Journal of Prevention, Diagnosis and Management of Human Diseases
Vol: 04, No. 02, Jan-June 2024
ISSN: 2799-1202, DOI: 10.55529/jpdmhd.41.82.94

Research Paper

Long non-coding rnas in kidney injury: a comprehensive review

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Article Info

Article History:
Received: 19 December 2023
Revised: 23 February 2024
Accepted: 02 March 2024
Published: 18 April 2024

Keywords:
Long Non-Coding RNAs
Acute Kidney Injury
Molecular Biomarkers
Apoptosis
Chronic Kidney Disease

ABSTRACT

Kidney injury, a global health challenge, necessitates a nuanced understanding of molecular intricacies for effective interventions. Long non-coding RNAs (lncRNAs), once dismissed as transcriptional noise, now emerge as pivotal players in orchestrating renal health. Dysregulation of specific lncRNAs like TUG1, MALAT1, H19, and NEAT1 provides molecular signatures, distinguishing physiological states from pathological conditions. In acute kidney injury (AKI), TUG1 and MALAT1 regulate apoptosis, inflammation, and fibrosis. Chronic kidney disease (CKD) involves lncRNAs like H19 and NEAT1 modulating cell proliferation and apoptosis. Beyond diagnostics, lncRNAs actively shape inflammation, apoptosis, and fibrosis, positioning them as master regulators in the intricate ballet of kidney health. Recent strides in research, coupled with cutting-edge genomics and bioinformatics tools, highlight their roles and therapeutic potential. Challenges in understanding their intricate roles and interactions necessitate the exploration of promising avenues, including single-cell RNA sequencing and artificial intelligence, paving the way for personalized interventions and regenerative medicine in kidney diseases.

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1. INTRODUCTION

The increasing global concern regarding kidney damage necessitates a focused exploration of its molecular intricacies for effective treatment strategies [1]. Long non-coding RNAs (lncRNAs), specifically those longer than 200 nucleotides, have emerged as key players in understanding kidney injury [2], [3]. These molecules, once considered transcriptional noise, now play crucial roles in epigenetic modification, chromatin remodeling, and gene regulation, influencing processes like differentiation, apoptosis, and proliferation [4]. Dysregulation of lncRNAs, such as TUG1, MALAT1, H19, and NEAT1, has been linked to acute kidney injury (AKI) and chronic kidney disease (CKD), providing potential molecular signatures for diagnosis [5].

Highlighted lncRNAs like TUG1, elevated in AKI, control inflammation and apoptosis, while MALAT1 is implicated in fibrosis [6], [7]. H19 and NEAT1 are involved in CKD, with NEAT1 elevated in inflammation and H19 regulating cell proliferation and apoptosis [8]. Additionally, lncRNAs like HOTAIR and GAS5 are relevant in diabetic nephropathy (DN), influencing apoptosis and fibrosis [9]. These molecules serve as biomarkers differentiating between healthy and pathological states, challenging the notion that they are mere transcriptional noise [10].

The integration of genomics and bioinformatics tools has enhanced our understanding of lncRNA contributions to inflammation, apoptosis, and fibrosis, turning them from passive observers to active conductors in kidney pathophysiology [11], [12], [13], [14], [15]. In the complex dance of kidney health and illness, lncRNAs now take center stage as master regulators of gene expression and cellular activities [16]. This review emphasizes the crucial need to identify molecular pathways underlying kidney injury, contributing to the evolving narrative of lncRNAs as conductors in the intricate symphony of kidney health.

