Kidney Diseases

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tRNA-Derived Small RNAs: A Novel Regulatory Small Noncoding RNA in Renal Diseases

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Abstract
Background: tRNA-derived small RNAs (tsRNAs) are an emerging class of small noncoding RNAs derived from tRNA cleavage. ***Summary:*** With the development of high-throughput sequencing, various biological roles of tsRNAs have been gradually revealed, including regulation of mRNA stability, transcription, translation, direct interaction with proteins and as epigenetic factors, etc. Recent studies have shown that tsRNAs are also closely related to renal disease. In clinical acute kidney injury (AKI) patients and preclinical AKI models, the production and differential expression of tsRNAs in renal tissue and plasma were observed. Decreased expression of tsRNAs was also found in urine exosomes from chronic kidney disease patients. Dysregulation of tsRNAs also appears in models of nephrotic syndrome and patients with lupus nephritis. And specific tsRNAs were found in high glucose model in vitro and in serum of diabetic nephropathy patients. In addition, tsRNAs were also differentially expressed in patients with kidney cancer and transplantation. ***Key Messages:*** In the present review, we have summarized up-to-date works and reviewed the relationship and possible mechanisms between tsRNAs and kidney diseases.

Introduction

tRNA is a cohesive molecule that ensures accurate and efficient protein synthesis by transferring amino acids corresponding to mRNA to peptide chains [1]. In recent years, it has been found that in addition to its conventional functions, tRNA can also be cleaved into a bioactive fragment of tRNA-derived small RNAs (tsRNAs) with the length of 18–50 nucleotides (nt). Early literature found that tsRNAs existed in various cells, tissues, organisms, and serum [2–6] and participated in the cellular stress response [7]. With the development of high-throughput sequencing, tsRNAs have been recognized as essential participants for cell growth and take on multiple biological roles [8]. It has been reported that tsRNAs are involved in the regulation of a variety of diseases, especially in neoplastic diseases, and are expected to be

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markers for the diagnosis, progression and prognosis of gynecological tumors, breast cancer, myeloma, and other malignant diseases [9–13]. It also provides a new direction for the prevention and treatment of nonalcoholic fatty liver disease [14], Alzheimer's disease [15], ovarian endometriosis, and other diseases [16]. Recently, more and more studies have been conducted on tsRNAs, which have also been found to be involved in kidney diseases. In this review, the classification, biological functions of tsRNAs and their association with renal system diseases are reviewed.

tsRNAs Classification

tsRNAs are roughly divided into two categories: tRNA-derived fragments (tRFs) and tRNA halves (tiRNAs). tRFs are a class of small RNAs with the length of 14–30 nt. According to the different cleavage position and length, tRFs can be divided into five subclasses: tRF-1, tRF-2, tRF-3, tRF-5, and i-tRF. tRF-1 is produced by cleavage of precursor tRNA by RNaseZ or ElaC Ribonuclease Z 2 (ELAC2), which contains the 3′-tail sequence of the poly-U sequence [17]. Under anoxic conditions, tRF-2 is produced by cleavage of the anticodon loop of tRNA such as tRNA-Tyr, tRNA-Gly, tRNA-Asp, and tRNA-Glu, which contains the anticodon loop and stem sequence but does not include the typical 5′- and 3′-terminal groups [18, 19]. tRF-3 is produced by cleavage of the TψC loop of mature tRNA by angiogenin (ANG), Dicer, or exonuclease and thus has a CCA trinucleotide structure at the 3′-end of mature tRNA [20, 21]. tRF-5 is formed from cutting at the D-loop of tRNA or the stem arm between the D-loop and the anticodon loop by Dicer [22, 23]. According to the length cleaved, it can be divided into three subcategories: tRF-5a (14–16 nt), tRF-5b (22–24 nt), and tRF-5c (28–30 nt). i-tRF originates from the inner region between the D and T loops of any mature tRNA [24, 25].

tiRNAs are a small noncoding RNAs produced in response to stress, 31–40 nt in length, resulting from cleavage of the anticoding loop of mature tRNA by ANG [26], and there are two main subtypes: 3′-tiRNA and 5′-tiRNA. 5′-tiRNA contains 5′-end of the mature RNA and the 3′-tiRNA contains 3′-end of the mature RNA [27]. Previous studies have suggested that tiRNA in mammals is cleaved by ANG [28]. But in recent studies, it was found that ANG is not the only ribonuclease that produces tiRNA. In mammalian cells, translation-inhibiting endoribonuclease, also called RNase L, can cleave tRNA and produce tiRNAs [29, 30]. Besides, tRNA can be cleaved in the extracellular environment by RNase 1 to tiRNAs [31].

