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Long Non-coding RNAs Regulate Cellular Autophagy in Kidney Disease

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Abstract. Autophagy is an intrinsic and universally present self-defense mechanism in eukaryotic cells, prevalent across a diverse array of cell types. Research has indicated that this process plays a significant role in the initiation and progression of kidney diseases, particularly through its involvement in endoplasmic reticulum stress, inflammatory responses, and mitochondrial dysfunction. LncRNAs, consist of over 200 nucleotides, primarily function as competing inhibit endogenous RNAs, and constituent complex with microRNAs, thereby influencing the expression of genes that are crucial to the autophagy process. Many studies have reported on the relationship between lncRNA and autophagy or between autophagy and kidney diseases, but few articles have summarized the interrelationships among lncRNA, autophagy, and kidney diseases. Therefore, this paper aims to elucidate the regulatory role of lncRNA in autophagy while exploring the interplay between autophagy and kidney diseases, thus establishing a close connection among the three. This exploration aims to deepen our understanding of the pathogenesis of kidney diseases and to pinpoint potential targets for therapeutic intervention.

Keywords: Long non-coding RNA, Autophagy, Kidney disease.

1. Introduction

Accordingly, we believe that regulating autophagy in renal cells by identifying specific LncRNAs may serve as an effective strategy to delay structural and functional damage in the kidney. In here, we disscuss mechanism about LncRNA regulation in the procession of autophagy and effection in various renal disorders [1]. In usual conditions, autophagy is a protective factor for body, maintaining cellular health. However, when autophagy is impaired, it can contribute to damage, particularly in response to environmental challenges like inflammation, fasting, or lack of oxygen. A wealth of evidence suggests that disruptions in autophagy can impact various pathological pathways, including oxidative stress, mitochondrial dysfunction, and the immune response, all of which are associated with the progression of kidney diseases [2]. LncRNAs constitute RNA molecules that exceed 200 nucleotides. Unlike messenger RNAs that are translated into proteins, LncRNAs encode none proteins in cells instead regulatory biological process within the cell [3]. Beyond the well-established regulators of autophagy, like mTOR, Beclin1—which is similar to yeast autophagy-associated gene ATG6—and the tumor protein p53, the involvement of LncRNAs has been recognized in intricate regulation of cellular autophagy. These long noncoding RNAs contribute to the modulation of this cellular process, adding another layer to our understanding of autophagy regulation [4].These long noncoding RNAs contribute

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However, many current articles only summarize the relationship between LncRNA and autophagy or the relationship between autophagy and renal diseases, without effectively linking molecular, phenotypic, and clinical aspects. Therefore, this paper aims to summarize these three aspects—molecular, phenotypic, and disease perspectives—in order to establish a solid theoretical foundation for future mechanistic studies and drug development and evaluation for various renal diseases.

2. Autophagy

Cellular autophagy was discovered in the 1960s, and was eventually shown to be a conserved physiological process which depend on lysosomes to degrade substances within our body [5]. This biological process unfolds through four distinct phases: initiation of autophagic vesicles, their growth into autophagosomes, fusion with lysosomes to create autolysosomes, and ultimately, the breakdown of impaired organelles and macromolecules within lysosomes. Over 40 autophagy interrelated genes (ATGs) have discovered in eucaryons, with these genes and their associated proteins forming complexes that are crucial to the entire autophagy process [6]. The Atg1/ULK1 kinase complex triggers autophagy, while Beclin1, activates the ATG14 or PI3K protein to generate the PI3P, facilitating autophagy protein localization and modulating autophagic activity. Two separate ubiquitylation-binding systems, the Atg5-Atg12 and LC3 systems, contribute to phagocytic membrane elongation and autophagosome maturation. The mTOR signaling pathway is currently recognized as the most classic and extensively researched regulator of cellular autophagy. mTOR is a target protein that negatively regulates cellular autophagy, possesses serine/serine protein kinase activity, and acts as a receptor of cellular nutritional status to regulate cell growth and differentiation [7]. When intracellular nutrients such as sugars and amino acids are deficient, mTOR1 activity was inhibited and took off from the ULK1 kinase. Subsequently, ULK1 binds to ATG13, FAK-FIP200, and ATG101, forming a complex accompanied by the dephosphorylation of ULK1 and ATG13, thereby inducing autophagy [8]. In the non-mTOG pathway, AMPK can sense the cellular energy state, and low-energy stimuli activate AMPK-mediated dephosphorylation of TSC2, inhibiting of mTOR activity, or activation of SIRT1 to initiate cellular autophagy [9]. In addition, Beclin1, p53, Bcl2, eIF-2α, etc. are also key regulators of cellular autophagy, and the interaction between multiple mediators and signaling pathways forms a complex regulatory network.

The regulatory pathways of autophagy are highly complex. As a result, autophagy can be regulated by many non-protein substances, such as LncRNA or microRNA. At the same time, autophagy can also influence a wide range of diseases. The activation and inhibition of autophagy are closely related to various diseases. Here, we discuss the mechanisms of LncRNA regulation of the activation and inhibition of autophagy and analyze its relationship with renal diseases.