2. RELATED WORK

- "Non-Coding RNAs in Kidney Diseases: The Long and Short of Them" by Moreno. This paper provides a comprehensive review of the role of lncRNAs in kidney diseases, their molecular mechanisms, and their function as emerging prognostic biomarkers for both acute and chronic kidney diseases [17].
- "Long Non-Coding RNAs in Kidney Disease" by Ignarski. This paper provides an overview of the current knowledge on lncRNAs in both glomerular and tubulointerstitial kidney disease [18].
- "Long noncoding RNAs in renal diseases" published in ExRNA. This review summarizes available studies indicating that lncRNAs are heavily involved in kidney development and disease and proposes lncRNAs as novel biomarkers for clinical diagnosis and potential therapeutic targets in renal diseases [19].
- "Non-Coding RNA and Renal Disease" published in Frontiers Research Topic. This paper broadly associates the role of some ncRNAs, such as microRNAs (miRNAs) and long-non-coding-RNAs (lncRNAs), with acute and chronic kidney disease, diabetic nephropathy, fibrosis, and renal cancer [20].
- "The Mission of Long Non-Coding RNAs in Human Adult Renal Stem" by MDPI. This paper discusses the tens of thousands of lncRNA sequences expressed in the kidney and their implications in all phases of renal disorders [21].

3. METHODOLOGY

- **Literature Search:** Conducted a thorough search in PubMed, ScienceDirect, and Google Scholar using keywords like "Long Non-coding RNAs," "Kidney Injury," and "lncRNAs in renal diseases." Identified relevant articles, reviews, and research papers in peer-reviewed journals.
- **Selection Criteria:** Focused on articles providing in-depth insights into molecular roles of lncRNAs in kidney injury, emphasizing specific ones like TUG1, MALAT1, H19, and NEAT1. Considered studies exploring functional roles of dysregulated lncRNAs in acute and chronic kidney diseases.

- **Inclusion of Key Studies:** Included seminal works like "Non-Coding RNAs in Kidney Diseases" by Moreno, "Long Non-Coding RNAs in Kidney Disease" by Ignarski, and relevant reviews from ExRNA, Frontiers Research Topic, and MDPI.
- **Data Extraction:** Extracted key data on lncRNAs' roles in kidney injury, emphasizing inflammation, apoptosis, and fibrosis modulation. Focused on studies using genomics, bioinformatics tools, and molecular biology techniques to elucidate lncRNAs' contributions.
- **Integration of Findings:** Synthesized information from various studies to construct a comprehensive narrative on lncRNAs' involvement in kidney health and pathology. Emphasized molecular mechanisms, crosstalk with other noncoding RNAs, and regulatory roles in inflammation, apoptosis, and fibrosis.

Dysregulated lncRNAs in Kidney Injury

There is a lot of promise for the dysregulated lncRNAs in renal damage as predictive and diagnostic biomarkers [22]. Blood and urine are two biological materials in which their altered expression patterns in kidney injury can be found [23]. Clinicians may be able to detect patients who are at risk of kidney damage or track the course of the illness by evaluating the levels of these lncRNAs [24]. When kidney damage occurs, a number of long non-coding RNAs (lncRNAs) are dysregulated [25]. While HOTAIR, NEAT1, LINC01619, LINC00355, and LINC00511 are upregulated, they also contribute to fibroblast activation, renal fibrosis, and the regulation of pro-inflammatory genes. MALAT1, TUG1, LINC00963, LINC00261, LINC00473, LINC00657, LINC00839, and LINC00908 are upregulated, promoting inflammation and apoptosis in kidney cells. Fibroblast growth is inhibited through downregulation of GAS5. These long noncoding RNAs (lncRNAs) are essential for the complex molecular regulation of kidney health and pathology, and they offer prospective targets for comprehension and manipulation of renal pathophysiology [26]. Table 1 lists the different lncRNAs and their roles in kidney damage.