Biological Roles of tsRNAs

As novel molecules in the field of the noncoding RNA biology, tsRNAs achieve their multiple biological functions by regulating mRNA stability, transcription, translation, and direct interaction with proteins and acting as epigenetic factors, which have been shown by numerous studies. Detailed description will be listed in the following subsections.

Regulation of mRNA Stability

tsRNAs are novel regulators of gene expression. Sequencing results showed that some tsRNAs were associated with Argonaute (AGO) proteins. Previous studies have confirmed that tsRNAs related to AGO proteins come from the 5′-tRNA, and they have approximately the same sequence length with mature microRNAs (miRNAs) [32]. Many studies have pointed out that tsRNAs have similar functions to miRNAs and can regulate mRNA stability [33]. However, there are some differences between tsRNAs and miRNAs in the specific mechanism of regulating mRNA stability. For example, tsRNAs were found to be more likely to bind AGO1, 3, and 4 than to bind AGO2, a major effector of miRNA function. Besides, both tsRNAs and miRNAs are able to bind AGO proteins at specific positions, which are known as "seed" sequences due to their high T to C mutation frequency [34]. In chondrocytes, tRF-3003A produced by the 3′- tRNA-Cys^{GCA} was found to inhibit Janus kinase 3 (JAK3) gene expression in an AGO-dependent mechanism [35]. In addition, studies have found the abnormal expression of tRF-3017A (derived from tRNA-Val-TAC) in gastric cancer (GC) tissues and cell lines, which further revealed that tRF-3017A and NEL Like Protein 2

(NELL2) directly interact with AGO, and which regulates NELL2 by combining with tumor suppressor gene protein to form RNA-induced silencing complex protein (RISC) [36]. In conclusion, tsRNAs can regulate gene expression through miRNA-like effects by binding to different AGOs.

Regulating Transcription

tsRNAs can play a specific role in transcription and gene expression regulation. Yang et al. [37] conducted a study on AS-tDR-007333, which showed significant upregulation in non-small cell lung cancer and a correlation with patient prognosis. Their subsequent investigations revealed that AS-tDR-007333 has a dual mechanism of action. It was observed that AS-tDR-007333 can enhance the activity of the MED29 promoter through its interaction with the small heat shock protein HSPB1 (HSPB1). This interaction leads

to an increase in MED29 activity. Meanwhile, AS-tDR-007333 was also found to upregulate MED29 expression by activating the transcription factor 4 (ELK4). This activation of ELK4 results in the increased transcription of MED29. As a consequence, the enhanced expression of AS-tDR-007333 was shown to promote the proliferation of non-small cell lung cancer cells [37]. These findings indicate that tsRNAs can regulate transcription by influencing promoters and the activity of transcription factors, ultimately impacting gene expression. These discoveries open up new avenues for exploring the role of tsRNAs in gene expression regulation.

Regulating Translation

tRNAs have a length of 70–90 nt, which is a cohesive molecule with its typical function in protein translation mechanism [38, 39]. Heretofore, many studies have revealed that tsRNAs are involved in the regulation of protein translation through various mechanisms. The terminal oligoguanine is important for tiRNA binding to the translation silencer Y-box binding protein 1 (YB-1). Ivanov et al. [40] found that 5′-tiRNA containing terminal oligoguanine displaced eIF4G/A from upstream mRNA and inhibited translation. The mechanism may be that 5′-tRF displaces the eukaryotic initiation factor eIF4G/A from the capped mRNA. However, the mechanism by which tsRNAs destabilize eIF4F still needs to be further studied [40]. Guzzi et al. [41] found that PUS7, a member of the pseuduridine synthase (PUSs) family, inhibits translation by mediating pseudouridylation (ψ) to induce tsRNAs. It has been found that the recruitment of tRF-binding proteins such as YB-1 and DEAH-box helicase 36 (DHX36) is inhibited by ψ [41]. Su et al. [42] found that the seed sequence region of specific tsRNAs contained N1-methyladenosine (m^1A) modifications in bladder cancer. These tsRNAs may inhibit AGO-dependent gene silencing mechanisms by reducing base pairing to target mRNA [42].

