BMC Nephrology

REVIEW Open Access

lncRNA TUG1 and kidney diseases

Tong Chen[1], Jian Lu[1] and Qiuling Fan[2*]

Abstract

Long noncoding RNAs (lncRNAs) cover a large class of transcribed RNA molecules that are more than 200 nucleotides in length. An increasing number of studies have shown that lncRNAs control gene expression through different mechanisms and play important roles in a range of biological processes including growth, cell differentiation, proliferation, apoptosis, and invasion. TUG1 was originally discovered in a genomic screen of taurine-treated mouse retinal cells. Previous evidences pointed out that lncRNA TUG1 could inhibit apoptosis and the release of inflammatory factors, improve mitochondrial function, thereby protecting cells from damage, and showing a protective role of TUG1 in diseases. Given that TUG1 has multiple targets and can interfere with multiple steps in the oncogenic process, it has been proposed as a therapeutic target. In this review, we summarize the research progress of lncRNA TUG1 in kidney diseases in the past 8 years, and discuss its related molecular mechanisms.

Keywords LncRNA TUG1, AKI, CKD, RCC, Glomerulonephritides

Kidney disease with mild inflammation, proteinuria, and function decline,or diagnosed with objective measures of kidney structure damage have been recognized as a major global health burden [1]. As a complex multi gene disease, the interaction and expression regulation of multiple genes often affect the occurrence and development of the kidney disease. Epigenetics has become one of the important mechanisms involved in the occurrence and development of kidney diseases by regulating gene transcription and translation [2].

lncRNAs cover a large class of transcribed RNA molecules that are more than 200 nucleotides in length [3–6]. In the past, non coding RNAs (ncRNAs) without the ability of coding protein were considered as non functional "junk" [7, 8]. However, increasing evidences have shown that lncRNAs control gene expression through different mechanisms and play important roles in a range of biological processes including growth, cell differentiation, proliferation, apoptosis, and invasion [9, 10]. lncRNAs have multiple modes of action, but are generally considered as important transcriptional regulators [3] (Fig. 1). In the cell nuclues, lncRNAs can regulate transcription factors (TF) as transcriptional co-activator or inhibitor. Enhancer RNAs are considered a subtype of lncRNA that are transcribed from the enhancer region and physically involved in looping the enhancer and promoter regions to regulate transcription. Some lncRNAs can act through DNA methylation, chromatin modification, histone modifications and RNA methylation, and to silence or enhance target gene expression. Other lncRNAs interfere with pre-mRNA splicing regulation [3, 11–14]. In the cytosol, lncRNAs can regulate mRNA expression by altering mRNA translation, stability, or by competing for microRNA binding [15–17]. Therefore, lncRNA is crucial in epigenetic regulation, gene transcription, gene translation, and mRNA processing, regulating various biological processes including in vivo balance, cell metabolism, proliferation, apoptosis, and differentiation [18–20].

Among all lncRNAs related to kidney disease, taurine upregulated gene 1 (TUG1) is a rising star. More and more evidences show that TUG1 plays an important role in many kidney diseases, such as acute kidney injury

*Correspondence:
Qiuling Fan
cmufql@163.com
[1] Department of Nephrology, Shenyang Seventh People's Hospital, Shenyang 110003, Liaoning, China
[2] Department of Nephrology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200940, China

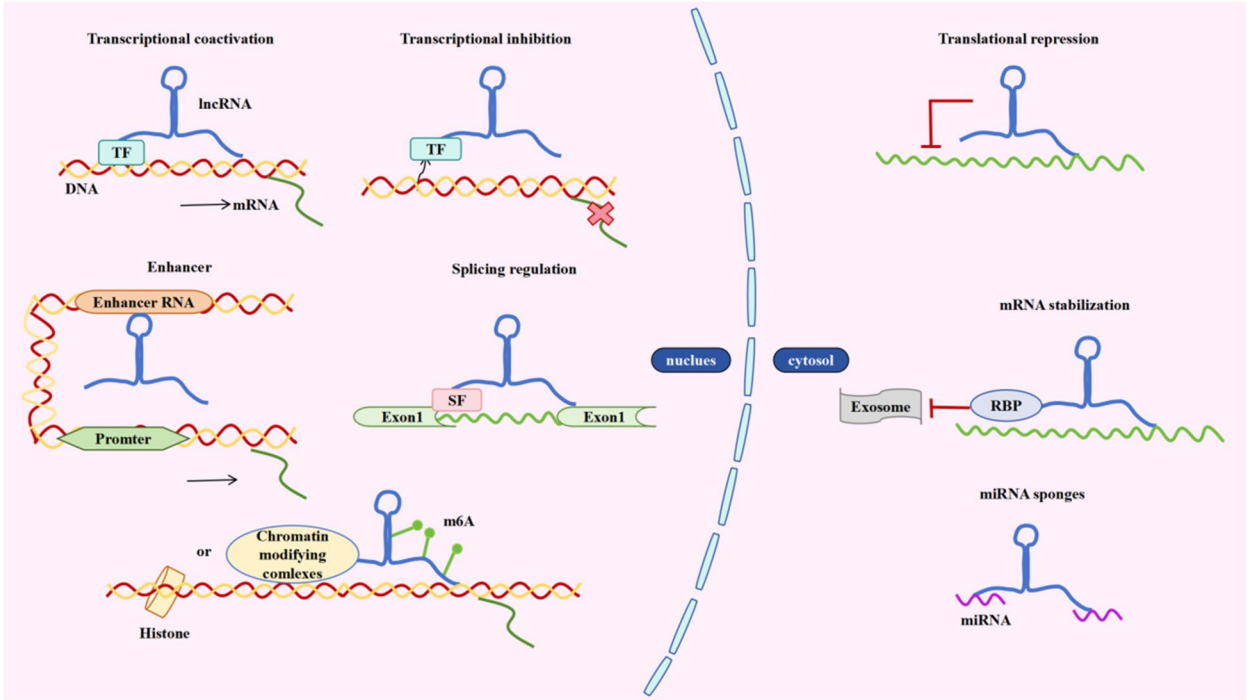

Fig. 1 lncRNAs regulate gene expressions at multiple levels.TF, transcription factor; SF, splicing factor; RBP, RNA binding protein

(AKI), chronic kidney disease (CKD), lupus nephritis (LN), diabetic kidney disease (DKD), renal interstitial fibrosis (RIF), glomerulonephritis, and renal cell carcinoma (RCC). The human lncRNA TUG1 gene (NCBI reference sequence NR_110492 transcript variant 1) is located on chromosome 22q12.2 and has 8 variant transcripts with a length range of 5.2–7.6 kb, while the mouse lncRNA TUG1 locus is located on chromosome 11 and has three variant transcripts (a, b, and c) with a length range of 4.1–6.7 kb [4]. TUG1 was originally discovered in a genomic screen of taurine-treated mouse retinal cells [21, 22]. The regulatory mechanisms of TUG1 gene expression involve its role as a molecular sponge for various microRNAs, which in turn modulate the expression of target genes or RBP affecting processes like cell proliferation, apoptosis, migration, cell cycle changes and inflammation in distinct diseases (relevant to endocrinology, metabolism, immunology, neurobiology) [23]. Previous evidences pointed out that lncRNA TUG1 could inhibit apoptosis and the release of inflammatory factors, improve mitochondrial function, thereby protecting cells from damage, showing a protective role of TUG1 in diseases [24]. Given that TUG1 has multiple targets and can interfere with multiple steps in the oncogenic process, it has been proposed as a therapeutic target [3]. In this review, we summarize the research progress of lncRNA TUG1 in kidney diseases in the past 9 years, and discuss its related molecular mechanism.

The biological function of TUG1 in kidney diseases

Kidney disease is an important public health problem. Although the function of lncRNA TUG1 remains unclear and somewhat controversial, It still has many significant research implications in kidney diseases (Fig. 2, Table 1).