Table 1. Upregulation or Downregulation of Specific Lncrnas and their Roles in Kidney Injury, Providing a Clear Overview of their Involvement in Various Aspects of Renal Health and Pathology

Sl. No.	lncRNA Name	Upregulation/Downregulation	Role in Kidney Injury	Reference
1	MALAT1	Upregulated	Promotes inflammation and apoptosis in kidney cells	[27]
2	HOTAIR	Upregulated	Promotes activation of fibroblasts and renal fibrosis	[28]
3	NEAT1	Upregulated	Regulates pro-inflammatory genes and promotes apoptosis	[29]
4	TUG1	Upregulated	Promotes inflammation and apoptosis in kidney cells	[30]
5	GAS5	Downregulated	Inhibits proliferation and activation of fibroblasts	[31]
6	LINC00963	Upregulated	Promotes inflammation and apoptosis in kidney cells	[32]
7	LINC01619	Upregulated	Regulates pro-inflammatory genes and promotes apoptosis	[33]
8	LINC00261	Upregulated	Promotes inflammation and apoptosis in kidney cells	[34]
9	LINC00355	Upregulated	Regulates pro-inflammatory genes and promotes apoptosis	[35]

10	LINC00473	Upregulated	Promotes inflammation and apoptosis in kidney cells	[36]
11	LINC00511	Upregulated	Regulates pro-inflammatory genes and promotes apoptosis	[37]
12	LINC00657	Upregulated	Promotes inflammation and apoptosis in kidney cells	[38]
13	LINC00707	Upregulated	Regulates pro-inflammatory genes and promotes apoptosis	[39]
14	LINC00839	Upregulated	Promotes inflammation and apoptosis in kidney cells	[40]
15	LINC00908	Upregulated	Regulates pro-inflammatory genes and promotes apoptosis	[41]

- **Functional Roles of lncRNAs:** Long noncoding RNAs (lncRNAs), once considered "junk" RNA, now emerge as crucial regulators influencing cellular functions and gene expression, especially in contexts like kidney damage [42]. This review explores their functional roles, emphasizing their involvement in fibrosis, apoptosis, inflammation, and interactions with other noncoding RNAs [43] Figure 1.
- **Regulation of Inflammation:** In kidney injury, lncRNAs play crucial roles in controlling the inflammatory response [30]. For instance, MALAT1 activates the NF-κB signaling pathway in renal tubular epithelial cells, inducing inflammation, while NEAT1 exposure in renal mesangial cells leads to the release of pro-inflammatory cytokines [44], [45]. These lncRNAs act as scaffolds, bringing transcription factors and chromatin modifiers together, and regulating inflammatory gene expression. Additionally, they can sequester miRNAs, acting as competitive endogenous RNAs (ceRNAs), and modulate signaling pathways linked to inflammation, such as JAK/STAT and NF-κB [46], [47].
- **Modulation of Apoptosis:** Apoptosis, a critical process in kidney injury, is regulated by numerous lncRNAs [32]. TUG1 induces mortality in renal tubular epithelial cells by sponging miR-27a, while HOTAIR inhibits renal cell death by interacting with the polycomb repressive complex 2 (PRC2) [48], [49], [50]. The intricate regulation of apoptosis involves interactions with essential apoptotic proteins, ceRNA mechanisms, and epigenetic changes affecting gene expression related to apoptosis [51], [52].
- **Impact on Fibrosis:** Renal fibrosis, a hallmark of chronic kidney disease, is influenced by various lncRNAs. MALAT1 promotes renal fibrosis by activating the TGF-β/Smad signaling pathway, inducing fibrotic gene production [53], [54]. The lncRNA H19, through suppression of its target gene COL1A1 and sponging miR-29b, contributes to renal fibrosis. LncRNAs regulate crucial signaling pathways involved in fibrosis, including TGF-β/Smad, Wnt/β-catenin, and Notch, by interacting with key components and regulating gene expression [55], [56].
- **Crosstalk with Other Noncoding RNAs:** LncRNAs interact with miRNAs, influencing gene expression and various processes in kidney injury. For instance, GAS5 sequesters miR-21, preventing renal fibrosis. The intricate regulatory mechanisms involve direct base pairing and indirect interactions mediated by RNA-binding proteins [43], [57].
- **Epigenetic Regulation by lncRNAs:** LncRNAs impact epigenetic changes, such as histone modifications and chromatin remodelling, in kidney damage. HOTAIR interacts with PRC2 and LSD1, regulating gene expression in renal cells. ANRIL recruits PRC1 and PRC2, repressing target genes associated with renal fibrosis. The extensive effects of lncRNA-mediated epigenetic regulation span critical processes like fibrosis, apoptosis, and inflammation [52], [58], [59], [60], [61], [62].