In addition, cellular stress can rapidly inhibit translation at the stage of translation initiation, and it is related to the assembly of stress granules (SGs) [43]. SGs are cytoplasmic ribonucleoprotein complexes consisting of 40S ribosomal subunits, mRNA, RNA-binding proteins, and translation initiation factors [44, 45]. According to the report, transfection of tiRNA into cells increases the formation of SGs. SGs promote cell recovery in stress environments by storing untranslated mRNAs, RNA-binding proteins, and signaling molecules [46, 47]. It was shown that ANG produced 5′-tiRNA or synthesized 5′-tiRNA^{Ala} induced SGs assembly in U2OS cells [44]. Furthermore, the translation silencer YB-1 is a direct target of 5′-tiRNA and required for tiRNA-induced SGs assembly [45, 48].

Direct Interaction with Proteins

Recent studies have revealed that tsRNAs can exert biological functions through direct interactions with target proteins. For instance, Cui et al. [49] discovered that the significantly upregulated tRF-Val in GC forms complexes by binding with EEF1A1 (eukaryotic translation elongation factor 1 alpha 1). These complexes are then transported to the nucleus, enhancing the interaction between EEF1A1 and the MDM2 proto-oncogene (MDM2), ultimately promoting GC progression [49]. Additionally, Zhao et al. [50] found that the upregulated tRF-Tyr in laryngeal squamous cell carcinoma enhances tumor progression by binding with lactate dehydrogenase A (LDHA), affecting its phosphorylation and leading to increased lactic acid accumulation [50]. These studies highlight the diverse biological roles of tsRNAs, which involve direct binding to target proteins, formation of complexes for intracellular transport, and regulation of posttranslational modifications.

Acting as Epigenetic Factors

With the improvement of sequencing methods and bioinformatics analysis, it has been found that the small RNA population in mature mouse sperm is mainly composed of tsRNAs [51]. In addition, tsRNAs were found to be extremely abundant in cardiac tissues with cardiac hypertrophy, which may increase the surface area of cardiomyocytes and the expression of hypertrophy genes. Interestingly, sperm tsRNAs may act as an epigenetic factor to transmit symptoms of cardiac hypertrophy to offspring [52]. Furthermore, it has been shown that ANG-mediated 5′-tsRNAs biosynthesis in sperm contributes to parental inflammation-induced metabolic disorders in offspring [53]. Therefore, studies on genetics of tsRNAs may have implications for pathogenesis and therapeutic strategies of human diseases.

tsRNAs in Renal Diseases

More and more studies have shown that tsRNAs participate in the occurrence and development of cardiovascular diseases, tumor, neurological diseases, and other diseases in various ways [54–59]. Meanwhile, strong evidence supports the involvement of tsRNAs in renal diseases. We will describe the recent advances in the study of relevant mechanisms of tsRNAs in various renal diseases.

tsRNAs and Acute Kidney Injury

Acute kidney injury (AKI) is characterized by a rapid decline in renal function and confirmed by elevated serum creatinine levels and decreased urine output [60]. It

is associated with many risk factors, such as volume insufficiency, hypoxia, use of nephrotoxic drugs, and sepsis [60, 61]. In particular, it has been reported that both tRNA and tsRNAs are involved in ischemia-reperfusion-induced AKI models [62, 63]. In AKI model induced by ischemia-reperfusion, our team observed that 152 tsRNAs were differentially expressed after renal ischemia 10 min and reperfusion 24 h in mice; after 30 min of ischemia and 24 h of reperfusion, 285 tsRNAs were differentially expressed, such as tiRNA-Asp-GTC-002, tiRNA-Glu-TTC-002, tiRNA-Lys-CTT-003. These differentially expressed tsRNAs were mainly enriched in renal immune, inflammatory and metabolic pathways [63], which revealed that tsRNAs were strongly involved in renal ischemia-reperfusion injury. Mishima et al. [64] also observed tRNA cleavage and tsRNAs production in damaged kidneys and plasma in both cisplatin- and ischemia-reperfusion-induced AKI models. Moreover, the increase of tsRNAs in plasma preceded the increase of kidney injury molecule 1 (KIM-1) and creatinine in urine [64], suggesting that tsRNAs may be suitable for predicting early tissue damage. In addition, RNA bands of 30–50 nt appeared in the endoplasmic reticulum stress-induced AKI model. Northern blot confirmed that these stress-induced RNAs were tsRNAs, and they may be involved in the translational inhibition under endoplasmic reticulum stress [65].