3. Mechanism of LncRNA regulation of autophagy

LncRNAs contribute to gene regulation not only by directly controlling epigenetic, transcriptional, and post-transcriptional processes but also through their involvement with microRNAs (miRNAs) [10]. Three primary modes of this indirect regulation exist: (1) LncRNAs serve as precursors or hosts for miRNAs; (2) They compete with miRNAs for mRNA binding; and (3) Functioning as endogenous competing RNAs (ceRNAs), LncRNAs sequester miRNAs, disrupting their binding to the 3' untranslated regions of target genes and hence modulating target gene expression. While the miRNAs is very importent in different aspects of cellular autophagy has been extensively explored, knowledge about LncRNAs and their regulatory mechanisms remains limited. Most current research suggests that LncRNAs primarily act as ceRNAs to absorb miRNAs, influencing cellular autophagy. For instance, Hu et al [11] discovered MALAT1 is a great abundance LncRNA in drug-resistant cells, associated with increased autophagy levels, and further investigation revealed that MALAT1 acted as a ceRNA for miR-23b-3p, counteracting its inhibitory effect on ATG12 and promoting its expression. Huang et al. also found a parallel between LncRNA PVT1 levels and ULK1 protein 1 expression in pancreatic cancer,

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where PVT1 acts as a ceRNA by competing with miR-20a-5p, augmenting ULK1 protein expression and promoting protective autophagy and pancreatic cancer cell growth. These studies collectively demonstrate how LncRNAs, as ceRNAs, canadsorption of specific miRNAs, impacting expression in miRNA-related autophagy proteins, thus altering cellular autophagy levels in diverse diseases. Furthermore, Liu et al. identified that LncRNA CAIF binds directly to p53, impeding its promoter region interaction with cardiac myosin, thereby suppressing p53-dependent cardiac myosin expression and autophagy induction in cardiomyocytes.

4. LncRNA regulation of autophagy in kidney disease

4.1. LncRNA regulation of autophagy in diabetic nephropathy

Diabetic nephropathy is particularly serious microvascular complications about diabetes mellitus and one of the major reason of end-stage renal disease [12]. Podocyte injury is a key link in causing proteinuria and glomerulosclerosis in diabetic nephropathy, which is a kind of terminally differentiated mature cell with autophagy level significantly higher than other renal intrinsic cells under physiological conditions, and dysfunction of autophagy of podocytes stimulated by high glucose causes podocyte injury.LncRNA TUG1, a highly conserved transcriptional regulator localized to chromosome 22q12.2.Zhao with the staff detected the TUG1 expression is in down-regulation state in the LPS-induced foot cell injury model; transfection of TUG1 inhibited LPS-induced autophagy in foot cells.Through bioinformatics analysis, they identified miRNA-197 as a key action factor of TUG1. Further studies demonstrated that TUG1 could increase the level of p-MAPK/MAPK by adsorbing miRNA-197 through "sea-oak" action, thus inducing autophagy to protect against LPS-induced podocyte damage.In addition, SPAG5 is located on chromosome 17q11.2, and its C' terminus binds to the spindle in mitosis S phase to help mitosis proceed smoothly, which is important for cell cycle and proliferation regulation [13]. A study on uroepithelial carcinoma of the bladder showed that SPAG5 activates the AKT/mTOR pathway to regulate autophagy.In another study, Xu et al. revealed that SPAG5 also contributed to autophagy induction through the AKT/mTOR cascade in podocyte damage caused by high glucose conditions, concurrently lessening foot cell apoptosis via the same signaling pathway. Concurrently, they identified a neighboring gene, SPAG5-AS1, using UCSC. Functional assays demonstrated that SPAG5-AS1 facilitated autophagy and repressed apoptosis, thereby mitigating injury to foot cells under high glucose circumstances [14]. Considering the prevalent link between various lncRNAs and their antisense RNAs - for instance, ZEB1-AS1 interacts with the histone methyltransferase MLL1, recruiting it to ZEB1's promoter region, thus activating ZEB1 transcription and promoting prostate cancer cell proliferation and migration - the researchers disclosed that SPAG5-AS1, via the miR-769-5p/YY1 axis, stimulated SPAG5 transcription, stabilized SPAG5 protein, activated the AKT/mTOR signaling, suppressing autophagy and alleviating damage to foot cells.

4.2. LncRNA regulation of autophagy in acute kidney injury

AKI is a renal disfunction decreases dramatically for a instantaneous state, and the main pathological changes are renal tubular damage, including necrosis, apoptosis, and detachment of renal tubular epithelial cells. Previously, AKI was thought to be a reversible pathology.However, statistics show that many patients with AKI have a poor prognosis and eventually develop chronic kidney disease.LncRNA NEAT1 is located on human chromosome 11, transcribed from RNA polymerase II, and has a strong response to immune diseases and other diseases.