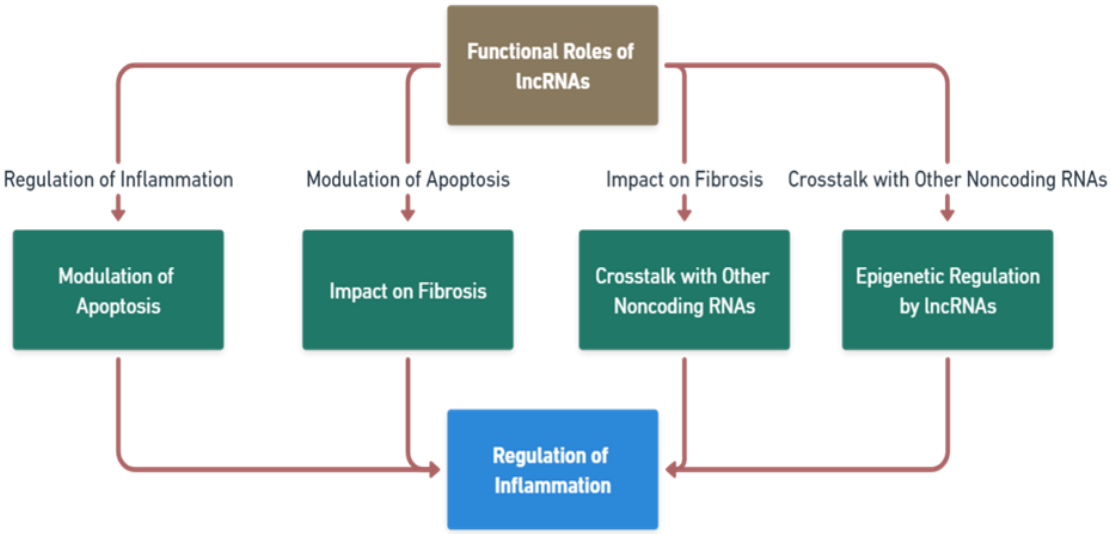


Figure 1. Functional Roles of Lncrnas

Molecular Mechanism of lncRNAs

Long noncoding RNAs (lncRNAs) have emerged as pivotal regulators of gene expression, intricately intertwined with diverse biological processes, including kidney damage and repair [63], [64]. Their profound impact on the cellular and molecular milieu of the kidneys is evident from meticulous investigations into the molecular pathways through which they influence kidney injury. In the realm of acute kidney injury (AKI), various functions of lncRNAs have been spotlighted, with documented evidence of their variable expression and involvement in critical biological processes [65]. Notably, specific lncRNAs play crucial roles in the initiation and progression of AKI, intricately regulating pivotal biochemical pathways. For instance, the lncRNA TUG1 orchestrates ischemia-reperfusion (I/R)-mediated AKI by modulating the miR-494-3p/E-cadherin axis, highlighting their intricate regulatory functions in pivotal biochemical pathways implicated in AKI pathophysiology [66].

The influence of lncRNAs extends to diabetic nephropathy (DN), where ENST0000436340 exacerbates podocyte damage by facilitating the interaction between PTBP1 and RAB3B. The role of lncRNAs in diabetic mesangial cell damage is gaining recognition, offering potential novel therapeutic targets for kidney diseases, including DN [67], [68]. Additionally, the dysregulation of Hoxb3os, an lncRNA regulating mTOR signaling, is associated with autosomal dominant polycystic kidney disease [69]. These findings underscore the diverse and context-specific roles of lncRNAs in modulating the pathophysiology of various kidney diseases by interacting with different molecular pathways [70].