Under stress conditions, cells would launch translational reprogramming, which is the process of reducing energy consumption by decreasing the overall translation of proteins while increasing the translation of a specific set of genes to promote cell survival and recovery [66]. Stress-induced translational reprogramming has also been reported in AKI [67]. When the kidney undergoes stress such as hypoxia, amino acid deficiency, ultraviolet radiation, heat shock, oxidative damage, and viral infection, tRNAs are cleaved into tiRNAs by ANG [57]. tiRNAs inhibit translation by replacing eIF4G/A from capped or uncapped mRNA [40] and by promoting the formation of SGs independent of phosphorylated eIF2α [44, 68]. In addition, tiRNAs can cooperate with YB-1 to prevent eIF4G/A from initiating translation [40], thereby reducing cell energy consumption and achieving cell homeostasis. Similarly, eIF4G2 was also found in the differential expressed protein of tiRNA-Lys-CTT-003 binding protein in our pull-down experiment (unpublished data), suggesting that tiRNA-Lys-CTT-003 may participate in the process of translation regulation by binding to eIF4G2. In addition to translational reprogramming, tiRNAs may also inhibit Cyt *c*/Apaf-1 mediated activation of apoptotic bodies by binding to Cyt c [69] (shown in Fig. 1). In our study, several apoptosis-related upstream molecules were also found in the protein binding to tiRNA-Lys-CTT-003, such as Dnaja3 and DAP5. Dnaja3, a member of the heat shock protein (Hsp) 40 family, is a regulator of apoptosis located in mitochondria, and its two protein subtypes 43-kDa and 40-KDa are known to have opposite roles in apoptosis [70]. Besides, DAP5, a member of the eIF4G family, is involved in programmed cell death and promotes the translation of apoptotic and anti-apoptotic mRNA [71]. In conclusion, these current studies indicate that tsRNAs are produced in response to AKI or stress, and these tsRNAs may play biological roles through regulating translation and inhibiting apoptosis. This could provide new directions and theoretical supports for the treatment of AKI.

tsRNAs and Chronic Kidney Disease

Studies show that chronic kidney disease (CKD) affects 8–16% of the global population, making it the 16th leading cause of life loss worldwide [72]. CKD is defined as a persistent abnormality of renal structure or function for more than 3 months, and its main pathological changes of CKD include inflammatory cell infiltration, fibroblast activation and proliferation, excessive production and deposition of extracellular matrix components, and sparse peritubular capillaries [73]. Khurana et al. [74] found that the abundance of tRF^{Val} and tRF^{Leu} in urine exosomes of CKD patients was significantly lower than that of healthy controls and also found that these tsRNAs may originate from renal associated cell types. Moreover, the abundance of mitochondrial tRNAs ($tRNA^{Cys}$, $tRNA^{Pro}$, and $tRNA^{Glu}$) in urine exosomes was also significantly decreased in CKD patients compared to healthy controls [74]. Previous studies have suggested that mitochondrial tRNAs are believed to be transported through cellular vesicles between mitochondria and lysosomes [75], while exosomes have also been found to contain mitochondrial tRNAs [76, 77]. This indicated that mitochondrial tRNA is not only transported to lysosomal catabolism but also excreted into urine through exosomes. Reduction of mitochondrial tRNAs and tRFs in urinary exosomes from CKD patients would imply decreased exosome transport, resulting in reduced excretion. In the meantime, in a cohort study, serum levels of tsRNAs were found to be elevated in CKD patients and highly associated with mortality [64]. They propose that the reason for the increased levels of tsRNAs is due to the persistent RNA damage induced by oxidative stress in CKD patients, and it is unclear whether this is also associated with reduced excretion [64]. Interestingly, in contrast to tsRNAs levels, miRNAs blood concentrations