LncRNA NEAT1 is located on human chromosome 11, transcribed from RNA polymerase II, and has a strong ability to regulate immune diseases and infectious diseases such as tuberculosis and HIV infection [15]. Feng et al. treated HK-2 cells with LPS for simulate AKI model, Beclin-1 expression with LC II/LCI ratio was significantly upregulated, NEAT1 was up-regulated, and miR-22-3p was down-regulated, accompanied by the phosphorylation IκBα and p65 [16].Neat1 knockdown, on the other hand, inhibited autophagy and IκBα and p65 phosphorylation in HK-2 cells, whereas miR-22-3p inhibitor transfection experiments reversed the NEAT1 knockdown effect. This suggests that silencing

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NEAT1 may attenuate renal tubular epithelial cell injury in septic AKI by regulating the miR-22-3p/NF-κB pathway.In another study, Xu et al. revealed that SPAG5 also contributed to autophagy induction through the AKT/mTOR cascade in podocyte damage caused by high glucose conditions, concurrently lessening foot cell apoptosis via the same signaling pathway. Concurrently, they identified a neighboring gene, SPAG5-AS1, using UCSC. Functional assays demonstrated that SPAG5-AS1 facilitated autophagy and repressed apoptosis, thereby mitigating injury to foot cells under high glucose circumstances [17]. Considering the prevalent link between various lncRNAs and their antisense RNAs - for instance, ZEB1-AS1 interacts with the histone methyltransferase MLL1, recruiting it to ZEB1's promoter region, thus activating ZEB1 transcription and promoting prostate cancer cell proliferation and migration - the researchers disclosed that SPAG5-AS1, via the miR-769-5p/YY1 axis, stimulated SPAG5 transcription, stabilized SPAG5 protein, activated the AKT/mTOR signaling, suppressing autophagy and alleviating damage to foot cells.

4.3. LncRNA regulation of autophagy and renal cancer

Renal cancer, originating from renal parenchymal urinary tubule epithelial cells, is a malignancy with renal clear cell carcinoma as its most frequent histological type. Research indicates that autophagy is a very important factor in the development, prognosis, drug resistance in renal cancer, suggesting that lncRNAs influencing autophagy could act more precise diagnostic and therapeutic biomarkers. HOTTIP, an lncRNA situated on chromosome 7p15.2, influences tumor growth, invasion, and metastasis [18]. As we know, HOTTIP was notably upregulated in renal cancer patients compared to healthy controls. In vitro and in vivo research revealed HOTTIP's promotion of autophagy-related molecules' expression, an effect that could be reversed by the autophagy inhibitor 3-MA. Functionally, HOTTIP might modulate autophagy in renal cancer cells via the PI3K/Akt/Atg13 signaling cascade, thereby facilitating tumor growth and metastasis. Enhanced autophagy has been shown to decrease tumor responsiveness to chemotherapy. An investigation into sorafenib resistance in renal cancer cells shows that KIF9-AS1 lncRNA overexpression enhanced cell viability, reduced apoptosis, heightened sorafenib resistance. MIR-497-5p, a pivotal downstream regulator of KIF9-AS1, is involved in TGF-β and autophagy signaling pathways that mediate drug resistance in renal carcinoma through the KIF9-AS1/miR-497-5p axis. However, the direct targeting of p62 by miR-497-5p to regulate autophagy remains unconfirmed.

4.4. LncRNAs and renal fibrosis

Renal fibrosis is the ultimate course of renal disease from various causes and is characterized by excessive deposition of extracellular matrix. LncRNAs associated with autophagy in the process of fibrosis have been little studied.Xiao et al. screened for differential expression of ENST00000453774.1 more than 10-fold in TGF-βstimulated HK-2 cellsThey further demonstrated that ENST00000453774.1 expression was significantly down-regulated in renal fibrosis clinical specimens.Overexpression of ENST00000453774.1 may reduce renal fibrosis by activating autophagy to promote enhancement of ROS defense in the Nrf2-keap1/HO-1/NQO-1 signaling pathway, and reduce extracellular matrix-associated protein, fibronectin, and type I collagen deposition, thus ENST00000453774.1 overexpression may represent a novel. Therefore, ENST00000453774.1 overexpression may represent a novel therapeutic approach against renal fibrosis.

5. Conclusion

Autophagy is widely found in eukaryotic cells and is involved in cellular metabolism, stress defense, growth and differentiation, etc. In renal diseases, abnormal autophagy severely affects the proliferation and apoptosis of renal cells. In renal diseases, abnormal autophagy seriously affects the proliferation and apoptosis of renal cells, and LncRNA is widely expressed in various tissues with tissue specificity, and a large number of researches have confirmed that it has the potential to be a biomarker for the treatment of renal diseases.Although studies on the role of LncRNA regulation of autophagy in renal diseases and related mechanisms are relatively limited, they reflect to some extent that co-targeting LncRNAs with autophagy is expected to be a novel and promising therapeutic strategy.

This paper provides an overview of the relationship between autophagy and LncRNA, elucidating the close connection between LncRNA and renal diseases. It lays a solid foundation for the subsequent development and evaluation of drugs targeting LncRNA. However, due to space limitations, many details about autophagy and renal diseases have not been thoroughly discussed. Future work will include comprehensive reviews of LncRNA, autophagy, and various renal diseases, along with further mechanistic studies.

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