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REVIEW

N6-methyladenine RNA Methylation Epigenetic Modification and Kidney Diseases

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RNA methylation modification is a rapidly developing field in epigenetics. N6-methyladensine (m^6A) is the most common internal modification in eukaryotic mRNA. m^6A group regulates RNA splicing, stability, translocation, and translation. Enzymes catalyzing this process were termed as writers, erasers, and readers. Recent studies have focused on exploring the role of RNA methylation in human diseases. RNA methylation modifications, particularly m^6A, play important roles in the pathogenesis of kidney diseases. In this review, we provide a brief description of m^6A and summarize the impact of m^6A on acute and chronic kidney disease (CKD) and possible future study directions for this research.

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KEYWORDS: AKD; AKI; CKD; eraser; reader; writer

Kidney disease diagnosed with objective measures of kidney structure damage or function decline has been recognized as a major public health burden.[1] Acute kidney injury (AKI) refers to a rapid decline in renal function associated with a dramatic increase in adverse outcomes. An estimated 17 million hospitalized patients per year experience AKI with significant increases in mortality, hospitalization length, and other serious comorbid conditions.[2] CKD is a progressive disorder with irreversible poor outcome and high morbidity and mortality that occurs commonly in the general adult population.[3] AKI and CKD are increasingly recognized as related entities representing a continuum of disease. Conditions of impaired kidney function unsuitable to be included in the criteria for either AKI or CKD but requiring clinical care are defined as acute kidney disease (AKD) to fill the gap between AKI and CKD.[4,5]

With high-throughput sequencing technology, epigenetic modifications have been identified and demonstrated to play important roles in regulating gene expression at transcriptional, translational, and posttranslational levels in human diseases. DNA methylation was first described in 1953,[6] and histones and noncoding RNA can be modified.[7] RNA methylation is a key process in the epigenetic regulation of posttranscriptional gene expression.[8] There are various types of RNA methylation, such as m^6A, C5-methylcytosine, N1-methyladenosine, and so on.[9] Abnormal epigenetic regulation mechanisms are involved in the occurrence of various diseases, including kidney diseases. Studies of RNA methylation mechanisms in kidney diseases have mainly focused on the role of m^6A.

This review provides an overview of RNA methylation modifications, focusing on m^6A methylation, and explores the role of m^6A in the pathogenesis of kidney diseases.

M^6A RNA METHYLATION MODIFICATION

An Overview of m^6A

m^6A is regarded as the addition of a methyl group to the sixth position nitrogen atom of adenine. Discovered in 1974,[10] this is the most common methylation modification in eukaryotic RNA, accounting for more than 80% of RNA methylation.[11,12] Since 2012, the advanced high-throughput sequencing, including methylated RNA immunoprecipitation sequencing (MeRIP-seq), has facilitated the identification of m^6A.

These biotechnics have enabled studies of m^6A methylation levels and methylated sites in

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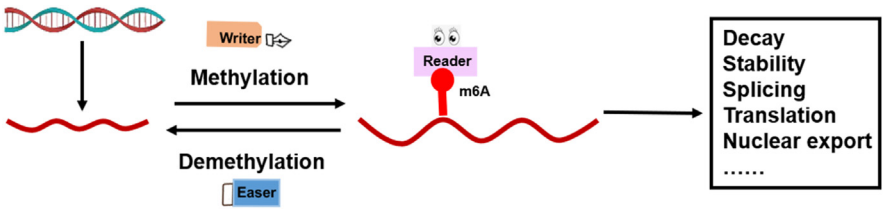

Figure 1. m^{6}A modification process and molecular function. Three types of enzymes mediate m^{6}A modification process: writers, erasers, and readers. Writers often form a multiprotein complex to catalyze RNA methylation, whereas erasers demethylate RNA that has been previously methylated. Next, modified base sites are recognized by readers, which fine tune the expression of modified transcripts to affect specific biologic functions of RNA, including, splicing, intracellular transport, translation, and stability.

transcriptomes.[13,14] In mammals, m^{6}A is most often located in 3 regions, including the 3′ untranslated regions, protein-coding regions, and especially long exons positioned near the termination codon. m^{6}A methylation often occurs on adenines of the RRACH RNA nucleotide sequence (where R=A or G ribonucleotides and H=U, A, or C nucleotides).[14,15]

m^{6}A affects RNA biological functions by influencing transcription, splicing, localization, translation, and stability, and by posttranscriptional regulation of gene expression. Furthermore, m^{6}A modification participates in diverse physiological and pathological processes.[16] (Figure 1)

Enzymes Involved in m^{6}A

Three classes of enzymes are involved in m^{6}A methylation modification, namely RNA methyltransferases (writers), demethylases (erasers), and methylation recognition protein (readers).[17] (Table 1)

m^{6}A Writers

Writers are methyltransferases that transfer methyl groups to RNA by forming an m^{6}A methyltransferase complex (MTC).[18] Three writers are core components in MTC, namely *METTL3*, *METTL14*, and *WTAP*.

METTL3, a catalytic subunit, binds S-adenosyl methionine (SAM) and replaces the hydrogen that is attached to sixth nitrogen atom of adenine with a methyl group provided by SAM. *METTL14* is highly homologous to *METTL3*. A disrupted SAM-binding motif presents in *METTL14* sequence, which indicates that it has no catalytic activity. Instead, *METTL14* serves as an RNA-binding protein that enhances *METTL3* methylation activity.[17] *METTL3* and *METTL14* often form a heterodimer and fulfill a key catalytic role.

WTAP, the third core component in MTC, has no methyltransferase activity but greatly enhances methyltransferase activity while interacting with the *METTL3-METTL14* heterodimer.[19] *WTAP* was originally identified as a splicing factor that binds to the Wilms' tumor 1 (WT1) protein and is essential for the cell cycle and early embryonic development in mammals.[20] WT1, a podocyte-specific transcription factor, is essential for glomeruli development and podocyte function.[21,22]

Recent studies have described a role for *WTAP* in human diseases via regulating WT1. *WTAP* may function as an oncogene or may regulate WT1 expression in human cancers. The *WTAP*-WT1 axis also participates in vascular smooth cell proliferation.[23,24] To date, there is no report about the mechanism of *WTAP* by regulating WT1 expression in kidney diseases. Therefore, this is an important future topic in kidney diseases.