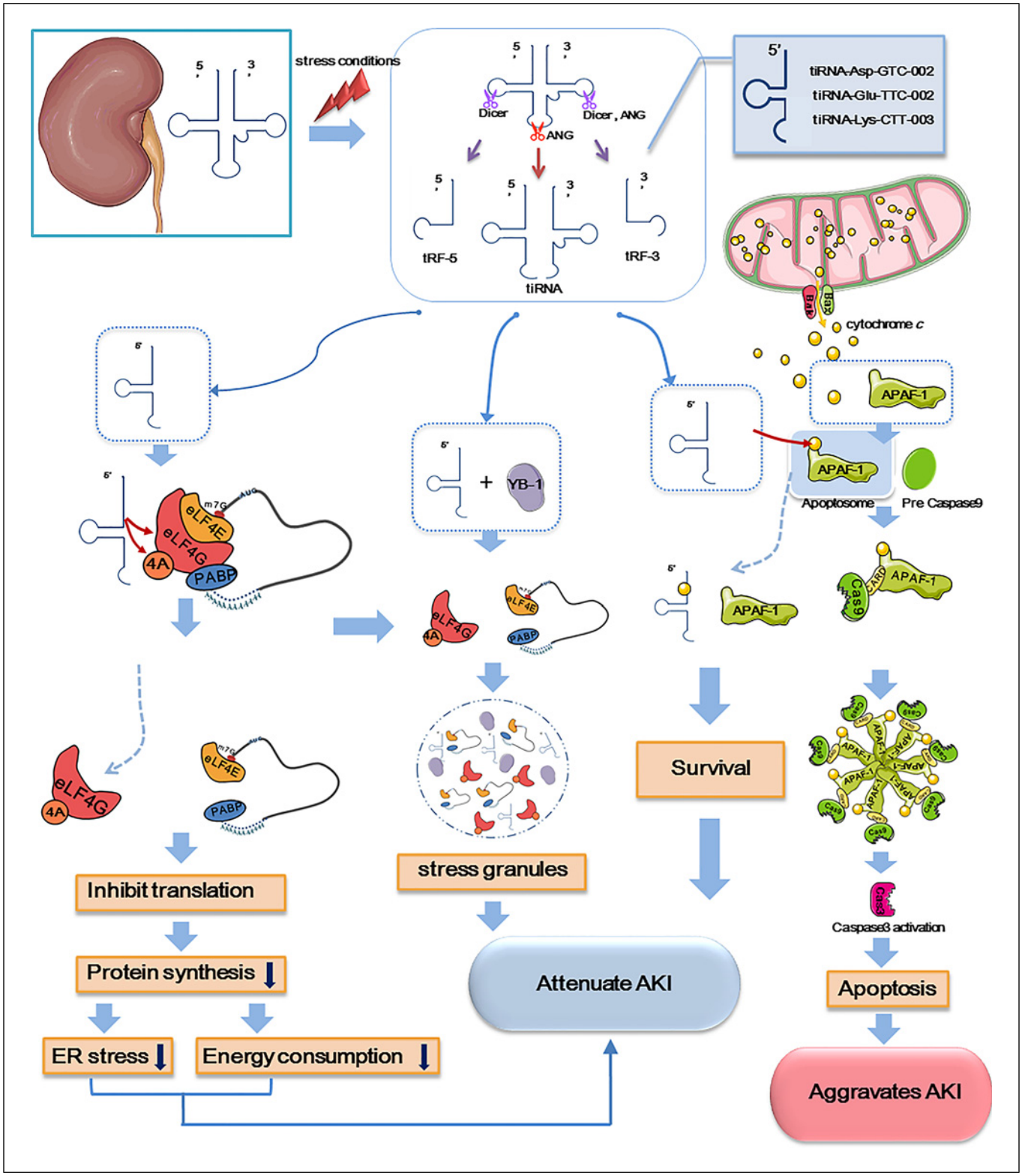

Fig. 1. Possible role of tsRNAs in AKI. tsRNAs may be involved in AKI by regulating translation, promoting the formation of SGs, and inhibiting apoptosis. tsRNAs, tRNA-derived small RNAs; AKI, acute kidney injury.