These context-dependent roles position lncRNAs as promising targets for innovative therapeutic approaches and potential biomarkers for early detection and prognosis of kidney disorders. To comprehensively understand their unique biological roles and intricate mechanisms in kidney damage and healing, further investigation is imperative. This exploration could pave the way for the development of lncRNA-based treatments for a spectrum of renal illnesses, emphasizing the versatility and significance of lncRNAs in kidney injury and repair, as well as their potential role in the development and progression of various kidney diseases [59], [71].

Clinical Implications and Therapeutic Potential of lncRNAs

(Figure 2) Long non-coding RNAs (lncRNAs) hold significant clinical implications and therapeutic potential, particularly in cancer, garnering attention for RNA-based medicines such as tiny interfering RNAs (RNAi) and antisense oligonucleotides (ASOs) with multiple FDA approvals highlighting their importance [72], [73], [74]. Serving as revolutionary biomarkers, elevated lncRNA H19 expression demonstrates remarkable sensitivity (90%) and specificity (85%) in early hepatocellular carcinoma (HCC) detection [75], [76], [77], [78]. LncRNAs like NEAT1 play a crucial role in real-time monitoring of pancreatic ductal

adenocarcinoma (PDAC), providing vital information for disease tracking and treatment evaluation [79], [80].

Across various cancers, lncRNAs, such as HOTAIR in ovarian cancer, serve as prognostic markers, aiding personalized treatment planning and predicting resistance to platinum-based chemotherapy [81], [82]. In colorectal cancer and non-small cell lung cancer (NSCLC), lncRNAs like MALAT1 and SNHG16 function as prognostic markers, indicating poor prognosis, tumor aggressiveness, and disease stage. The correlation between elevated GAS5 levels and a better prognosis in heart failure patients suggests a potential biomarker for predicting outcomes in cardiovascular disorders [83]. Targeting specific lncRNAs shows therapeutic potential in diverse disease domains, such as suppressing HOXA11 in cancer, demonstrating promise in reducing breast cancer cell proliferation and preventing tumor growth [84]. The overexpression of BDNF-AS in neurodegenerative diseases like Alzheimer's presents a potential treatment strategy, while CRISPR/Cas9-mediated removal of ANRIL in cardiovascular research improves heart function and fosters cardiac repair in mice after myocardial infarction [85]. Additionally, NEAT1 knockdown proves beneficial in the metabolic domain, enhancing insulin sensitivity and glucose metabolism in diabetic mice, suggesting a potential treatment target for type 2 diabetes [86].