Other components identified in MTC include the virus-like m^{6}A methyltransferase-associated protein, RNA-binding motif protein 15/15b, zinc finger CCCH-type containing 13, Cbl proto-oncogene like 1, and others. These components mostly serve as regulatory subunits that coordinate *METTL3* activity.[25-29]

Table 1. Enzymes involved in m6A

Writer	Eraser	Reader
METTL3	*FTO*	*YTHDC1-2*
METTL14	*ALKBH5*	*YTHDF1-3*
WTAP		*HNRNPA2B1*
METTL5		*HNRNPC*
METTL16		*IGF2BP1-3*
TRMT112		*FMRP*
VIRMA		*FMR1*
RBM15/15b		*LRPPRC*
ZCCHC4		*MRB1*
ZC3H13		*ELAVL1*
CBLL1		*eIF3*

m^{6}A Erasers

In contrast to the methylation writers, m^{6}A demethylases are responsible for removing SAM from adenines in RNA. Therefore, demethylases are named erasers. In eukaryotes, 2 demethylases, *FTO* and *ALKBH5*, have been identified. Both belong to the AlkB family of DNA repair enzymes.[30-32] *FTO* mostly distributes in the cellular nucleus. Its C-terminal domain can demethylate mRNA and further regulates gene expression.[33] By catalyzing mRNA demethylation, *ALKBH5* is also engaged in the nuclear export and processing of mRNA,[34] in addition to its role in mRNA stability, splicing, and translation.

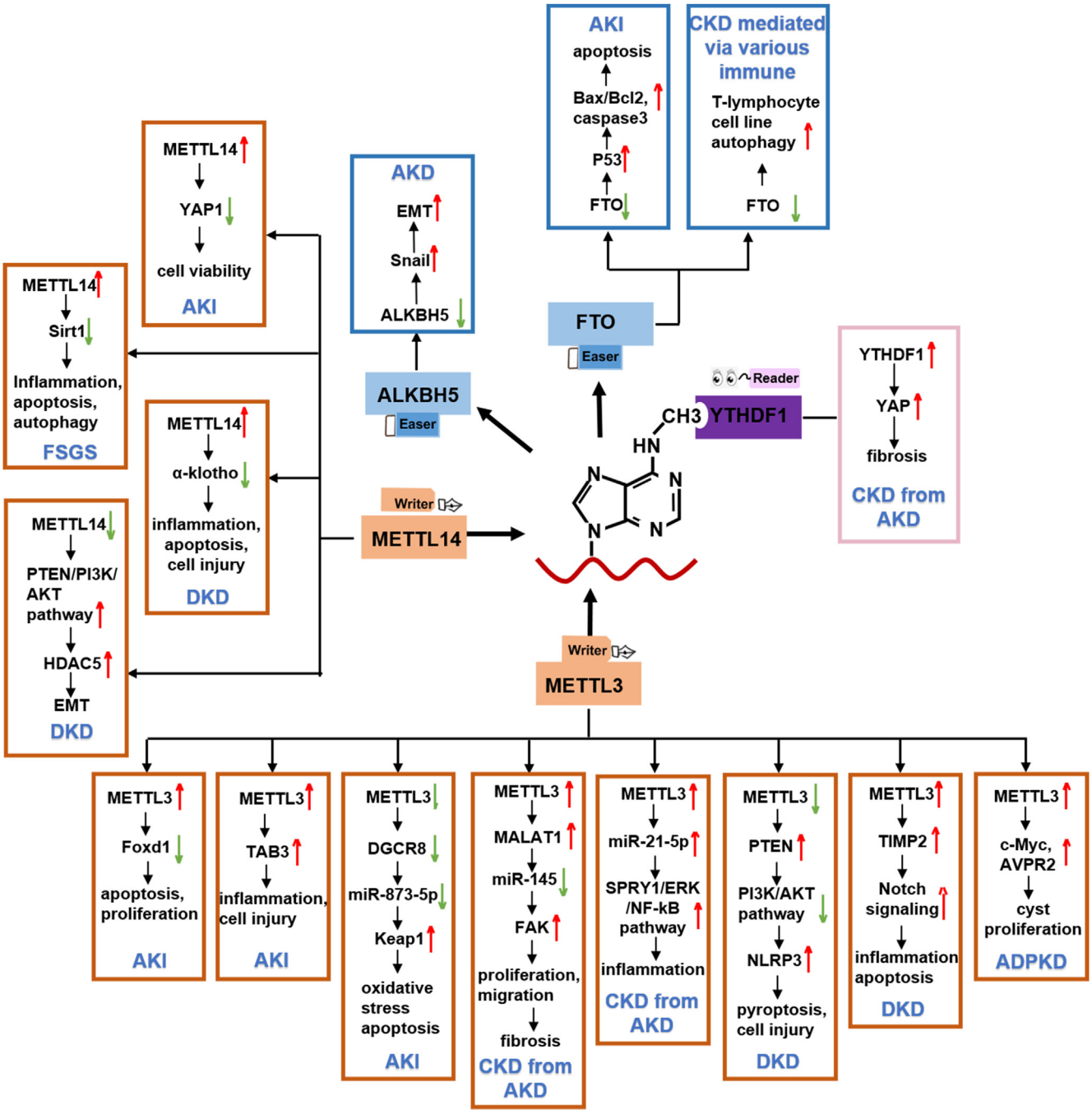

Figure 2. Role of m^{6}A modification in kidney diseases. Writers, erasers, and readers catalyze m^{6}A methylation modification through modulating mRNA and related signaling pathways in kidney diseases. ADPKD, autosomal dominant polycystic kidney disease; AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; DKD, diabetic kidney disease; EMT, epithelial-mesenchymal transition; FSGS, focal segmental glomerulosclerosis.

m^{6}A Readers

The evidence that m^{6}A acts on the modified transcripts including mRNA is based on it recognizing the binding sites of RNAs and the methylated proteins. These enzymes are named as readers.[35] During m^{6}A scanning of RNA, readers recognize and bind m^{6}A-modified RNAs and further recruit different RNA-binding proteins to their mRNA targets. Readers may also induce a change in the secondary structure of target mRNAs.[36,37] Currently, the most well characterized readers in eukaryotes have been identified as *YT521*-B homology (YTH) domain-containing family proteins. These proteins are divided into 3 subclasses, namely YTH N^6-methyladenosine family (*YTHDF1-YTHDF3*), *YTHDC1*, and *YTHDC2*. *YTHDF1*, *YTHDF2*, and *YTHDF3* and *YTHDC2* mainly locate in the cytoplasm.[38]

YTHDF2 modulates RNA decay, whereas *YTHDF1* and *YTHDF3* regulate the translation efficacy of their