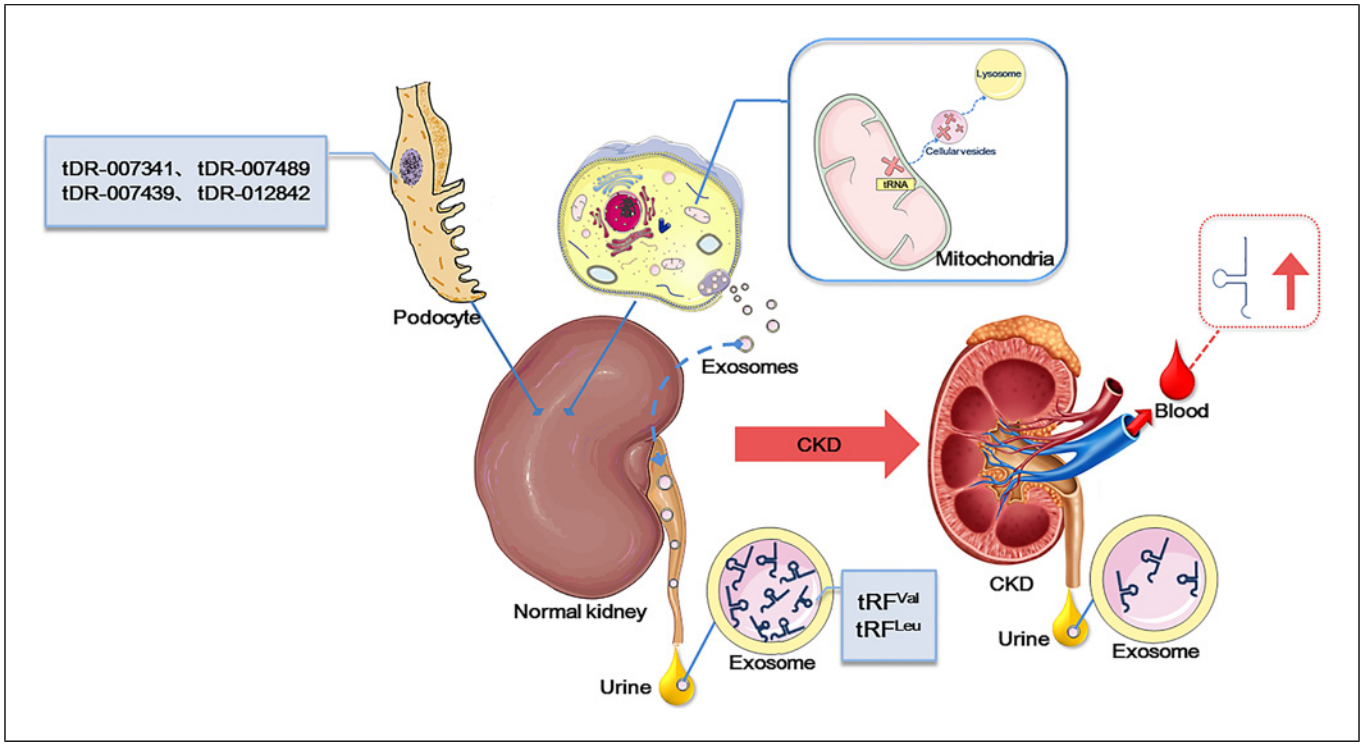

Fig. 2. Possible role of tsRNAs in CKD. The abundance of tsRNAs in urine exosomes of CKD patients was significantly lower than that of healthy controls. tRFs in urinary exosomes may be associated with the pathogenesis of CKD. CKD, chronic kidney disease.

decrease with the progression of CKD, such as miRNA-126, miRNA-223 [78]. It has been reported that low-molecular weight proteins (such as RNases) accumulate significantly in patients with renal failure [79], and increased levels of these enzymes may lead to increased degradation of circulating miRNAs. While Laurent Metzinger's group showed serum RNA levels after extraction did not alter with the progression of CKD stage [78]. Some scholars believe that the decrease of circulating miRNA level may also be related to the pathogenesis of albuminuria and uremia [80]. So far, the mechanism of decreasing circulating miRNA levels in patients with CKD remains unclear, which may need further investigations.

Damage to glomerular filtration barrier is one of the key causes of CKD [81, 82], among them, podocytes are essential for maintaining the integrity of the glomerular filtration barrier [83]. Some studies show that podocyte damage underlies the molecular mechanism of many proteinuria glomerular diseases [84]. Huimin's group later added the observation that 139 tsRNAs were differentially expressed in differentiated podocytes compared with undifferentiated podocytes, of which 69 were upregulated and 70 were downregulated, such as tDR-007341, tDR-007489, tDR-007439, and tDR-012842. Biological analysis showed that these tsRNAs were associated with PI3K-Akt, Rap1, Ras, MAPK and Wnt signaling pathway [85]. These results suggest that differentially expressed tsRNAs may play an important role in the regulation of podocyte differentiation, which provides novel interventions for the progression of CKD (shown in Fig. 2). In short, these reports reveal a close association and conjecture between tsRNAs and CKD; nevertheless, the specific mechanism is still mysterious and needs to be further explored.

tsRNAs and Nephrotic Syndrome

The main clinical features of nephrotic syndrome (NS) are massive proteinuria, hypoproteinemia, edema, and hyperlipidemia [86], and clinically, podocyte injury is the initial cause of NS [87]. Li et al. [88] found that compared to the control group, after adriamycin intervention, the group of podocyte damage has 551 tsRNAs differentially expressed, among which 102 were upregulated and 101 were downregulated ($q < 0.05$, $|\log2FC|>2$), such as AS-tDR-008924, AS-tDR-011690, tDR-003634,