AKI

AKI is defined by abnormalities of kidney function with an increase in serum creatinine (SCr) by 50% within 7 days or an increase in SCr by 0.3 mg/dl within 2 days or oliguria for ≥ 6 h. Models to mimic AKI in clinical practice usually include I/R, cisplatin and LPS. Growing evidences suggest that lncRNA TUG1 can regulate mRNA splicing, transcription, and expression of target genes by acting as microRNA (miRNA) sponges and protein scaffolds. Chen et al. found that lncRNA TUG1 alleviated I/R induced AKI via serving as a miR-494-3p sponge to disinhibit E-cadherin [18]. Chang et al. found that overexpressing lncRNA TUG1 attenuated the protective effect of total glucosides of paeony (TGP) on AKI induced by I/R via competing for miR-29 to improve phosphatase and tensin homolog (PTEN) expression [26]. Xu et al. found that knocking down lncRNA TUG1 by binding to miR-29 to silence PTEN can alleviate I/R-induced autophagy and improve AKI in rats [27]. Sheng et al. found that lncRNA TUG1 acts as an endogenous sponge of miR-144-3p, targeting nuclear respiratory factor 2 (Nrf2) to alleviate ischemia–reperfusion induced

Table 1. The regulatory machinery of TUG1 in kidney diseases

Disease	Models	Location	Materials	Expression	Mechanism	Methods of Prediction & Validation	Reference	Year
AKI	I/R	Tubulointerstitum	H/R-treated HK-2 cells I/R-induced C57BL/6J mice kidney (3d)	Down	miR-494-3p/E-cadherin	lncBase predicted v.2 bioinformatics tools Dual luciferase reporter gene assay	18	2021
		Tubulointerstitum	H/R-treated HK-2 cells I/R-induced Sprague-Dawley rats kidney (3d)	Up	miR-29a/PTEN	StarBase v2.0 RNA pull-down assay Dual luciferase reporter gene assay	26	2021
		Tubulointerstitum	H/R-treated TCMK-1 cells I/R-induced Wistar mice kidney (3d)	Up	miR-29a/PTEN	bioinformatics website Dual luciferase reporter gene assay RNA pull-down assay	27	2021
		Tubulointerstitum	H/R-treated TCMK-1 cells I/R-induced C57BL6 mice kidney (3d)	Up	miR-144-3p/Nrf2	TargetScan, microRNA.org, miRDB Luciferase report assay RIP	28	2021
		Tubulointerstitum	H/R-treated HK-2 cells I/R-induced C57BL6 mice kidney (3d)	Down	SRSF1/ASCL4	Subcellular fractionation analysis FISH RNA pull-down assay RIP	30	2022
	Cisplatin	Tubulointerstitum	Sprague-Dawley rats kidney (72h)	Down	unknown	unknown	33	2022
	LPS	Glomeruli	LPS-exposed MPC5	Down	miR-197/MAPK1	bioinformatics	29	2019
		Tubulointerstitum	LPS-exposed RMCs Sprague-Dawley rats kidney (6,18,24h) under CLP surgery	Down	Nrf2/HO-1	RNA pull-down assay RIP	32	2020
CKD	RIF	Tubulointerstitum	TGF-β1-treated HK-2 cells UUO established BALB/c mice (3, 7, or 14 days)	Up	miR-141-3p/β-catenin	bioinformatics prediction software Luciferase reporter assay	34	2020
		Tubulointerstitum	HEK293T cells Oral administration of adenine in Sprague-Dawley rats kidney (6wk)	Up	miR-140-3p/CtsD	RNA22 website Luciferase reporter assay cell lysate pull-down assays	37	2022
		Tubulointerstitum	TGF-β1-treated HK-2 cells UUO established C57BL6 mice (7d) UIRI established C57BL6 mice (10d)	Down	miR-223-3p/KP1	RNAhybrid Luciferase reporter assay FISH	38	2024
	DKD	Glomeruli	HG-treated Mice MCs db/db mice kidney(16wk)	Down	miR-377/PPARγ	TargetScan, miRanda, PicTar and miRGen Luciferase reporter assay	43	2017
		Tubulointerstitum	HG-treated NRK-52E cells db/db mice kidney	Down	miR-21/TIMP3	StarBase, TargetScan Dual luciferase reporter gene assay RIP	44	2019
		Tubulointerstitum	HG-treated HK-2 cells	Down	miR-29c-3p/SIRT1	DIANA-tool LncBase bioinformatics software Dual luciferase reporter gene assay	39	2021
		Tubulointerstitum	HG-treated HK-2 cells STZ-induced C57BL/6J mice kidney (8wk)	Down	miR-145-5p/DUSP6	RAID v2.0 TargetScan, miRDB, PicTar, ENCORI Luciferase report assay	45	2023
		Glomeruli	HG-treated mouse podocytes db/db mice kidney (24wk)	Down	PGC1-α	unknown	3	2016
		Glomeruli	HG-treated mouse podocytes db/db mice kidney	Down	PGC1-α/ChREBP	Luciferase assays Subcellular fractionation analysis FISH, RNA ISH RIP, CHIRP, CHIRP-seq	4	2016
		Glomeruli	HG-treated MPC5 cells STZ-induced Sprague-Dawley mice	Down	TRAF5	RNA pull-down RIP	48	2018
		Glomeruli	HG-treated mouse mesangial cells STZ-induced Sprague-Dawley mice	Down	PI3K/AKT	unknown	49	2019
		Glomeruli	HG-treated mouse podocytes,TCMK-1 cells,Hela cells,HEK293T cells db/db mice kidney (16 or 24wk)	Down	ChREBP	Luciferase reporter assay ChIP-qPCR biotin-labeled oligonucleotide pull-down strepavidin pull-down	46	2020
		Glomeruli	HG-treated MPC5 cells,HEK293T cells db/db mice kidney (16 or 20wk)	Down	PGC1-α	Dual luciferase reporter gene assay	47	2021
		Tubulointerstitum	HG-treated HK-2 cells STZ-induced mice kidney (8wk)	Down	m6A modification-METTL14 TUG1/MAPK1/ERK	RNA pull-down RIP	50	2023
	LN	Glomeruli and tubulointerstitum	pristane induced BALB/c female mice kidney (16wk)	Down	NF-κB	unknown	24	2020
		Glomeruli and tubulointerstitum	LPS-induced HRMC	Down	miR-153-3p/Bcl-2	StarBase or TargetScan Dual luciferase reporter gene assay	52	2023
	CKD with CHF	Plasma	CKD patients with CHF	Down	unknown	unknown	55	2015
	Hypertensive Nephropathy	Tubulointerstitum	Ang II-treated HK-2 cells fibrotic renal tissues from patients with hypertensive nephropathy	Up	miR-29b-3p/MR	http://pridb.gdcb.iastate. edu/RPISeq/ FISH, ISH Dual luciferase reporter assay RIP, ChIRP	54	2021
	glomerulonephr-itides	Urine	patients with biopsy confirmed FSGS	Down	miR-204-5p	GeneAnalytics TargetScan	11	2020
Cancer	RCC	Tissue	ccRCC patients	Up	unknown	unknown	60,61	2016,2017
		Tissue	ccRCC patients	Up	miR-9/YAP	unknown	62	2018
		Glomeruli and tubulointerstitum	ACHN cells and OS-RC-2 cells	Up	miR-299-3p/VEGF	bioinformatics analysis Dual luciferase reporter assay	59	2019

Table 1. (continued)

Abbreviation H/R hypoxia/reoxygenation, *HK-2 cell* human kidney-2 cell (Human renal proximal tubular cell), *I/R* ischemia-reperfusion, *TCMK-1 cells* mouse renal tubular epithelial cells, *LPS* lipopolysaccharide, *RMCs* rat mesangial cells, *CLP* Cecal Ligation and Puncture,*TGF* transforming growth factor; *UUO* unilateral ureteral obstructive, *HEK293T* human embryonic kidney 293t, *UIRI* unilateral ischemiareperfusion injury, *MCs* mesangial cells, *NRK-52E cell* rat proximal renal epithelial cell, *STZ* streptozotocin,*MPC5* mouse podocyte, *HRMC* human renal mesangial cell, *CHF* congestive heart failure;*ccRCC* clear cell renal cell carcinoma, *ACHN* human renal cell adenocarcinoma,*OS-RC-2* the human RCC cell lines