Table 2. The regulatory machinery of m6A in kidney diseases

Disease	Models	Location	Materials	Methylation	Enzyme	Expression	Mechanism	Reference
AKI	I/R	Tubulointerstitum	H/R-treated NRK-52E cells I/R-induced rat kidney (2 d)	Up	*METTL3*	Up	Foxd1	61
		Tubulointerstitum	H/R-treated HK-2 cells I/R-induced mice kidney (3 d) AKI patient renal biopsies	Up	*METTL14*	Up	YAP1	62
	Cisplatin	Tubulointerstitum	Cisplatin-treated HK2 cells Cisplatin-induced mice kidney (3 d)	Up	*FTO*	Down	P53, Bax/Bcl-2, Caspase-3	65
		Tubulointerstitum	Cisplatin-treated TECs Cisplatin-induced mice kidney (3 d) AKI patient renal biopsies	Up	*METTL3*	Up	TAB3, IGF2BP2	68
	CIN	Tubulointerstitum	Colistin-treated mRTECs Colistin-induced mice kidney (7 d)	Down	*METTL3*	Down	Keap1/Nrf2, DGCR8, miR-873	71,72
	LPS	Tubulointerstitum	LPS-exposed TECs LPS-induced mice kidney (3 d)	Up	*METTL3*	Up	TAB3, IGF2BP2	68
	TNF	Tubulointerstitum	TNF-treated TECs	Unknown	*METTL3*	Up	TAB3, IGF2BP2	68
AKD	UUO	Tubulointerstitum	UUO mice kidney (3 d)	Up	*METTL3* *FTO*	Up Down	Unknown	68
	UUO	Tubulointerstitum	TGF-β–treated HK-2 cells UUO mice kidney (7 d)	Up	*ALKBH5*	Down	Snail	80
CKD	From AKD	Tubulointerstitum	TGF-β–treated HK-2 cells UUO mice kidney ON patient renal biopsies	Up	*METTL3*	Up	MALAT1/miR-145/FAK	85
		Tubulointerstitum	UUO mice kidney (3–14 d)	Up	*METTL3*	Up	MiR-21-5p, SPRY1/ERK/NF-kB	79
		Tubulointerstitum	TGF-β–treated MMCs UUO mice kidney (14 d) CKD patient fibrotic kidney	Unknown	*YTHDF1*	Up	YAP	87
	FSGS	Glomeruli	ADR-treated podocytes ADR-induced mice kidney (6 wk) FSGS patient renal biopsies	Up	*METTL14*	Up	Sirt1	91
	DKD	Glomeruli	HG-treated MPC-5 cells	Down	*METTL3*	Down	Pyroptosis, NLRP3, PTEN/PI3K/Akt	93
		Glomeruli	HG-treated MPC5 cells STZ-induced mice kidney (12 wk) db/db mice kidney DKD patient renal biopsies	Up	*METTL3*	Up	TIMP2, IGF2BP2-dependent	94
		Glomeruli	HG-treated HRGECs db/db mice kidney DKD patient renal biopsies	Up	*METTL14*	Up	α-klotho	95
		Tubulointerstitum	HG-treated HK-2 cells STZ-induced mice kidney (8 wk)	Down	*METTL14*	Down	PTEN, PI3K/Akt, HDAC5	96
	LN	Glomeruli and tubulointerstitum	LN human biopsies (separate glomeruli, tubulointerstitum, and whole kidney tissue samples)	Unknown	*NMETTL3* *WTAP* *YTHDC2* *YTHDF1* *FMR1* *FTO*	Down	m6A regulator signature, comprised METTL3, WTAP, YTHDC2, YTHDF1, FMR1, and FTO, was downregulated and could distinguish LN and healthy individuals	105
	ADPKD	Inherited	Ksp-Cre, Ksp-rtTA, tetO-Cre and Pkd1F/F, Pkd1RC/RC mice kidney ADPKD human renal tissues	Up	*METTL3*	Up	SAM, cAMP and c-Myc	109
	Age-related	Whole kidney	Rat kidney with different ages (27, 36, and 96 wk)	Unknown	*WTAP* *ALKBH5* *FTO*	Up Down Up	Unknown	113
	CKD mediated via various immune	Immune cells	Indoxyl sulfate–stimulated Jurkat T cells PBMCs from patients with stage 5 CKD	Down	*FTO*	Up	T-cell autophagy	116

ADPKD, autosomal dominant polycystic kidney disease; ADR, Adriamycin; AKD, acute kidney disease; AKI, acute kidney injury; CIN, colistin-induced nephrotoxicity; CKD: chronic kidney disease; DKD, diabetic kidney disease; FA, folic acid; FSGS, focal segmental glomerulosclerosis; HG, high glucose; HK-2 cell, human kidney epithelial cell; H/R, hypoxia/reoxygenation; HRGEC, human renal glomerular endothelial cell; I/R, ischemia-reperfusion; LN, lupus nephritis; LPS, lipopolysaccharide; NRK-52E cell, rat renal epithelial cell; MPC-5, mouse podocyte; mRTEC, mouse renal tubular epithelial cell; ON, obstructive nephropathy; PBMC, peripheral blood mononuclear cell; STZ, streptozotocin; TEC, tubular epithelial cell; TGF, transforming growth factor; TNF, tumor necrosis factor; UUO, unilateral ureteral obstructive.

target mRNAs.[39-41] By contrast, *YTHDC1* is a nuclear m^{6}A reader that can facilitate alternative splicing of pre-RNA and nuclear export of mRNA.[42-44] m^{6}A methylation relies on the readers such as *YTHDC2* and other m^{6}A recognition proteins including heterogeneous nuclear ribonucleoprotein A2B1, heterogeneous nuclear ribonucleoproteins C, fragile X mental retardation protein, *IGF2BP*, and many others.[45-51]

The process of m^{6}A RNA methylation starts from the formation of MTC-containing writers, particularly at RNA sites. The methylation can be reversed by erasers, indicating that this process is dynamic and reversible. Readers can recognize the information on RNA methylation modification and further contribute to the process of translation and degradation of modified RNA.[45]

The Biological Function of m^{6}A in Kidney Diseases

As the most well-studied posttranscriptional modification of mRNA, m^{6}A is involved in development (e.g., nervous system development) and pathogenesis (e.g., cancer and metabolic diseases). m^{6}A performs these functions by regulating the expression of target key genes, as recent work has shown.[52-55]

With regard to kidney diseases, there are established roles for m^{6}A in AKI, AKD, CKD including CKD from AKD, focal segmental glomerulosclerosis (FSGS), diabetic kidney disease (DKD), lupus nephritis (LN), autosomal dominant polycystic kidney disease (ADPKD), age-related kidney dysfunction, and CKD mediated via various immune (Figure 2 and Table 2).

