a potential biomarker with high sensitivity and specificity to differentiate acute kidney injury patients from control subjects (59). It has also been reported that serum levels of MALAT1 had a direct correlation with urinary MALAT1 and miRNA-124 serum levels and negatively with miRNA 29a serum levels and eGFR (68). Zhou et al. revealed that the MALAT1 expression profile in peripheral blood mononuclear cells was increased in diabetic kidney disease groups compared to control. They also reported that MALAT1 expression levels were correlated with ACR, urine β2-microglobulin, urine α1-microglobulin, and creatinine (69). Recent studies have shown that the expression levels of MALAT1 are increased in the urine samples of type 1 diabetes patients with diabetic kidney disease (21).

Conclusion

Increasing evidence has demonstrated that lncRNA, especially MALAT1, plays a critical role in the pathogenesis and progression of DN. Accordingly, this review explored and clarified the sophisticated research and progress with the possible roles of MALAT1 in DN. MALAT1 exerts its effect through interaction with miRNAs and modulating their effects on important signaling pathways involved in the development and progression of DN. Furthermore, based on the literature discussed above, pharmacological and diagnostic targeting of MALAT1 may serve as a potential alternative strategy for the diagnosis and treatment of DN.

Conflict of Interest

Author has no conflict of interest.

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