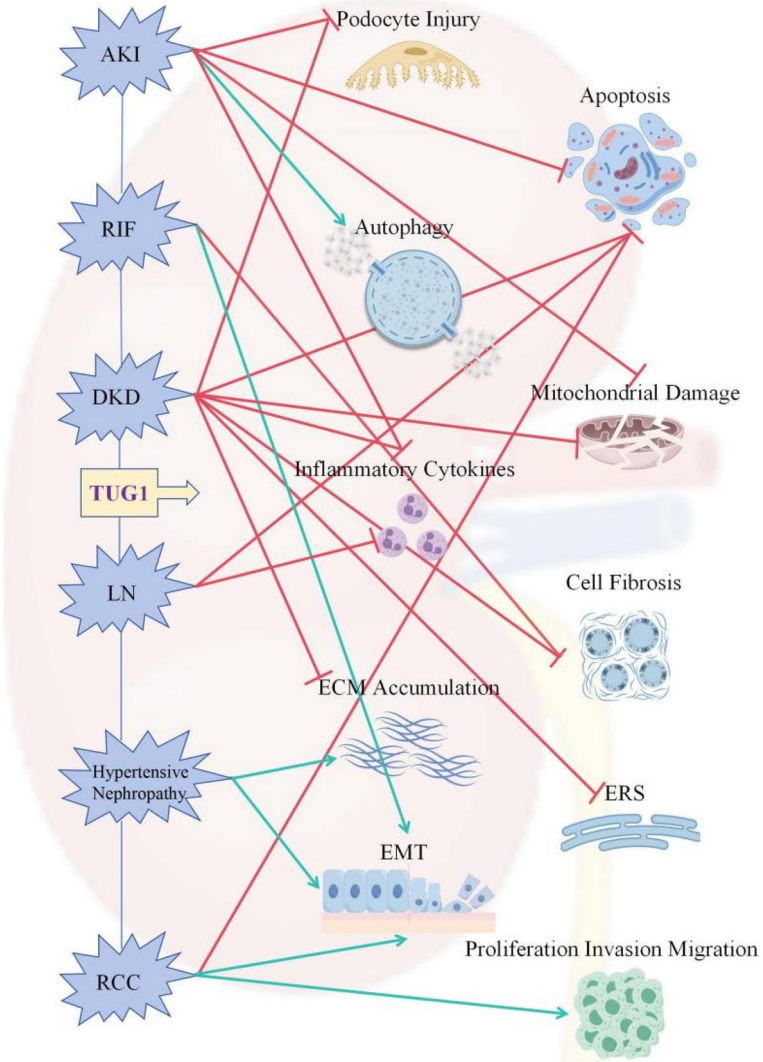

Fig. 2 The role of TUG1 in all kidney diseases. Abbreviation: ECM, extracellular matrix; ERS, endoplasmic reticulum stress; EMT, epithelial-mesenchymal transition

AKI [28]. Zhao et al. found that TUG1 alleviated LPS-induced podocyte injury by competing for miR-197 to disinhibit mitogen activated protein kinase1 (MAPK1) [29]. lncRNA TUG1 can also regulate mRNA expression by altering mRNA stability. Sun et al. found that lncRNA TUG1 attenuated I/R induced AKI by regulating the stability of Acyl-CoA synthetase long-chain family 4 (ACSL4) mRNA via interacting with RNA-binding protein serine/arginine-rich splicing factor 1 (SRSF1) [30]. Nrf2 is one of the key TF regulating cells against oxidative damage [31]. Wang et al. found that TUG1 can regulate Nrf2 as transcriptional co-activator to alleviate LPS induced AKI [32]. Amini N et aL. found that lncRNA TUG1 may be involved in process of gallic acid (GA) protecting the kidney against cisplatin-induced nephrotoxicity through antioxidant, anti-inflammatory, and anti-apoptosis properties, however the mechanism was unclear [33].

CKD

CKD is defined by abnormalities of kidney function and/or structure with implications for health and with a duration of > 3 months. Previous studies have shown that TUG1 participated in renal fibrosis and progression of CKD including RIF, DKD, LN, hypertensive nephropathy, glomerulonephritides.

RIF

RIF is characterized by excessive extracellular matrix deposition and involves EMT [34], and is a dynamically developing irreversible process leading to the destruction of tissue structure and loss of organ function [35, 36]. Animal models were considered at day 3, day 7 or day 14 after UUO and day 10 after UIRI in mice because a-SMA, TGF-β and EMT were increased [34, 37]. Zhang et al. found that silencing of the lncRNA TUG1 alleviated EMT via serving as a miR-141-3p sponge to inhibit β-catenin [34]. Another study established by Zhang et al. revealed that TUG1 inhibition upregulates miR-140-3p to ameliorate renal fibrosis in hyperuricemic rats by inhibiting cathepsin D (CtsD) [37]. Zhang et al. found that knockdown of lncRNA TUG1 by binding to miR-223-3p to aggravate klotho loss and worsen cellular senescence, whereas klotho-derived peptide 1 (KP1) can alleviate those fibrotic kidney disorders [38].

DKD

DKD begins with hyperglycemic stimuli, and is the most common and refractory microvascular complication of diabetes, and the main cause of end-stage renal disease (ESRD) worldwide. The main pathological characteristics of diabetes nephropathy are glomerulosclerosis, ECM deposition and tubulointerstitial fibrosis [39–41]. The concept of the renal tubular center of DKD emphasizes the key role of proximal tubule (PT) and tubulointerstitial part in the development of DKD [4, 42]. However, the glomerular theory, especially podocyte injury, has received particular attention in the process of DKD. The specific molecular characteristics and epigenetic modification in recent studies indicate that TUG1 plays a key role in the progress of DKD.

As miRNA sponges, Duan et al. found that lncRNA TUG1 acts as an endogenous sponge for miR-377, targeting peroxisome proliferator activated receptor gamma (PPAR γ) to alleviate mesangial cell proliferation and extracellular matrix accumulation in DN [43]. Wang et al. found that lncRNA TUG1 improves renal fibrosis in diabetes nephropathy by inhibiting miR-21 and promoting tissue inhibitor of metalloproteinase 3 (TIMP3) expression [44]. Wang et al. found that lncRNA TUG1 can inhibit the SIRT1 axis via endogenous competition of miR-29c-3p to regulate the injury of renal tubular epithelial cells mediated by endoplasmic reticulum stress in diabetes nephropathy models [39]. Wang et al. TUG1 directly sponged to miR-145-5p alleviating kidney injury in DN mice and decreasing the inflammatory response and fibrosis of high glucose-stimulated HK-2 cells via dual-specificity phosphatase 6 (DUSP6) pathway [45]. As enhancer, Li et al. and Long et al. found that decreasing of TUG1 are mainly located in glomerular podocytes of db/db mice and human diabetes kidney samples [3, 4]. The high glucose environment promotes the carbohydrate response element binding protein (ChREBP) inhibiting TUG1 transcription through the carbohydrate response elements (ChoRE) motif in the promoter region of TUG1 [46]. TUG1 acts as a bridge between the 400 kb upstream enhancer and promoter of Ppargc1a, interacting with the TUG1 binding site upstream of the Ppargc1a promoter region, triggering transcriptional upregulation of Ppargc1a mRNA, and then regulating mitochondrial function in podocytes by targeting the transcription factor PPARγ coactivator 1α (PGC-1α, encoded by Ppargc1a) [3, 4]. The decrease of PGC-1α level will lead to damage of mitochondrial function, which will lead to energy depletion, increase of reactive oxygen species (ROS) production, and eventually lead to the development of diabetes nephropathy [3, 4, 47]. As translational inhibitor, Lei et al. found that increasing of TUG1 by astragaloside IV (AS-IV) can alleviated inflammation and podocyte apoptosis via inhibiting TNFR-associated factor 5 (TRAF5) in DN rats [48]. Zang et al. found that overexpression of TUG1 could suppress the proliferation and ECM accumulation of mesangial cells via inhibiting the protein levels of phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT) in diabetes nephropathy [49]. lncRNA TUG1 can also act through DNA methylation. Zheng et al. revealed that TUG1 overexpression protected against STZ-induced renal lesions and renal fibrosis via inactivating MAPK1/extracellular signal-regulated kinase (ERK) signaling in DKD mouse in a methyltransferase 14 (METTL14)-dependent manner [50].