AKI

AKI is a potentially severe complication in patients because of high morbidity and mortality.[56] In intensive care unit settings, the prevalence is up to 50%.[57] In response to injury, a repair process of tubular epithelial cells ensues and includes dedifferentiation, proliferation, and redifferentiation. Growing evidence suggests that epigenetic machinery may distinctly modulate the long-term effects of AKI on kidney tissues.[58]

Ischemia-Reperfusion–Induced AKI

Ischemic and septic acute tubular necrosis are the predominant causes of AKI in hospitalized and intensive care unit patients, accounting for 37.1% and 78.6% of mortality rate, respectively.[59] Renal ischemia/reperfusion injury animals and hypoxia/reoxygenation-treated kidney tubular cells are clinically relevant in *in vivo* and *in vitro* models to mimic AKI caused by cardiac-pulmonary bypass in clinical practice.[60] In hypoxia/reoxygenation-exposed rat renal epithelial cells (NRK-52E) and ischemia/reperfusion-induced AKI rat model, *METTL3* expression and RNA m^{6}A levels are upregulated. As assessed by MeRIP-seq followed by MeRIP-qRT-PCR and quantitative qRT-PCR in ischemia/reperfusion mice kidney, *Foxd1* mRNA is downregulated and gene methylation is increased. These alterations likely contribute to renal injury by regulating apoptosis and cell proliferation.[61]

Similarly, levels of m^{6}A methylated RNA and *METTL14* expression are elevated in human kidney tubular epithelial (HK-2) cells following hypoxia/reoxygenation injury and in ischemia/reperfusion-induced AKI mouse model.[62] To further explore regulatory mechanisms, Xu *et al.*[62] transfected hypoxia/reoxygenation-induced HK-2 cells with *METTL14* siRNA. They also established a *Mettl14* knockout mouse model. Through MeRIP-seq and MeRIP-qRT-PCR analysis, they confirmed *YAP1* as a downstream target of *METTL14*. Specifically, they showed *YAP1* expression is downregulated, with the most deregulated m^{6}A signal located near the stop codon of *YAP1* mRNA. This study demonstrates that the role of *METTL14* in AKI progression relies on the methylation of *YAP1* gene and the suppression of *YAP1* protein expression. Moreover, kidney biopsies from patients with AKI also show increasing m^{6}A level and *METTL14* mRNA expression.[62]

Cisplatin-Induced AKI

Chemotherapeutic agent cisplatin is more slowly metabolized in kidney cells than in blood, resulting in its accumulation in kidney cells, particularly in renal tubular epithelial cells.[63] Apoptosis of renal tubular epithelial cells usually occurs several hours after the injection of cisplatin and peaks at 48 hours to 72 hours.[64] In HK-2 cells and in kidneys from mice treated with cisplatin, eraser *FTO* is downregulated and m^{6}A methylation is increased, leading to an increased p53 expression. After treating cisplatin-induced AKI mice with meclofenamic acid, an *FTO* inhibitor, m^{6}A expression increases and kidney injury is exacerbated through p53-mediated apoptosis pathways.[65]

Shen *et al.*[66] studied the m^{6}A methylome in kidneys from cisplatin-induced AKI mice. First, they identified differentially methylated genes and differentially methylated m^{6}A sites in 2 comparisons: an injury group versus a control group (I vs. C, IvC) and a berberine-pretreated injury group versus an injury group (T vs. I, TvI). Next, using gene ontology and Kyoto Encyclopedia of Genes and Genomes databases, they found that differentially methylated genes are enriched in metabolic processes and cell death in IvC, whereas in TvI, differentially methylated genes are enriched in tissue development. Furthermore, several differentially methylated m^{6}A sites and differentially methylated genes involved in important pathways

related to cisplatin-AKI show opposite methylation or expression trends in both the IvC and TvI comparisons.[66]

m^{6}A RNA profiles combined with microarray profiles are performed in kidneys from cisplatin-induced AKI mice. After exposure to cisplatin, the protein levels of *METTL3* and *WTAP* are increased, whereas *FTO* protein level is decreased. These findings are consistent with the trend in global m^{6}A changes, whereby Mettl14 and Alkbh5 protein levels are decreased. Likewise, 618 mRNAs and 98 lncRNAs show differential methylation patterns between control and cisplatin groups. Interestingly, the increased methylated RNA levels are predominantly involved in metabolic processes.[67]

In addition to this study of the m^{6}A methylome in cisplatin-induced AKI, another study has also examined the role of m^{6}A in AKI caused by various stimuli. Wang *et al*. [68] focused on the study of m^{6}A RNA methylation in AKI caused by various approaches. *METTL3* expression is consistently induced in tubular epithelial cells exposed to cisplatin, tumor necrosis factor, or lipopolysaccharides (LPS). Through sequencing and intervention experiments, the authors identified *METTL3* as promoting inflammation and injury via enhancing m^{6}A RNA methylation, via the increased stability of TGF-β–activated kinase 1 (*MAP3K7*) binding protein 3 (*TAB3*) through *IGF2BP2*-dependent mechanisms. The global RNA m^{6}A content is upregulated in a murine model of cisplatin-induced AKI, which suggests a role in tubular injury or response to injury *in vivo*. Further, upregulated METTL3 expression was also detected in AKI patient biopsies in the study by Wang *et al*.[68] Genetic (e.g., RNAi) and pharmacologic inhibition of *METTL3* attenuates renal injury and inflammation in AKI.