AS-tDR-013354, tDR-011031, AS-tDR-001008, and AS-tDR-007319. Biological analysis showed that these differentially expressed tsRNAs may participate in podocyte injury through PI3K-Akt signaling pathway, Wnt signaling pathway, and Ras signaling pathway [88]. In addition, focal segmental glomerular sclerosis (FSGS) is an important cause of NS [89]. Marie et al. [90] found significant differences in tsRNAs levels in the glomeruli and tubulointerstitial regions of normal tissue between healthy controls and FSGS patients. When FSGS score 0, there were 43 differentially expressed 3′-tRF (mitochondrial 9, cytosolic 34) and 51 differentially expressed 3′-tRF (mitochondrial 3, cytosolic 48) in glomerular and tubulointerstitial regions, such as M3-tRNA-Phe-GAA-1-6_24, M3-tRNA-Gln-TTG-3-3_14, M5-tRNA-Lys-TTT-5-1_15, S5-tRNA-Ala-AGC-6_16, and most of which were upregulated [90]. These data indicate that changes in tsRNAs precede changes in histological lesions. This also suggests that tsRNAs can be used as an early warning signal of kidney disease and provide a new research direction for future clinical detection. In brief, these studies revealed that tsRNAs participated in the occurrence and development of NS, providing a new insight for exploring the pathogenesis of NS.

tsRNAs and Lupus Nephritis

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease [91] which affects the kidneys in about 40–60% of patients in different studies and patient populations [92, 93]. Lupus nephritis (LN) is a major risk factor for morbidity and mortality in SLE [92]. Geng et al. [94] demonstrated that the expression level of tRF-3009 produced by tRNA-Leu-TAA cleaving was significantly higher in patients with active LN than in those without LN. They also found that tRF-3009 level was positively correlated with IFN-α level and participates in metabolic modulation of oxidative phosphorylation in SLE patients [94]. Furthermore, Yang et al. [95] found that the serum expression of tRF-His-GTG-1 in SLE patients with LN was significantly lower than that in SLE patients without LN, and the possible mechanism is that the damaged kidney may excrete more tRF-His-GTG-1 in the urine. And they added the observation that tRF-His-GTG-1 is transported via serum exosomes [95]. This suggests that tsRNAs can be used as a biomarker for LN to support future clinical applications. In conclusion, these reports suggest that tsRNAs may be involved in the development of LN, in which tsRNAs may play an important biological role, and provide a new direction for future research.

tsRNAs and Diabetic Nephropathy

Diabetic nephropathy (DN) is characterized by distinctive pathological changes in kidney structure and function caused by diabetes in patients [96]. Alarmingly, approximately 40% of individuals with diabetes develop DN [97]. In a noteworthy study conducted by Zhang's team, they conducted an analysis of differentially expressed tsRNAs in primary mouse tubular epithelial cells subjected to high glucose (HG) treatment using high-throughput sequencing. Remarkably, they identified a total of 554 differentially expressed tsRNAs, with 54 of them specifically expressed in the HG group. One particular tsRNA of interest, tRF-1:30-Gln-CTG-4, displayed a significant reduction in expression levels following HG treatment. Notably, a similar decrease in tRF-1:30-Gln-CTG-4 expression was also observed in the serum of patients with DN. Intriguingly, the researchers found that overexpressing tRF-1:30-Gln-CTG-4 in renal tubular epithelial cells led to a reduction in extracellular matrix deposition induced by HG, suggesting a potential protective role [98]. In a subsequent phase of their investigation, the researcher examined diabetic patients with and without albuminuria, identifying six differentially expressed tsRNAs (tRF5-GluCTC, tRF5-AlaCGC, tRF5-ValCAC, tRF5-GlyCCC, tRF3-GlyGCC, and tRF3-IleAAT) [99]. These findings provide compelling evidence supporting the potential involvement of tsRNAs in diabetic kidney injury, suggesting their significance as promising biomarkers and potential therapeutic targets for DN.

tsRNAs and Kidney Cancer and Transplantation

Now, many studies on tsRNAs focus on various types of tumors, such as gastrointestinal tumors, pancreatic cancer, breast tumors, liver cancer, and so on [100–103]. There are many types of kidney cancer, of which renal cell carcinoma (RCC) accounts for about 90% of all kidney cancers [104]. The most common RCC is clear cell renal cell carcinoma (ccRCC), which accounts for 75% of all cases [105]. In renal tumors, ccRCC has been shown to be associated with tsRNAs. Ellinger et al. [106] showed that tsRNAs could be used as biomarkers for ccRCC. The expression levels of 5′tiRNA (5′-tRNA-Arg-CCT, 5′-tRNA-Glu-CTC, 5′-tRNA-Leu-CAG, and 5′-tRNA-LES-TTT) in serum and tissues of patients were down-regulated, and tsRNAs may also be related to the stage and grade of tumors [106]. In addition, tsRNAs have also been preliminarily explored in the field of kidney transplantation. Enver Akalin's team identified 30 differentially expressed tsRNAs in transplant glomerulopathy patients, compared with normal allograft function

[107]. Further studies on renal tumors and transplantation and tsRNAs are scarce, and more in-depth studies are needed.