LN

LN is caused by autoimmune and inflammatory reactions which can activate complement cascades and proinflammatory pathways, injuring resident renal cells (including renal tubular cells, podocytes, mesangial cells and endothelial cells) [51]. Accumulating evidence has shown that lncRNA TUG1 plays a key role in inhibiting cell injury and inflammatory regulation. Cao et al. found that up-regulating lncRNA TUG1 by pyrrolidine dithiocarbamate (PDTC) can inhibite NF-κB on renal injury in SLE mice [24]. Liu et al. found that lncRNA TUG1 directly

sponged to miR-153-3p alleviating LPS-induced HRMC injury through regulation of Bcl-2 in LN [52].

Other kidney diseases related to TUG1

For those patients with abnormalities in kidney function and/or structure who meet neither the definition of AKI nor CKD, the term acute kidney disease (AKD), has been introduced as an important construct to address this. AKD is defined by abnormalities of kidney function and/or structure with implications for health and with a duration of ≤ 3 months [25]. However, relevant study of TUG1 in AKD is barely established.

Heart and kidney are closely related in the clinical syndrome of heart failure (HF). It is now clear that renal dysfunction often occurs in all phenotypes of HF, and it is associated with higher mortality and morbidity [53]. Despite the multifactorial pathophysiology of CKD, renal artery sclerosis and chronic renal ischemia leading to CKD with worsened prognosis can be seen everywhere in clinical practice. Zhang et al. found that lncRNA TUG1 can promote angiotensin II(Ang II)–induced renal fibrosis via endogenous competition of miR-29b-3p by binding to mineralocorticoid receptor(MR) [54]. In the next year, Zhao et al. revealed that TUG1 was lowly expressed in CHF patients and was further downregulated in CHF patients complicated with progressive CKD [55].

Urinary non-coding RNAs are a promising non-invasive tool that can reflect kidney disease, assist in appropriate diagnosis, and guide therapeutic choices [10, 56–58]. Salazar Torres et al. found that lncRNA TUG1 is also present in urinary sediment, and its expression is significantly reduced in patients with biopsy-confirmed glomerulonephritides, especially those diagnosed with focal segmental glomerulosclerosis (FSGS) [11]. PGC-1 α and mitochondrial transcription factor A (TFAM) can also be detected in urine and are significantly correlated with TUG1 expression levels [10]. However, there was no significant correlation between the expression level of TUG1 and glomerular filtration rate (GFR), proteinuria, or albuminuria. Further studies are required to evaluate urinary TUG1 as a potential biomarker of glomerulonephritides in early stage other than ESRD, and to determine its association with kidney dysfunction and patient prognosis.

RCC is one of the top ten deadly malignant tumors in the world. Accumulating evidences showed that TUG1 play a crucial role in the progression of various cancers [59]. In earlier years, Wang et al.and Zhang et al. both found that the relative level of TUG1 was significantly higher in ccRCC tissues compared to the adjacent non-tumor tissues [60, 61]. In recent years, Liu et al. found that TUG1 can positively control yes-associated protein (YAP) expression and promote cell proliferation and migration in RCC by inhibiting miR-9 [62]. Li et al. found that knocking down TUG1 can inhibit the formation of RCC, including the proliferation, invasion, metastasis, and EMT process of ACHN cells, by suppressing vascular endothelial growth factor (VEGF) through endogenous competition of miR-299-3p [59].

Discussion and prospect

LncRNAs are ncRNA sequences, with cell or tissue specificity, poor conservation, and are expressed at low levels [63]. It plays an important role in multiple cellular processes [64]. TUG1, as a novel lncRNA, is predominantly located in the nucleus, and has been shown to be abnormally expressed in various types of kidney diseases, and its dysregulation is closely related to disease progression [65]. Current research are mainly focused on the abnormal expression of TUG1 in biopsies or cells, which could be used as potential biomarkers for the diagnosis, progression, and prognosis of kidney diseases and serve as therapeutic implications (Table 2). Interestingly, the results and conclusions seem inconsistent in AKI and CKD. Fortunately, the role of TUG1 in the study of DKD, LN, CKD with CHF and focal segmental glomerulonephritis is affirmative and protective despite of the differences of animal species and cell lines. However, the role of TUG1 in the studies of hypertensive nephropathy and RCC seems harmful. Nevertheless, it seems that TUG1 is closely related to podocyte injury, apoptosis, autophagy, regulation of inflammatory factors, mitochondrial bioenergetics, ECM accumulation, ERS, EMT, cell proliferation, invasion and migration (Fig. 1).

In AKI, despite of animal strains and cell lines used in the experiments, 75% of the published literature identify TUG1 of renal protective. The inconsistency of the effects of TUG1 on autophagy, cell apoptosis, and inflammatory factors mainly depends on the degree of damages to cells and mouse kidneys, these may be due to the differences in animal species, ischemia or reperfusion time, or distinct disease states. In CKD caused by renal fibrosis, the inconsistency of the effects of TUG1 mainly depends on animal species, the concentration and intervention time of TGF-β1, some may lack cell counting kit-8 assay. Also independently bred animal will undergo genetic drift over time, which may affect phenotypic differences and the consistency of experimental outcomes [66]. Moreover, as compared with mRNA, lncRNA has a wide range of variation and a shorter half-life [67], so it's widely believed that one lncRNA can interact with multiple miRNAs and produce multiple transcripts, which may have opposite effects. Predicting and experimentally verifying lncRNA-miRNA interactions involves a combination of high-throughput experimental techniques like

Table 2. Diagnostic and therapeutic implications of TUG1

Disease	Specimens	Expression	Intervention	Conclusions and Effects	Role of TUG1	Reference
AKI	HK-2 cells MPC5 RMCs C57BL6 mice & Sprague-Dawley rats renal biopsies	Down	PCDNA3.1-TUG1 USC-Exo Diosmetin GA	1.Alleviate cell apoptosis 2.Decrease inflammatory cytokines 3.Alleviate podocyte injury	Protective	18,29,30, 32,33
AKI	HK-2 cells Sprague-Dawley rats renal biopsies	Up	TGP(inhibit TUG1)	1.Attenuate autophagy 2.Reduce the levels of inflammatory factors	Harmful	26
	TCMK-1 cells Wistar renal biopsies	Up	TUG1 knockdown	1.Inhibit cell apoptosis 2.Promote autophagy	Harmful	27
AKI	TCMK-1 cells C57BL6 mice renal biopsies	Up	ASO-TUG1(TUG1 knockdown)	1.Exacerbate cell apoptosis 2.Aggravate kidney damage through oxidative stress and mitochondrial damage	Protective	28
CKD	HK-2 cells BALB/c mice & Sprague-Dawley rats renal biopsies	Up	TUG1 siRNA sh-TUG1	1.Attenuate the EMT 2.Attenuate kidney injury 3.Decrease 24-h urine protein,UA, BUN, and SCr	Harmful	34,37
CKD	HK-2 cells C57BL6 mice renal biopsies	Down	KP1(increase TUG1)	1.Inhibit cellular senescence 2.Alleviate kidney fibrosis	Protective	38
DKD	MPC5 cells HK-2 cells Mice MCs NRK-52E cells TCMK-1 cells,Hela cells HEK293T cells db/db mice renal biopsies STZ-induced C57BL/6J & Sprague-Dawley mice renal biopsies	Down	CRISPR/Cas9-mediated targeting and transgenic mice PCDNA-TUG1 pCDH-TUG1 AS-IV LV-TUG1 METTL14 knockdown	1.Attenuate ROS formation 2.Reduce albuminuria, and histopathological changes 3.Decrease apoptosis and ERS 4.Attenuate cell proliferation, ECM accumulation and inflammation 5.Reduce renal fibrosis 6.Inhibit podocyte apoptosis 7 Restore mitochondrial bioenergetics	Protective	3,4,39，43-50
LN	BALB/c female mice renal biopsies	Down	PDTC treatment	1.Decrease levels of pro-inflammatory factors, ANA, anti-dsDNA, BUN and Cr	Protective	24
	HRMC	Down	TUG1-plasmid(TUG1 overexpression)	1.Relieve LPS-induced cell injury 2.Increase cell viability, inhibit cell apoptosis 3.Reduce secretion of inflammatory cytokines	Protective	53
CKD with CHF	Plasma samples	Down	angioten sin-converting enzyme inhibitors beta-blockers angiotensin receptor blockers dialysis	1.Low levels were signifcantly correlated with the high incidence of progressive CKD among CHF patients 2.Predict the development, survival and the treatment outcome of CKD with CHF	Protective	55
Hypertensive Nephropathy	HK-2 cells Human renal biopsies	Up	TUG1 knockdown	1.Suppress expression of partial EMT and extracellular matrix-related proteins	Harmful	54
glomerulonephrit ides(with FSGS)	Human renal biopsies Urine	Down	none	1.Correlate with podocyte marker expression and mitochondrial biogenesis markers	Protective	11
RCC	Humna renal biopsies ACHN cells and OS-RC-2 cells	Up	TUG1 siRNA sh-TUG1	1.Inhibit the proliferation, migration, invasion, EMT processes and promote apoptosis	Harmful	59-62