Colistin-Induced Nephrotoxicity

Colistin is a widely used antibiotic effective in the treatment of infections caused by multidrug-resistant Gram-negative bacteria.[69] However, up to 60% of patients develop colistin-induced nephrotoxicity.[70] To clarify the underlying mechanisms, Wang *et al*.[71] exposed mouse renal tubular epithelial cells to colistin and administered colistin to mice; m^{6}A assays were performed. In colistin-stimulated mouse renal tubular epithelial cells, *METTL3* interacted with the microprocessor subunit protein *DGCR8*. Furthermore, microRNAs (miR)-873-5p was regulated by *METTL3*-mediated m^{6}A modification, enhancing *DGCR8* recognition of pri-miR-873 and facilitating miR-873-5p maturation. Mature miR-873-5p inhibited the expression of its target, Kelch-like ECH-associated protein-1 (Keap1), and activates the nuclear respiratory factor (Nrf2)/heme oxygenase-1 pathway, which reduced oxidative stress and apoptosis.[71]

Another report showed that renal m^{6}A expression was significantly decreased in mice receiving 15 mg/kg of colistin by i.v. route twice a day for 7 days, accompanied by decreasing expression of *METTL3*. Renal *METTL3* expression is significantly correlated with apoptosis-related proteins. The data suggest that m^{6}A methylation modifications contribute to oxidative stress–mediated apoptosis in colistin-induced AKI.[72]

Cell Proliferation and Inflammation Under LPS Condition

LPS is used experimentally to mimic sepsis and infection-induced inflammation. Renal cells and mice kidney treated with LPS mimic sepsis-induced AKI *in vitro* and *in vivo* respectively.[73,74] Moreover, under the stimulation of LPS, cells secrete a variety of inflammatory cytokines, resulting in inflammatory response and cell damage, consistent with the pathological manifestations of kidney repair after septic AKI.[75,76] Mesangial cells are a stromal cell type unique to the glomerulus and contribute to the response to injury.[77] Recent reports have described alterations in the m^{6}A epitranscriptome profile in LPS-induced mouse mesangial cells *in vitro*, with a goal of understanding the molecular features of m^{6}A modification in the pathogenesis of glomerulonephritis. Integrating MeRIP-seq with RNA-seq analyses, 64 genes manifested differential m^{6}A modification and expression levels are found in LPS groups compared with control groups. Of these genes, 5 displayed hypermethylation and upregulation, 42 displayed hypermethylation and downregulation, 11 displayed hypomethylation and upregulation, and 8 displayed hypomethylation and downregulation. Biological processes and pathways that conducted these genes were related to coagulation, fatty acid oxidation, apoptosis, complement, and peroxisome proliferator activator signaling pathways, and several of these genes have been implicated in immune and inflammatory responses.[78]

Inflammatory Reaction and Injury in Response to Tumor Necrosis Factor In Vitro

The functions of *METTL3* in response to inflammatory stimuli have been examined in detail. Researchers used tumor necrosis factor–stimulated HK-2 cells to conduct MeRIP-seq analysis and RNA-seq with or without silencing of *METTL3*. The results showed that TAB3 is a potential target of *METTL3*. They concluded that *METTL3* promotes renal inflammation and by increasing *TAB3* m^{6}A RNA methylation while increasing *TAB3* mRNA stability.[68]

AKD in Early Stage of Unilateral Ureteral Obstruction

AKD is a transition term from AKI to CKD.[5] A relevant animal model was considered at day 3 or day 7 after unilateral ureteral obstruction (UUO) in mice because α-SMA and epithelial-mesenchymal transition (EMT) were increased on day 3 and day 7 after UUO.[79,80] In our previous study, α-SMA and PCNA increased on day 5 after UUO.[81] Wang *et al*. performed MeRIP-seq followed by Kyoto Encyclopedia of Genes and Genomes enrichment analysis in 3-day UUO mice kidney and found m^{6}A methylation pattern to be closely related to inflammatory pathways. Using an m^{6}A enzyme-linked immunosorbent assay, they found that m^{6}A RNA modifications were substantially elevated in UUO nephropathy. The mRNA and protein abundance of *METTL3* was upregulated, whereas *FTO* mRNA and protein abundance was lower in UUO nephropathy than in controls.[68] The renal total m^{6}A levels increased, and there was a marked repression of *ALKBH5* on day 7 after UUO in mice. Pretreatment of genistein, an angiogenesis inhibitor, reverses *ALKBH5* loss and mitigates renal fibrosis through regulation of the zinc finger transcriptional factor *SNAIL1* and EMT markers.[80]

Chronic Kidney Disease

Previous studies have shown that epigenetic modifications promote renal fibrosis and progression of CKD by modulating the abnormal expression of genes involved in inflammation, EMT, and fibrosis.[82,83] Emerging evidence suggests that m^{6}A methylation modification is also involved in the development of CKD through the above pathological mechanisms.

CKD from AKD

Severe or persistent AKI often results in maladaptation and incomplete kidney repair, leading to tubular inflammation, EMT, and renal fibrosis, and eventually progresses to CKD.[84]

Liu *et al*.[85] investigated whether m^{6}A methylation was involved in the regulation of lncRNA *MALAT1* in HK-2 cells exposed to TGF-β. Global m^{6}A levels were elevated in TGF-β–treated HK-2 cells. *METTL3* positively modulates *MALAT1* via m^{6}A modifications, which could affect the *MALAT1*/miR-145/FAK pathway in promoting renal fibrosis. In UUO mice kidney of renal fibrosis, activation of the *MALAT1*/miR-145/FAK axis was also detected, and antagonism of this axis was demonstrated for antifibrotic drug dihydroartemisinin *in vivo*.[85]

Although most studies agree that particular functional miRs promote renal fibrosis, the maturation process of miRs remains to be fully characterized.[86] *METTL3*-mediated m^{6}A modification may promote miR-21-5p maturation by promoting recognition and processing of pri-miR-21. Follow-up studies suggest that the mature miR-21-5p promote inflammation by activating the SPRY1/ERK/NF-κB signaling pathway and ultimately drive renal fibrosis.[79]

Xing *et al*.[87] reported that *YTHDF1* binds *YAP* mRNA, promoting its translation in cultured mouse mesangial cells, and YAP siRNA also inhibits *YTHDF1* expression. This indicates a positive feedback loop involving *YTHDF1* and YAP, potentially promoting renal fibrosis. The researchers established a triple-intervention tubulointerstitial fibrosis mouse model, involving 14-day UUO, high-dose folic acid administration and unilateral ischemia-reperfusion injury. *YTHDF1* is significantly upregulated in this mouse model.[87]

In contrast, another study of the epitranscriptomic profile in the UUO (1, 3, 4, 7, and 14 days) mouse model reports that global m^{6}A levels of renal RNA are generally decreased, accompanied by decreased expression of *METTL3* and *METTL14* RNA and increased expression of *FTO* RNA; these changes may be responsible for the changes of total m^{6}A in RNA at particular time points. Using combined analyses of MeRIP-seq and RNA-seq, researchers identified 173 significantly different m^{6}A peaks. These peaks correspond to 91 genes, most of which are implicated in the processes of EMT, leukocyte migration, inflammation, and fibroblast activation, all pathways associated with progressive renal interstitial fibrosis.[88] YTHDF1 protein is also present in human fibrotic kidney tissues and is more abundant than in control tissues, and its expression is positively correlated with YAP expression.[87]