Discussion

Although a growing number of studies have focused on tsRNAs, there are still many problems to be solved. First of all, there is not unified naming system and standardized writing way of tsRNAs. Notably several databases on tsRNAs have been developed and established, such as tRFdb, MINTbase, tRFexplorer, tRF2Cancer, and OncotRF [108], these databases have provided us the precise sequence of each tsRNA obtained as well as their basic biological characters. Second, the breakdown of tsRNAs is also rarely reported. The mechanisms responsible for the degradation and removal of tsRNAs are still not fully understood. In addition, despite the fact that tsRNAs have been reported to be involved in the process of NS with various etiologies, the exact mechanisms underlying tsRNAs remain to be elucidated.

Besides, the detection techniques of tsRNAs are also challenging. Whether detected by sequencing or Northern blot, tsRNAs must be pretreated first. Because tsRNAs contain a variety of specific RNA modifications, such as 3′ -phosphoric acid (3′-P),2 ′,3′ -cyclic phosphoric acid (2′3′-cP), and RNA methylations including m^1A, m^3C, m^1G and $m^{2,2}G$ and 3-methylcytidine (m^3C), and these modifications can block or interfere with the detection process [109, 110]. In order to discover modified sncRNAs that escape conventional RNA-Seq, Todd M Lowe's group has developed enzymatic treatment protocols to address specific RNA modifications [109]. More recently, Qi Chen's team has discovered a new sequencing method, PANDORA-seq, which uses a combinatorial enzyme processing to remove key RNA modifications and more broadly and accurately reveals previously unrecognized modified sncRNAs in mouse and human tissues and cells [110]. Nevertheless, whether there are other undiscovered terminal modifications in tsRNAs, as well as the inevitable degradation of tRNA during sequencing operations, still require further study.

tsRNAs hold promise as a novel noninvasive biomarker. Saumya Das's group has demonstrated that tsRNAs outperform miRNAs in distinguishing various stress responses and exhibit higher sensitivity under different stress conditions, such as nutritional deprivation (glucose and serum deprivation), hypoxia, and oxidative stress. Notably, they observed identical tsRNAs in different cell types under the same stress, implying the presence of specific tsRNAs as potential "universal markers" [111]. This discovery offers a valuable direction for exploring the etiology of kidney disease, and in the future, the expression profile of tsRNAs could potentially help determine the underlying causes of the disease. Moreover, the specificity and sensitivity of tsRNAs provide solid theoretical support for their potential as clinical biomarkers for renal diseases. For instance, Shen's team was the first to employ tsRNAs as a diagnostic indicator for SLE patients [95].

While tsRNAs have shown promise as indicators for predicting early renal tissue damage, their widespread adoption in clinical practice remains limited. Presently, related studies on tsRNAs in kidney diseases are relatively scarce, with a notable absence of research on secondary nephropathies like IgA nephropathy and polycystic kidney disease. Furthermore, current tsRNAs research primarily centers on tumor biology, neurological disorders, and infectious diseases. In the context of kidney diseases, studies are mostly focused on differential tsRNAs expression in disease models and their potential as biological markers for diagnosis and prognosis. The lack of in-depth studies elucidating the specific mechanisms of tsRNAs in kidney disease underscores the need for further research in this field.

Conclusion

Studies of tsRNAs have revealed their biological roles in regulating of mRNA stability, transcription, protein translation, direct interaction with proteins and as epigenetic factors. Based on current work, tsRNAs may play an emerging biological role in AKI through translational reprogramming and inhibition of apoptosis. Moreover, they have been implicated in the pathogenesis of various kidney disorders, including CKD, NS, LN, DN, and kidney cancer. tsRNAs could serve as promising biomarkers as well as therapeutic target in kidney diseases. However, to fully grasp their complexities and clinical implications, further comprehensive studies on tsRNAs in renal diseases are warranted in shaping the future of kidney research and healthcare.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Dan Li and Xian Xie wrote the manuscript. Ni Yin and Xueqin Wu revised the manuscript. Bin Yi made suggestions. Hao Zhang and Wei Zhang finished the final revision.

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