Abbreviation USC-EXo urine-derived stem cells-derived exosomes, *GA* gallic acid, *TGP* total glucosides of paeony, *ASO* antisense oligonucleotide, *KP1* Klotho-derived peptide 1, *CRISPR* Clustered Regularly Interspaced Short Palindromic Repeats, *AS-IV* Astragaloside IV, *PDTC* pyrrolidine dithiocarbamate, *UA* uric acid, *BUN* blood urea nitrogen, *SCr* serum creatinine, *ERS* endoplasmic reticulum stress, *ANA* antinuclear antibody

cross-linking and immunoprecipitation (CLIP) [68]; sophisticated computational models, including deep learning [69], network analysis [70–73], graph convolution [73], and matrix factorization [74, 75]; and experimental techniques for cellular location of events or interactions, including subcellular fractionation assay, RNA fuorescence in situ hybridization (FISH) assay, RNA Immunoprecipitation (RIP) PCR, luciferase assays and RNA pull-down assay. Most of the cited papers in this review varify a mechanism for lncRNA-miRNA interactions in the above-mentioned methods, but few only describe vague associations using overexpression and knockdown experiments or database prediction, leaving the strength of the evidence they present weak (Table 1). Furthermore, as TUG1 exists in both the nucleus and cytoplasm, and different miRNA and RBP targets of TUG1 may yield different conclusions, highlighting cellular location of events and stoichiometry of lncRNA and miRNA including cell lysate pull-down assays, total internal reflection fluorescence (TIRF)-based single-vesicle imaging assays and Argonaute (Ago)-based FISH can offer high specificity, sensitivity, and spatial resolution [76, 77]. Unfortunately, there are only 6 cited papers in this review provide comprehensive explanations (Table1). Additionally, different mouse and human cell lines may affect TUG1 expression and the significance of the cited works, for immortalization of cell lines can influence observed

Table 3. Different mouse and human cell lines may affect TUG1 expression and the significance of the cited works

Disease	Cell lines	Expressio	The effect of TUG1 on cells	Reference
AKI	HK-2 cells	Down	Alleviate cell apoptosis Promote autophagy Decrease inflammatory factors	18,26,30
	TCMK-1 cells	Up	Affect cell apoptosis Reduce mitochondrial damages	27,28
	MPC5	Down	Alleviate podocyte injury Promote autophagy	29
	RMCs	Down	Inhibit cell apoptosis Decrease inflammatory factors	32
CKD	HK-2 cells	Up	Promote EMT	34
		Down	Inhibit cellular senescence and fibrosis	38
DKD	Mice MCs	Down	Attenuate cell proliferation and ECM	43,49
	NRK-52E cells	Down	Reduce cell fibrosis	44
	HK-2 cells	Down	Decrease cell apoptosis and ERS Reduce inflammation and ECM secretion	39,45,50
	Mouse podocytes/MPC5 cells	Down	Attenuate ROS formation and cell apoptosis Improve podocyte foot process effacement Reduce glomerular basement membrane thickening	3,4,44,48
LN	HRMC	Down	Increase cell viability Inhibit cell apoptosis Reduce secretion of inflammatory cytokines	52
Hypertensive Nephropathy	HK-2 cells	Up	Increase expression of partial EMT and ECM-related proteins	54
RCC	ACHN cells and OS-RC-2 cells	Up	Promote proliferation, invasion, migration and EMT processes, and inhibit cell apoptosis	59

phenotypes by affecting differentiation potential, and maintaining or altering specific cellular functions and markers (Table 3). Thus, more resarch is needed to confirm the role of TUG1 in kidney diseases and may help address the etiology of diseases.

In summary, the regulatory network of TUG1 varies greatly in most biological processes. However, TUG1 seems to primarily mediate these processes by regulating transcription factors to affect target gene expression or sponging to miRNAs to inhibit target gene expression, while the upstream regulatory mechanisms of lncRNA TUG1 in kidney diseases are scarcely reported. With increasing research investment in lncRNAs, especially TUG1, the study of the TUG1 signaling pathway in kidney diseases may open up new ideas for many new therapeutic methods in the future, and TUG1 is expected to achieve clinical applications eventually.

Acknowledgements
We would like to thank Qiuling Fan(Department of Nephrology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine) for her help with the ideas and article revision.

Authors' contributions
Tong Chen conducted the literature search, collected, analysed and interpreted the data and drafted the first manuscript. Qiuling Fan and Jian Lu revised the manuscript for intellectual content. All authors have read and approved the final version of the manuscript.

Funding
This study was supported by Chinese Nature Science Foundation (No.82070754) of founder Qiuling Fan.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable. Author contribution statement.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 27 November 2024 Accepted: 25 February 2025
Published online: 20 March 2025