FSGS

FSGS is a manifestation of podocyte injury that can be summarized as 6 syndromes, most of which have multiple causes.[89] Models of podocyte injury and depletion have been used to investigate FSGS pathogenesis.[90] To clarify the role of m^{6}A modification in podocytopathies, Lu *et al*.[91] performed a dual-luciferase reporter assay in cultured human podocytes stimulated with Adriamycin (doxorubicin) or advanced glycation end products. The results indicate that *METTL14* promotes *SIRT1* mRNA m^{6}A modification and degradation. *METTL14* knockdown alleviates podocyte injury, characterized by activation of autophagy and inhibition of apoptosis and inflammation. Moreover, the authors observed elevated m^{6}A RNA levels and upregulated *METTL14* expression in kidneys from Adriamycin-induced FSGS in mice and from the *db*/*db* mice model of diabetic nephropathy. *METTL14* expression is also increased in renal biopsy samples

from patients with FSGS, diabetic nephropathy, and minimal change disease. This suggests that the assessment of the m^{6}A RNA levels and *METTL14* expression could be used as a novel diagnostic biomarker of progressive podocytopathies.[91]

DKD

DKD begins with hyperglycemic stimuli, which alters the biology of nearly all types of renal cells ranging from glomerulus, tubulointerstitum, to the surrounding vasculature. Both damage of glomerular cells, including mesangial cells, podocytes, and endothelial cells, and injury of tubular cells contribute to the progression of diabetic nephropathy.[92] Several studies show that m^{6}A modification is involved in the development of DKD, by regulating IGF2BP and effecting the dysfunction of diverse renal cells.[93-96]

Podocytes play an important role in maintaining the integrity of the glomerular filtration barrier.[97] Two studies have highlighted the mechanism of *METTL3*-mediated m^{6}A methylation modification in podocyte injury in DKD. Liu *et al*. examined podocyte pyroptosis, a regulated form of inflammatory cell death, and the mechanism by which *Abelmoschus manihot* (total flavones of abelmoschus manihot) flavones protect podocytes. In the mouse podocyte cell-5 line (MPC-5) cultured in high-glucose medium, the *NLRP3* inflammasome and the PTEN/PI3K/Akt pathway are activated. Simultaneously, there is altered expression of the 3 methyltransferases that are involved in m^{6}A modification; *METTL3* expression is downregulated, whereas the levels of *METTL14* and *WTAP* protein are unchanged. Total flavones of abelmoschus manihot flavones enhance *METTL3* methyltransferase activation in high-glucose–induced podocytes in a dose-dependent manner. Specifically, total flavones of abelmoschus manihot ameliorates pyroptosis and injury of podocytes cultured in high-glucose media by targeting *METTL3*-dependent m^{6}A modification via the regulation of *NLRP3*-inflammasome activation and PTEN/PI3K/Akt signaling.[93]

Another study of podocyte injury in DKD that includes models of both type 1 diabetes and type 2 diabetes enable a more comprehensive study of the mechanisms of DKD. In high-glucose–stimulated podocytes, *METTL3* is highly expressed and is associated with an increase in the m^{6}A modification of *TIMP2* via an *IGF2BP2*-dependent mechanism. This enhances *TIMP2* protein stability and contributes to inflammation and apoptosis through upregulating Notch pathway signaling.[94]

In vivo studies have established a role for therapeutic implications through targeting *METTL3*. Approaches included (i) a conditional podocyte *METTL3* knockout mouse in streptozotocin-induced diabetes, and (ii) silencing *METTL3* with AAV9-shMETTL3 in streptozotocin-induced diabetic mice, an approach that reduces albuminuria and tissue injury in DKD. Furthermore, there was increased expression of *METTL3* protein in podocytes in kidney biopsies from patients with DKD. The level of *METTL3* protein expression correlated positively with serum creatinine and 24-hour urinary albumin excretion. This suggests that it could be used as a noninvasive indicator of disease severity in clinical DKD.[94]

Accumulating evidence has shown that glomerular endothelial dysfunction promotes progression of DKD.[98] In human renal glomerular endothelial cells cultured under high-glucose condition and in db/db mice intervention experiments, *METTL14* exacerbated cell injury, inflammation, and cell apoptosis through m^{6}A modification of α-klotho.[95] Furthermore, *METTL14* is highly expressed in the human DKD tissues, both at mRNA and protein levels, suggesting a potential therapeutic target.[95]

In *in vitro* study of high-glucose–exposed HK-2 cells, Xu *et al*.[96] reported that METTL14 mediated PTEN m^{6}A RNA methylation and regulated the PI3K/Akt signaling pathway on *HDAC5*-mediated EMT. Specifically, m^{6}A RNA methylation level is suppressed, and this induces PI3K/Akt signaling pathway activation via *PTEN*, leading to the upregulation of *HDAC5* and finally to EMT.[96] However, their existence *in vivo* is still debated in the research field.[99] Humphreys *et al*.[100] reported that it is pericytes and not the epithelial origin of myofibroblasts that contribute to kidney fibrosis. In contrast, Inoue *et al*.[101] reported that the contribution of EMT to renal fibrosis differs among kidney disease models. Therefore, the mechanism of m^{6}A RNA methylation needs further deep investigation *in vivo*.

LN

LN is caused by autoimmune and inflammatory reactions in response to endogenous immune complexes. These processes activate complement cascades and proinflammatory pathways, injuring resident renal cells.[102] Serologic testing does not fully define the immune status of the kidney. Recent research has focused on immune aspects of kidney injury, including immune cell infiltration.[103] Furthermore, epigenetic changes induced by environmental factors contribute to the pathogenesis of LN.[104]

A comprehensive analysis of m^{6}A regulator–mediated RNA methylation modification patterns and immune signatures of human LN has been reported by Zhao *et al*.[105] In this study, expression of regulators of m^{6}A regulators expression was found to differ in glomeruli, tubulointerstitium, and whole kidney tissue, comparing

samples from patients with LN and healthy donors. Specifically, the authors identified an m^{6}A-associated RNA expression signature that included *METTL3*, *WTAP*, *YTHDC2*, *YTHDF1*, *FMR1*, and *FTO*. This signature readily distinguished between patients with LN and healthy donors. On the basis of 18 m^{6}A regulators identified in glomeruli, 2 distinct m^{6}A subtypes are determined in LN, with significant differences in m^{6}A-associated gene expression, immune microenvironments, biological functional pathways, and clinical characteristics. Importantly, 7 m^{6}A markers are shown to correlate with GFR, indicating that they may be potential prognostic biomarkers.[105]