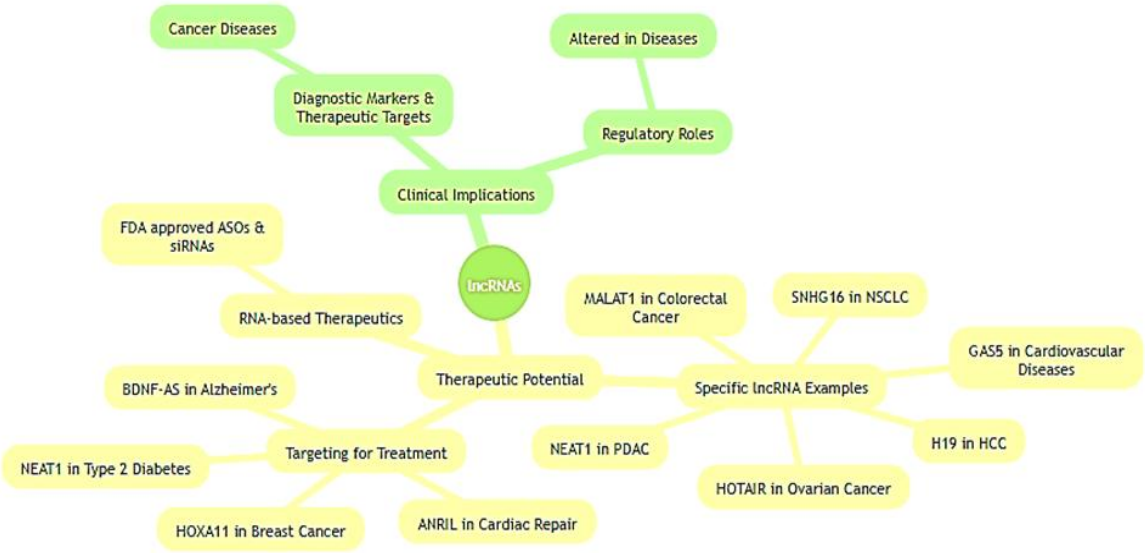


Figure 2. Clinical Implications and Therapeutic Potential of Lncrnas

4. RESULTS AND DISCUSSION

The evolving landscape of long non-coding RNAs (lncRNAs) in kidney injury presents both exciting possibilities and challenges. The intricate functional diversity of lncRNAs complicates the identification of specific roles in complex processes like kidney damage, hampering targeted therapy options. Understanding their activities across different cell types and their interactions with biomolecules remains a daunting task [83]. The lack of precise knowledge about how lncRNAs impact renal damage limits opportunities for targeted therapy [64]. Identifying reliable kidney injury biomarkers for tailored treatment and early intervention proves challenging, given the difficulty of distinguishing disease-specific lncRNAs from those indicating general stress responses [84].

Recent breakthroughs, notably single-cell RNA sequencing (scrRNA-seq), have revolutionized our understanding of lncRNA expression patterns in various kidney cell types [85], [86]. ScrRNA-seq studies have unveiled novel lncRNAs like lnc-NEAT1, providing insights into their roles in podocyte destruction and chronic kidney disease (CKD) progression. Exploration of circular RNAs (circRNAs) has revealed their potential involvement in renal damage, with circRNA SMARCA5 identified as a regulator of autophagy to counter cisplatin-induced acute kidney injury [64].

The integration of artificial intelligence (AI) to predict lncRNA functions and therapeutic targets represents a significant advancement. AI applications, particularly in forecasting lncRNAs regulating inflammation in acute kidney injury, pave the way for innovative anti-inflammatory treatments, with ongoing development of machine learning techniques [85], [86].

Future directions in lncRNA research suggest promising avenues, including the development of focused kidney damage treatments and non-invasive diagnostic tools through the identification of disease-specific lncRNAs [82]. Research on lncRNA-based regenerative medicine explores the potential use of lncRNAs to promote kidney regeneration and healing post-injury. The concept of personalized treatment based on lncRNA expression patterns for specific kidney injury types and underlying genetic factors is intriguing [83]. As research progresses, close attention to ethical concerns related to the use of lncRNA-based therapies and the evaluation of benefits and drawbacks remains imperative.

5. CONCLUSION

Dysregulated long non-coding RNAs (lncRNAs) like MALAT1 and TUG1 serve as molecular indicators for detecting renal illness, playing a significant role as regulators in kidney damage. These lncRNAs directly impact complex biological processes, including inflammation, fibrosis, and apoptosis. Beyond diagnostics, lncRNAs such as H19 and NEAT1 intricately interact with miRNAs, influencing the aetiology of renal diseases. With RNA-based therapeutics gaining prominence, lncRNAs emerge as potential therapeutic targets and diagnostic indicators in clinical settings, aided by recent advancements in single-cell RNA sequencing and artificial intelligence for a deeper understanding and treatment of kidney injury.

Acknowledgments

The authors have no specific acknowledgments to make for this research.

Funding Information

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
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Preeti Shanbhag	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓		

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed Consent

All participants were informed about the purpose of the study, and their voluntary consent was obtained prior to data collection.

Ethical Approval

The study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and approved by the relevant institutional authorities.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to Cite: Ramdas Bhat, Preeti Shanbhag. (2024). Long non-coding rnas in kidney injury: a comprehensive review. Journal of Prevention, Diagnosis and Management of Human Diseases (JPDMHD), 4(2), 82-94. https://doi.org/10.55529/jpdmhd.42.39.52

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