References

1. Eckardt KU, Coresh J, Devuyst O, Johnson RJ, Köttgen A, Levey AS, Levin A. Evolving importance of kidney disease: from subspecialty to global health burden. Lancet. 2013;382(9887):158–69. https://doi.org/10.1016/S0140-6736(13)60439-0. (Epub 2013 May 31 PMID: 23727165).
2. Jurkowski TP, Ravichandran M, Stepper P. Synthetic epigenetics-towards intelligent control of epigenetic states and cell identity. Clin Epigenetics. 2015;7(1):18. https://doi.org/10.1186/s13148-015-0044-x.PMID:25741388;PMCID:PMC4347971.
3. Li SY, Susztak K. The long noncoding RNA Tug1 connects metabolic changes with kidney disease in podocytes. J Clin Invest. 2016;126(11):4072–4075. https://doi.org/10.1172/JCI90828. Epub 2016 Oct 17. PMID: 27760046; PMCID: PMC5096895.
4. Long J, Badal SS, Ye Z, Wang Y, Ayanga BA, Galvan DL, Green NH, Chang BH, Overbeek PA, Danesh FR. Long noncoding RNA Tug1 regulates mitochondrial bioenergetics in diabetic nephropathy. J Clin Invest. 2016;126(11):4205–4218. https://doi.org/10.1172/JCI87927. Epub 2016 Oct 17. PMID: 27760051; PMCID: PMC5096930.
5. Ransohoff JD, Wei Y, Khavari PA. The functions and unique features of long intergenic non-coding RNA. Nat Rev Mol Cell Biol. 2018;19(3):143–157. https://doi.org/10.1038/nrm.2017.104. Epub 2017 Nov 15. PMID: 29138516; PMCID: PMC5889127.
6. Ulitsky I, Bartel DP. lincRNAs: genomics, evolution, and mechanisms. Cell. 2013;154(1):26–46. https://doi.org/10.1016/j.cell.2013.06.020.PMID:23827673;PMCID:PMC3924787.
7. Jin Y, Cao J, Hu X, Cheng H. Long noncoding RNA TUG1 upregulates VEGFA to enhance malignant behaviors in stomach adenocarcinoma by sponging miR-29c-3p. J Clin Lab Anal. 2021;35(12):e24106. https://doi.org/10.1002/jcla.24106. Epub 2021 Nov 11. PMID: 34762771; PMCID: PMC8649340.
8. Mattick JS, Makunin IV. Non-coding RNA. Hum Mol Genet. 2006;15 Spec No 1:R17–29. https://doi.org/10.1093/hmg/ddl046. PMID: 16651366.
9. Anastasiadou E, Jacob LS, Slack FJ. Non-coding RNA networks in cancer. Nat Rev Cancer. 2018;18(1):5–18. https://doi.org/10.1038/nrc.2017.99. Epub 2017 Nov 24. PMID: 29170536; PMCID: PMC6337726.
10. Slack FJ, Chinnaiyan AM. The Role of Non-coding RNAs in Oncology. Cell. 2019;179(5):1033–55. https://doi.org/10.1016/j.cell.2019.10.017.PMID:31730848;PMCID:PMC7347159.
11. Salazar-Torres FJ, Medina-Perez M, Melo Z, Mendoza-Cerpa C, Echavarria R. Urinary expression of long non-coding RNA TUG1 in non-diabetic patients with glomerulonephritides. Biomed Rep. 2021;14(1):17. https://doi.org/10.3892/br.2020.1393. Epub 2020 Nov 20. PMID: 33365127; PMCID: PMC7716717.
12. Kopp F, Mendell JT. Functional Classification and Experimental Dissection of Long Noncoding RNAs. Cell. 2018;172(3):393–407. https://doi.org/10.1016/j.cell.2018.01.011.PMID:29373828;PMCID:PMC5978744.
13. Mongelli A, Martelli F, Farsetti A, Gaetano C. The Dark That Matters: Long Non-coding RNAs as Master Regulators of Cellular Metabolism in Non-communicable Diseases. Front Physiol. 2019;10:369. https://doi.org/10.3389/fphys.2019.00369.PMID:31191327;PMCID:PMC6539782.
14. Fernández-Justel JM, Santa-María C, Martín-Vírgala S, Ramesh S, Ferrera-Lagoa A, Salinas-Pena M, Isoler-Alcaraz J, Maslon MM, Jordan A, Cáceres JF, Gómez M. Histone H1 regulates non-coding RNA turnover on chromatin in a m6A-dependent manner. Cell Rep. 2022;40(11): 111329. https://doi.org/10.1016/j.celrep.2022.111329.PMID:36103831;PMCID:PMC7613722.
15. Canaud G, Bienaimé F, Viau A, Treins C, Baron W, Nguyen C, Burtin M, Berissi S, Giannakakis K, Muda AO, Zschiedrich S, Huber TB, Friedlander G, Legendre C, Pontoglio M, Pende M, Terzi F. AKT2 is essential to maintain podocyte viability and function during chronic kidney disease. Nat Med. 2013;19(10):1288–96. https://doi.org/10.1038/nm.3313. (Epub 2013 Sep 22 PMID: 24056770).
16. Cheng Z, Guo S, Copps K, Dong X, Kollipara R, Rodgers JT, Depinho RA, Puigserver P, White MF. Foxo1 integrates insulin signaling with mitochondrial function in the liver. Nat Med. 2009;15(11):1307–11. https://doi.org/10.1038/nm.2049. Epub 2009 Oct 18. PMID: 19838201; PMCID: PMC3994712.
17. Zhang Y, Xu Y, Feng L, Li F, Sun Z, Wu T, Shi X, Li J, Li X. Comprehensive characterization of lncRNA-mRNA related ceRNA network across 12 major cancers. Oncotarget. 2016;7(39):64148–64167. https://doi.org/10.18632/oncotarget.11637. PMID: 27580177; PMCID: PMC5325432.
18. Chen L, Xu JY, Tan HB. LncRNA TUG1 regulates the development of ischemia-reperfusion mediated acute kidney injury through miR-494-3p/E-cadherin axis. J Inflamm (Lond). 2021;18(1):12. https://doi.org/10.1186/s12950-021-00278-4.PMID:33663500;PMCID:PMC7934407.
19. Lorenzen JM, Thum T. Long noncoding RNAs in kidney and cardiovascular diseases. Nat Rev Nephrol. 2016;12(6):360–73. https://doi.org/10.1038/nrneph.2016.51. (Epub 2016 May 3 PMID: 27140855).
20. Moghaddas Sani H, Hejazian M, Hosseinian Khatibi SM, Ardalan M, Zununi VS. Long non-coding RNAs: An essential emerging field in kidney pathogenesis. Biomed Pharmacother. 2018;99:755–65. https://doi.org/10.1016/j.biopha.2018.01.122. (Epub 2018 Feb 20 PMID: 29710473).
21. Li FP, Lin DQ, Gao LY. LncRNA TUG1 promotes proliferation of vascular smooth muscle cell and atherosclerosis through regulating miRNA-21/PTEN axis. Eur Rev Med Pharmacol Sci. 2018;22(21):7439–7447. https://doi.org/10.26355/eurrev_201811_16284. PMID: 30468492.
22. Khalil AM, Guttman M, Huarte M, Garber M, Raj A, Rivea Morales D, Thomas K, Presser A, Bernstein BE, van Oudenaarden A, Regev A, Lander ES, Rinn JL. Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. Proc Natl Acad Sci U S A. 2009;106(28):11667–72. https://doi.org/10.1073/pnas.0904715106. Epub 2009 Jul 1. PMID: 19571010; PMCID: PMC2704857.
23. Guo C, Qi Y, Qu J, Gai L, Shi Y, Yuan C. Pathophysiological Functions of the lncRNA TUG1. Curr Pharm Des. 2020;26(6):688–700. https://doi.org/10.2174/1381612826666191227154009. (PMID: 31880241).
24. Cao HY, Li D, Wang YP, Lu HX, Sun J, Li HB. The protection of NF-κB inhibition on kidney injury of systemic lupus erythematosus mice may be correlated with lncRNA TUG1. Kaohsiung J Med Sci. 2020;36(5):354–62. https://doi.org/10.1002/kjm2.12183. (Epub 2020 Jan 13 PMID: 31930775).
25. Lameire NH, Levin A, Kellum JA, Cheung M, Jadoul M, Winkelmayer WC, Stevens PE; Conference Participants. Harmonizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2021;100(3):516–526. https://doi.org/10.1016/j.kint.2021.06.028. Epub 2021 Jul 9. PMID: 34252450.
26. Chang X, Zhang P, Xu XX, Pang B. Total Glucosides of Paeony Inhibited Autophagy and Improved Acute Kidney Injury Induced by Ischemia-Reperfusion via the lncRNA TUG1/miR-29a/PTEN Axis. Drug Des Devel Ther. 2021;15:2229–42. https://doi.org/10.2147/DDDT.S286606.PMID:34079224;PMCID:PMC8164873.
27. Xu Z, Huang X, Lin Q, Xiang W. Long non-coding RNA TUG1 knockdown promotes autophagy and improves acute renal injury in ischemia-reperfusion-treated rats by binding to microRNA-29 to silence PTEN. BMC Nephrol. 2021;22(1):288. https://doi.org/10.1186/s12882-021-02473-0.PMID:34429073;PMCID:PMC8385981.
28. Zhao S, Chen W, Li W, Yu W, Li S, Rao T, Ruan Y, Zhou X, Liu C, Qi Y, Cheng F. LncRNA TUG1 attenuates ischaemia-reperfusion-induced apoptosis of renal tubular epithelial cells by sponging miR-144–3p via targeting Nrf2. J Cell Mol Med. 2021;25(20):9767–9783. https://doi.org/10.1111/jcmm.16924. Epub 2021 Sep 21. PMID: 34547172; PMCID: PMC8505827.
29. Zhao D, Liu Z, Zhang H. The protective effect of the TUG1/miR-197/MAPK1 axis on lipopolysaccharide-induced podocyte injury. Mol Med Rep. 2019;20(1):49–56. https://doi.org/10.3892/mmr.2019.10216. (Epub 2019 May 9 PMID: 31115515).
30. Sun Z, Wu J, Bi Q, Wang W. Exosomal lncRNA TUG1 derived from human urine-derived stem cells attenuates renal ischemia/reperfusion injury by interacting with SRSF1 to regulate ASCL4-mediated ferroptosis. Stem Cell Res Ther. 2022;13(1):297. https://doi.org/10.1186/s13287-022-02986-x.PMID:35841017;PMCID:PMC9284726.
31. Shi S, Lei S, Tang C, Wang K, Xia Z. Melatonin attenuates acute kidney ischemia/reperfusion injury in diabetic rats by activation of the SIRT1/Nrf2/HO-1 signaling pathway. Biosci Rep. 2019;39(1):BSR20181614. 10.1042/BSR20181614. PMID: 30578379; PMCID: PMC6331666.
32. Wang W, Zhang S, Yang F, Xie J, Chen J, Li Z. Diosmetin alleviates acute kidney injury by promoting the TUG1/Nrf2/HO-1 pathway in sepsis rats. Int Immunopharmacol. 2020;88: 106965. https://doi.org/10.1016/j.intimp.2020.106965. (Epub 2020 Sep 18 PMID: 33182044).
33. Amini N, Badavi M, Mard SA, Dianat M, Moghadam MT. The renoprotective effects of gallic acid on cisplatin-induced nephrotoxicity through anti-apoptosis, anti-inflammatory effects, and downregulation of lncRNA