ADPKD

ADPKD manifests many tubular-derived cysts that expand over time, resulting in massive enlargement of both kidneys. Approximately 85% of affected individuals develop kidney failure.[106-108] Ramalingam *et al*.[109] first reported that the *METTL3*-m^{6}A axis participates in the pathogenesis of tubular cyst growth in ADPKD. In this study, high levels of m^{6}A and *METTL3* and methionine-SAM expression, the contributors for all methylation reactions, are demonstrated in multiple ADPKD mouse models. *METTL3* promotes cyclic adenosine monophosphate and cMyc signaling via increasing methylation and translation of *AVPR2* and cMyc mRNA, both of which enhance renal cyst proliferation. Moreover, m^{6}A content is also increased in kidney tissues of patients with ADPKD. The authors suggest 2 complementary preventive or treatment strategies for ADPKD, namely dietary methionine restriction and a potential *METTL3* inhibitor therapeutic.[109]

Age-Related Kidney Dysfunction

Aging is accompanied by numerous intrinsic processes (e.g., thymic involution) and extrinsic stimuli (e.g., infection, obesity), and these processes may impair immune response or promote tissue inflammation, including in the kidney.[110] To investigate the role of RNA methylation in glucose and lipid metabolism,[111,112] Aquila *et al*.[113] measured global levels of m^{6}A residues in total RNA samples extracted from the heart, liver, and kidney of differently aged rats (27, 36, and 96 weeks of age), which had been fed for 6 months with standard diet or low-calorie diet. The investigators' goal was to assess the impact of nutrition on age-related epigenetic RNA modifications. In the kidney, a progressive increase in m^{6}A levels across the life span was observed with standard diet, and low-calorie diet accelerated this phenomenon. The authors also evaluated the expression of writer, reader, and eraser genes that encode enzymes involved in m^{6}A. Writers, including *WTAP*, demonstrate progressively increasing expression with age. Readers also show increased expression with age. Similarly, expression of the erasers *ALKBH5* decreases and *FTO* (also known as alpha-ketoglutarate-dependent dioxygenase) increases between 27 and 36 weeks of age. In response to low-calorie diet, significant variations occur mainly in the expression levels of the readers. RNA expression of *IGF2BP1*, *IGF2BP2*, *YTHDF1*, and *YTHDF2* increased at age 27 weeks, and that of *YTHDF1* and *YTHDC1* increased at age 36 and 96 weeks, respectively. Meanwhile, RNA expression of *YTHDC2*, *IGF2BP2*, and *YTHDC1* genes decreased at 27, 36, and 96 weeks of age, respectively.[113]

CKD Mediated via Various Immunological Factors

CKD is often asymptomatic and is easily missed in diagnoses in the early stages. When patients develop clinical manifestations, they often progress to kidney failure.[114] Substantial evidence supports a critical role for autophagy in kidney physiology and pathology.[115] In peripheral blood mononuclear cells from patients with stage 5 CKD, m^{6}A abundance is significantly downregulated and *FTO* expression is elevated. Studies using the Jurkat human T-lymphocyte cell line as *in vitro* experimental model confirmed that the uremic toxin indoxyl sulfate activates autophagic flux by modulating *FTO* and RNA m^{6}A modifications. Notably, knockdown of *FTO* or inhibiting the m^{6}A by 3-deazaadenosine impeded the effects of indoxyl sulfate on autophagy activation. The investigators suggested 3 implications of m^{6}A levels in patients with CKD as follows: indicators of autophagy function, markers for multiple organ function, and a therapeutic target.[116] (Table 2)

APPLICATIONS AND FUTURE DIRECTIONS

The detection of dysregulated m^{6}A modification levels and abnormally expressed m^{6}A-related regulatory pathways in patients has implications for diagnosis and therapy to human kidney diseases (Table 3). Current research is mainly focused on the abnormal expression of various modified enzymes in biopsies or peripheral blood mononuclear cells, which could be used as potential biomarkers for the diagnosis, progression, and prognosis of kidney diseases. Moreover, these abnormally expressed enzymes can interact with their downstream transcription factors to affect mRNA synthesis process and promote or inhibit the occurrence and development of kidney diseases. RNA methylation modification is a dynamic and reversible process; reversing aberrant RNA methylation by targeting m^{6}A regulators in kidney disease might delay the progression of kidney disease and increase kidney survival.

Table 3. Diagnostic, therapeutic implications and future opportunities

Diagnostic implications

Disease	Specimens	Enzyme	Expression	Conclusion of authors	Reference
AKI	Renal biopsies	*METTL14*	Upregulation	Positively correlate with sCr	62
AKI	Renal biopsies	*METTL3*	Upregulation	Unknown	68
CKD from AKD	Renal tissues	*YTHDF1*	Upregulation	Unknown	87
FSGS	Renal biopsies	*METTL14*	Upregulation	Unknown	91
MCD	Renal biopsies	*METTL14*	Upregulation	Unknown	91
DKD	Renal biopsies	*METTL3*	Upregulation	Positively correlate with URTP and creatinine negatively correlate with eGFR	94
DKD	Renal biopsies	*METTL14*	Upregulation	Unknown	95
ADPKD	Renal tissues	*METTL3*	Upregulation	Unknown	109
CKD	PBMCs	*FTO*	Upregulation	Unknown	116

Therapeutic implications

Animal models	Intervention	Approaches	Dose and duration	Effects	
I/R-induced AKI mice	METTL14 knockout	Unknown	Unknown	Attenuate kidney injury Reduce sCr, BUN	62
Cis-AKI mice	Meclofenamic acid (*FTO* inhibitor)	IP	1 h before and 24 h and 48 h after cisplatin injection, 10 mg/kg	Inhibit FTO Promote renal damage Increase apoptosis	65
Cis-AKI mice	*METTL3*-cKO	Unknown	Unknown	Reduce renal dysfunction, inflammation, apoptosis	68
Cis-AKI mice	AAV9-packaged *METTL 3* knockdown plasmid	Renal pelvis injection	1×10^{12} virus genome/ml	Reduces renal inflammation, apoptosis	68
Cis-AKI mice	Cpd-564	IP	12 h before cisplatin injection and 24, 48, and 72 h after cisplatin injection, 20 mg/kg	METTL3 inhibitor Reno-protective effects	68
UUO mice	Genistein (increased *ALKBH5*)	IP	24 h before the UUO, 10 mg/kg	Restored ALKBH5 loss Reduce inflammatory Reduce fibrosis	80
UUO mice	YTHDF2 siRNA	IV	100 nM in saline once every 3 days	Inhibit YTHDF1 Minimize renal fibrosis	87
ADR-induced FSGS mice	Podocyte-specific deletion of *METTL14*	Unknown	Unknown	Alleviate podocyte injury Inhibit inflammation Inhibit apoptosis Promote autophagy	91
STZ-induced DKD mice, db/db DKD mice	Podocyte-specific deletion of *METTL3*; AAV9-shRMETTL3	Unknown	Unknown	Reduce kidney injury Reduce podocyte loss	94
db/db DKD mice	rAAV-*METTL14*	Unknown	Unknown	Promote renal injury	95
STZ-induced DKD mice	HDACi TSA (*METTL14* agonist)	IP	0.5 mg/kg 3 times per week	Decrease EMT, ECM accumulate	96
Pkd1F/RC-KO mice	Pkd1F/RC-Mettl3-DKO	Unknown	Unknown	Slow cyst growth	109