TUG1. Naunyn Schmiedebergs Arch Pharmacol. 2022;395(6):691–701. https://doi.org/10.1007/s00210-022-02227-1. (Epub 2022 Mar 18 PMID: 35303125).
34. Zhang B, Zhao C, Hou L, Wu Y. Silencing of the lncRNA TUG1 attenuates the epithelial-mesenchymal transition of renal tubular epithelial cells by sponging miR-141-3p via regulating β-catenin. Am J Physiol Renal Physiol. 2020;319(6):F1125–34. https://doi.org/10.1152/ajprenal.00321.2020. (Epub 2020 Nov 2 PMID: 33135476).
35. Djudjaj S, Boor P. Cellular and molecular mechanisms of kidney fibrosis. Mol Aspects Med. 2019;65:16–36. https://doi.org/10.1016/j.mam.2018.06.002. (Epub 2018 Jun 22 PMID: 29909119).
36. Jun JI, Lau LF. Resolution of organ fibrosis. J Clin Invest. 2018;128(1):97–107. https://doi.org/10.1172/JCI93563. Epub 2018 Jan 2. PMID: 29293097; PMCID: PMC5749507.
37. Zhang Y, Zhang H, Hu L, Wei J, Ma C. lncRNA TUG1 regulates hyperuricemia-induced renal fibrosis in a rat model. Acta Biochim Biophys Sin (Shanghai). 2022;54(9):1365–75. https://doi.org/10.3724/abbs.2022128.PMID:36148952;PMCID:PMC9828301.
38. Zhang X, Li L, Tan H, Hong X, Yuan Q, Hou FF, Zhou L, Liu Y. Klotho-derived peptide 1 inhibits cellular senescence in the fibrotic kidney by restoring Klotho expression via posttranscriptional regulation. Theranostics. 2024;14(1):420–35. https://doi.org/10.7150/thno.89105.PMID:38164143;PMCID:PMC10750200.
39. Wang S, Yi P, Wang N, Song M, Li W, Zheng Y. LncRNA TUG1/miR-29c-3p/SIRT1 axis regulates endoplasmic reticulum stress-mediated renal epithelial cells injury in diabetic nephropathy model in vitro. PLoS ONE. 2021;16(6): e0252761. https://doi.org/10.1371/journal.pone.0252761.PMID:34097717;PMCID:PMC8183992.
40. Keri KC, Samji NS, Blumenthal S. Diabetic nephropathy: newer therapeutic perspectives. J Community Hosp Intern Med Perspect. 2018;8(4):200–7. https://doi.org/10.1080/20009666.2018.1500423.PMID:30181826;PMCID:PMC6116149.
41. Dewanjee S, Bhattacharjee N. MicroRNA: A new generation therapeutic target in diabetic nephropathy. Biochem Pharmacol. 2018;155:32–47. https://doi.org/10.1016/j.bcp.2018.06.017. (Epub 2018 Jun 22 PMID: 29940170).
42. Vallon V, Thomson SC. Renal function in diabetic disease models: the tubular system in the pathophysiology of the diabetic kidney. Annu Rev Physiol. 2012;74:351–75. https://doi.org/10.1146/annurev-physiol-020911-153333.PMID:22335797;PMCID:PMC3807782.
43. Duan LJ, Ding M, Hou LJ, Cui YT, Li CJ, Yu DM. Long noncoding RNA TUG1 alleviates extracellular matrix accumulation via mediating microRNA-377 targeting of PPARγ in diabetic nephropathy. Biochem Biophys Res Commun. 2017;484(3):598–604. https://doi.org/10.1016/j.bbrc.2017.01.145. (Epub 2017 Jan 28 PMID: 28137588).
44. Wang F, Gao X, Zhang R, Zhao P, Sun Y, Li C. LncRNA TUG1 ameliorates diabetic nephropathy by inhibiting miR-21 to promote TIMP3-expression. Int J Clin Exp Pathol. 2019;12(3):717–729. PMID: 31933879; PMCID: PMC6945187.
45. Wang T, Cui S, Liu X, Han L, Duan X, Feng S, Zhang S, Li G. LncTUG1 ameliorates renal tubular fibrosis in experimental diabetic nephropathy through the miR-145-5p/dual-specificity phosphatase 6 axis. Ren Fail. 2023;45(1):2173950. https://doi.org/10.1080/0886022X.2023.2173950.PMID:36794657;PMCID:PMC9937007.
46. Long J, Galvan DL, Mise K, Kanwar YS, Li L, Poungavrin N, Overbeek PA, Chang BH, Danesh FR. Role for carbohydrate response element-binding protein (ChREBP) in high glucose-mediated repression of long noncoding RNA Tug1. J Biol Chem. 2020;295(47):15840–15852. https://doi.org/10.1074/jbc.RA120.013228. Epub 2020 May 28. PMID: 32467232; PMCID: PMC7681008.
47. Li L, Long J, Mise K, Galvan DL, Overbeek PA, Tan L, Kumar SV, Chan WK, Lorenzi PL, Chang BH, Danesh FR. PGC1α is required for the renoprotective effect of lncRNA Tug1 in vivo and links Tug1 with urea cycle metabolites. Cell Rep. 2021;36(6): 109510. https://doi.org/10.1016/j.celrep.2021.109510.PMID:34380028;PMCID:PMC8369494.
48. Lei X, Zhang L, Li Z, Ren J. Astragaloside IV/lncRNA-TUG1/TRAF5 signaling pathway participates in podocyte apoptosis of diabetic nephropathy rats. Drug Des Devel Ther. 2018;12:2785–93. https://doi.org/10.2147/DDDT.S166525.PMID:30233141;PMCID:PMC6132489.
49. Zang XJ, Li L, Du X, Yang B, Mei CL. LncRNA TUG1 inhibits the proliferation and fibrosis of mesangial cells in diabetic nephropathy via inhibiting the PI3K/AKT pathway. Eur Rev Med Pharmacol Sci. 2019;23(17):7519–7525. https://doi.org/10.26355/eurrev_201909_18867. PMID: 31539141.
50. Zheng Y, Zhang Z, Zheng D, Yi P, Wang S. METTL14 promotes the development of diabetic kidney disease by regulating m6A modification of TUG1. Acta Diabetol. 2023;60(11):1567–80. https://doi.org/10.1007/s00592-023-02145-5. (Epub 2023 Jul 10 PMID: 37428236).
51. Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE, Mohan C. Lupus nephritis Nat Rev Dis Primers. 2020;6(1):7. https://doi.org/10.1038/s41572-019-0141-9. (PMID: 31974366).
52. Liu L, Zhang Y, Zhong L. LncRNA TUG1 relieves renal mesangial cell injury by modulating the miR-153-3p/Bcl-2 axis in lupus nephritis. Immun Inflamm Dis. 2023;11(4): e811. https://doi.org/10.1002/iid3.811.PMID:37102641;PMCID:PMC10091205.
53. Damman K, Testani JM. The kidney in heart failure: an update. Eur Heart J. 2015;36(23):1437–44. https://doi.org/10.1093/eurheartj/ehv010. Epub 2015 Apr 2. PMID: 25838436; PMCID: PMC4465636.
54. Zhang J, Zhang Y, Gao J, Wang M, Li X, Cui Z, Fu G. Long Noncoding RNA Tug1 Promotes Angiotensin II-Induced Renal Fibrosis by Binding to Mineralocorticoid Receptor and Negatively Regulating MicroR-29b-3p. Hypertension. 2021;78(3):693–705. https://doi.org/10.1161/HYPERTENSIONAHA.120.16395. (Epub 2021 Aug 2 PMID: 34333990).
55. Zhao W, Zhang Y, Zhang M, Zhi Y, Li X, Liu X. LncRNA-TUG1 Downregulation is Correlated with the Development of Progressive Chronic Kidney Disease Among Patients with Congestive Heart Failure. Mol Biotechnol. 2022;64(5):493–8. https://doi.org/10.1007/s12033-021-00427-3. (Epub 2021 Nov 30 PMID: 34846690).
56. Tian H, Wu M, Zhou P, Huang C, Ye C, Wang L. The long non-coding RNA MALAT1 is increased in renal ischemia-reperfusion injury and inhibits hypoxia-induced inflammation. Ren Fail. 2018;40(1):527–33. https://doi.org/10.1080/0886022X.2018.1487863.PMID:30277425;PMCID:PMC6171433.
57. Sun IO, Lerman LO. Urinary microRNA in kidney disease: utility and roles. Am J Physiol Renal Physiol. 2019;316(5):F785-F793. https://doi.org/10.1152/ajprenal.00368.2018. Epub 2019 Feb 13. PMID: 30759023; PMCID: PMC6580242.
58. Brandenburger T, Salgado Somoza A, Devaux Y, Lorenzen JM. Noncoding RNAs in acute kidney injury. Kidney Int. 2018;94(5):870–81. https://doi.org/10.1016/j.kint.2018.06.033. (PMID: 30348304).
59. Li Y, Zheng D, Pan L, Dai Y, Cai S, Zhao L, Zhu H. Knockdown of TUG1 by shRNA inhibited renal cell carcinoma formation by miR-299-3p/VEGF axis in vitro and in vivo. Eur J Pharmacol. 2019;860: 172536. https://doi.org/10.1016/j.ejphar.2019.172536. (Epub 2019 Jul 13 PMID: 31310753).
60. Wang PQ, Wu YX, Zhong XD, Liu B, Qiao G. Prognostic significance of overexpressed long non-coding RNA TUG1 in patients with clear cell renal cell carcinoma. Eur Rev Med Pharmacol Sci. 2017;21(1):82–6 (PMID: 28121352).
61. Zhang M, Lu W, Huang Y, Shi J, Wu X, Zhang X, Jiang R, Cai Z, Wu S. Downregulation of the long noncoding RNA TUG1 inhibits the proliferation, migration, invasion and promotes apoptosis of renal cell carcinoma. J Mol Histol. 2016;47(4):421–8. https://doi.org/10.1007/s10735-016-9683-2. Epub 2016 Jun 20. Erratum in: J Mol Histol. 2020;51(4):469–470. https://doi.org/10.1007/s10735-020-09890-9. PMID: 27323757.
62. Liu S, Yang Y, Wang W, Pan X. Long noncoding RNA TUG1 promotes cell proliferation and migration of renal cell carcinoma via regulation of YAP. J Cell Biochem. 2018;119(12):9694–706. https://doi.org/10.1002/jcb.27284. (Epub 2018 Aug 21 PMID: 30132963).
63. Zhou H, Sun L, Wan F. Molecular mechanisms of TUG1 in the proliferation, apoptosis, migration and invasion of cancer cells. Oncol Lett. 2019;18(5):4393–4402. https://doi.org/10.3892/ol.2019.10848. Epub 2019 Sep 10. PMID: 31611948; PMCID: PMC6781668.
64. Wang WY, Wang YF, Ma P, Xu TP, Shu YQ. Taurine-upregulated gene 1: A vital long non-coding RNA associated with cancer in humans (Review). Mol Med Rep. 2017;16(5):6467–71. https://doi.org/10.3892/mmr.2017.7472. (Epub 2017 Sep 12 PMID: 28901436).
65. Svenson KL, Von Smith R, Magnani PA, Suetin HR, Paigen B, Naggert JK, Li R, Churchill GA, Peters LL. Multiple trait measurements in 43 inbred mouse strains capture the phenotypic diversity characteristic of human populations. J Appl Physiol (1985). 2007;102(6):2369–78. https://doi.org/10.1152/japplphysiol.01077.2006. Epub 2007 Feb 22. PMID: 17317875.
66. Shi X, Wei W, Zou Y, Dong L, Wu H, Jiang J, Li X, Chen J. LncRNA Taurine Up-Regulated 1 plays a proapoptotic role by regulating