Future opportunities

In vitro models	Relevant in vivo models	Target	Intervention	Effect of intervention	
H/R-treated NRK-52E cells	I/R-induced AKI	*METTL3*	siRNA transfection	Inhibit cell apoptosis and alleviate H/R injury	61
H/R-treated HK-2 cells	I/R-induced AKI	*METTL14*	siRNA transfection	Protect cell against H/R-reduced cell viability	62
Cis-treated HK-2 cells	Cisplatin-induced AKI	*FTO*	MA stimulation FTO plasmid or siRNA transfection	MA inhibit FTO and promote apoptosis FTO overexpression block the pro-apoptotic effect of MA knockdown of FTO-promoted apoptosis	65
LPS/Cis/TNF treated HK-2 cells or mTECs	LPS/Cis/TNF-α–induced AKI	*METTL3*	siRNA transfection	Reverse inflammation and cell injury	68
Cis-treated HK-2 cells	Cpd-564	*METTL3*	Coculture with cisplatin	Inhibit inflammatory reaction and apoptosis	68
Colistin-treated mTECs	CIN-induced AKI	*METTL3*	Overexpression plasmid transfection	Reduce oxidation stress and apoptosis	71
TGF-β–treated HK-2 cells	UUO-induced CKD	*ALKBH5*	Genistein-treated HK-2 cells Overexpression vector transfection	Restore ALKBH5 and reduce inflammatory renal fibrosis	80

(Continued on following page)

Table 3. (Continued) Diagnostic, therapeutic implications and future opportunities

Future opportunities					
In vitro models	**Relevant in vivo models**	**Target**	**Intervention**	**Effect of intervention**	
TGF-β–treated HK-2 cells	UUO-induced CKD	*METTL3*	siRNA transfection	Attenuate cell viability (EMT), proliferation, migration	85
TGF-β–treated MMCs	UUO-induced CKD	*YTHDF1*	siRNA transfection	Minimize renal fibrosis	87
ADR-treated podocytes	ADR-induced FSGS	*METTL14*	siRNA transfection	Alleviate inflammation, apoptosis, autophagy	91
HG-treated MPC5 cells	DKD	*METTL3*	TFA coculture with HG siRNA transfection	Ameliorate pyroptosis, injury in podocytes	93
HG-treated MPC5 cells	DKD	*METTL3*	siRNA transfection	Alleviate inflammation and apoptosis	94
HG-treated HRGECs	DKD	*METTL14*	siRNA transfection	Alleviate inflammation, apoptosis, promote cell proliferation	95
HG-treated HK-2 cells	DKD	*METTL14*	pcDNA3.1-METTL14 plasmid transfection	Inhibit EMT and reverse the effect of high-glucose stimulation	96
Indoxyl sulfate–stimulated Jurkat T cells	CKD mediated via various immune	*FTO*	siRNA transfection	Attenuates the result of indoxyl sulfate lowering m6A levels	116

ADPKD, autosomal dominant polycystic kidney disease; ADR, Adriamycin; AKI, acute kidney disease; BUN, blood urea nitrogen; CIN, colistin-induced nephrotoxicity; Cis, cisplatin; CKD, chronic kidney disease; DKD, diabetic kidney disease; ECM, extracellular matrix; eGFR, estimated glomerular filtration rate; EMT, epithelial-mesenchyme transition; FA, folic acid; FSGS, focal segmental glomerulosclerosis; HG, high glucose; HK-2 cell, human kidney epithelial cell; H/R, hypoxia/reoxygenation; HRGEC, human renal glomerular endothelial cell; IP, intraperitoneal injection; I/R, ischemia-reperfusion; IV, intravenous injection; LN, lupus nephritis; LPS, lipopolysaccharide; MA, meclofenamic acid; MCD, minimal change disease; MPC-5, mouse podocytes; mTEC, mouse renal tubular epithelial cell; NRK-52E cell, rat renal epithelial cell; ON, obstructive nephropathy; PBMC, peripheral blood mononuclear cell; sCr, serum creatinine; siRNA, small interfering RNA; STZ, streptozotocin; TGF, transforming growth factor; TFA, total flavones of abelmoschus; TSA, trichostatin A; URTP, 24-h total urinary protein; UUO, unilateral ureteral obstructive.

Currently, the understanding of RNA methylation and biological function is nascent, and new experimental methods are being discovered productively. Deep explorations of the relationship between RNA methylation and kidney diseases are ongoing. In addition, there are various epigenetic modifying agents such as histone modifiers (histone deacetylases inhibitors), DNA methylation inhibitors (5′-azacytidine and 5-aza-2′ -deoxycytidine), and DNA demethylation activators (hydralazine) that have been tested in preclinical studies of kidney diseases.[117]

Although many novel therapeutic m^{6}A methylation targets have been reported, currently there is no drug related to RNA methylation modification that is on clinical trial for kidney diseases. Therefore, high-quality preclinical studies to target methylation-related enzymes are needed to provide strong evidence to convince pharmaceutical researchers to conduct clinical trials in treating kidney diseases.

CONCLUSION

m^{6}A RNA methylation plays important roles in epigenetic modification in kidney diseases including AKI, AKD, and CKD. The enzymes involved in m^{6}A methylation process are classified into writers, erasers, and readers. The dysregulated m^{6}A modification levels are involved in the development and pathogenesis of kidney diseases. The cell- and tissue-specific m^{6}A methylation enzymes have diagnostic and therapeutic implications and future opportunities for gene-targeted treatment in kidney diseases. Currently, high quality preclinical studies that target m^{6}A methylation enzymes need to be widely spread. Clinical trials of the agents that regulate m^{6}A RNA methylation are lacking and need future investigations.

DISCLOSURE

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