nuclear-cytoplasmic shuttle of HuR under the condition of neuronal ischemia. Neuroreport. 2022;33(18):799–811. https://doi.org/10.1097/WNR.0000000000001848. Epub 2022 Oct 27. PMID: 36367790; PMCID: PMC9648984.
67. Paraskevopoulou MD, Georgakilas G, Kostoulas N, Reczko M, Maragkakis M, Dalamagas TM, Hatzigeorgiou AG. DIANA-LncBase: experimentally verified and computationally predicted microRNA targets on long non-coding RNAs. Nucleic Acids Res. 2013;41(Database issue):D239–45. https://doi.org/10.1093/nar/gks1246. Epub 2012 Nov 28. PMID: 23193281; PMCID: PMC3531175.
68. Tang X, Ji L. Predicting Plant miRNA-lncRNA Interactions via a Deep Learning Method. IEEE Trans Nanobioscience. 2023;22(4):728–33. https://doi.org/10.1109/TNB.2023.3275178. (Epub 2023 Oct 3 PMID: 37167036).
69. Zhang L, Yang P, Feng H, Zhao Q, Liu H. Using Network Distance Analysis to Predict lncRNA-miRNA Interactions. Interdiscip Sci. 2021;13(3):535–45. https://doi.org/10.1007/s12539-021-00458-z. (Epub 2021 Jul 7 PMID: 34232474).
70. Xu M, Chen Y, Lu W, Kong L, Fang J, Li Z, Zhang L, Pian C. SPMLMI: predicting lncRNA-miRNA interactions in humans using a structural perturbation method. PeerJ. 2021;9: e11426. https://doi.org/10.7717/peerj.11426.PMID:34055486;PMCID:PMC8140594.
71. Wang W, Zhang L, Sun J, Zhao Q, Shuai J. Predicting the potential human lncRNA-miRNA interactions based on graph convolution network with conditional random field. Brief Bioinform. 2022;23(6):bbac463. https://doi.org/10.1093/bib/bbac463. PMID: 36305458.
72. Huang YA, Huang ZA, You ZH, Zhu Z, Huang WZ, Guo JX, Yu CQ. Predicting lncRNA-miRNA Interaction via Graph Convolution Auto-Encoder. Front Genet. 2019;10:758. https://doi.org/10.3389/fgene.2019.00758.PMID:31555320;PMCID:PMC6727066.
73. Zhang W, Tang G, Zhou S, Niu Y. LncRNA-miRNA interaction prediction through sequence-derived linear neighborhood propagation method with information combination. BMC Genomics. 2019;20(Suppl 11):946. https://doi.org/10.1186/s12864-019-6284-y.PMID:31856716;PMCID:PMC6923828.
74. Cai L, Gao M, Ren X, Fu X, Xu J, Wang P, Chen Y. MILNP: Plant lncRNA-miRNA Interaction Prediction Based on Improved Linear Neighborhood Similarity and Label Propagation. Front Plant Sci. 2022;13: 861886. https://doi.org/10.3389/fpls.2022.861886.PMID:35401586;PMCID:PMC8990282.
75. Tsanov N, Samacoits A, Chouaib R, Traboulsi AM, Gostan T, Weber C, Zimmer C, Zibara K, Walter T, Peter M, Bertrand E, Mueller F. smiFISH and FISH-quant - a flexible single RNA detection approach with super-resolution capability. Nucleic Acids Res. 2016;44(22):e165. https://doi.org/10.1093/nar/gkw784. Epub 2016 Sep 5. PMID: 27599845; PMCID: PMC5159540.
76. Chen KH, Boettiger AN, Moffitt JR, Wang S, Zhuang X. RNA imaging. Spatially resolved, highly multiplexed RNA profiling in single cells. Science. 2015;348(6233):aaa6090. https://doi.org/10.1126/science.aaa6090. Epub 2015 Apr 9. PMID: 25858977; PMCID: PMC4662681.
77. Foster LM, Phan T, Verity AN, Bredesen D, Campagnoni AT. Generation and analysis of normal and shiverer temperature-sensitive immortalized cell lines exhibiting phenotypic characteristics of oligodendrocytes at several stages of differentiation. Dev Neurosci. 1993;15(2):100–9. https://doi.org/10.1159/000111322. (PMID: 8168435).

Publisher's Note