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Histone Modifications in Acute Kidney Injury

Jun Wang[a] Fengchen Shen[a] Feng Liu[a] Shougang Zhuang[a, b]

[a]Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China;
[b]Department of Medicine, Rhode Island Hospital and Alpert Medical School, Brown University, Providence, RI, USA

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Abstract
Background: Acute kidney injury(AKI) is a serious clinical problem associated with high morbidity and mortality worldwide. The pathophysiology and pathogenesis of AKI is complex and multifactorial. In recent years, epigenetics has emerged as an important regulatory mechanism in AKI. ***Summary:*** There are several types of histone modification, including methylation, acetylation, phosphorylation, crotonylation, citrullination, and sumoylation. Histone modifications are associated with the transcription of many genes and activation of multiple signaling pathways that contribute to the pathogenesis of AKI. Thus, targeting histone modification may offer novel strategies to protect kidneys from AKI and enhance kidney repair and recovery. In this review, we summarize recent advances on the modification, regulation, and implication of histone modifications in AKI. ***Key Messages:*** Histone modifications contribute to the pathogenesis of AKI. Understanding of epigenetic regulation in AKI will aid in establishing the utility of pharmacologic targeting of histone modification as a potential novel therapy for AKI.

Introduction

Acute kidney injury (AKI) is manifested by a rapid decline of renal function and is associated with high morbidity and mortality. It is responsible for approximately 1.7 million deaths per year worldwide and is associated with increased length of hospital stay among hospitalized patients as well as high costs [1–3]. AKI is also a critical risk for chronic kidney disease and end-stage renal disease. The primary causes of AKI include sepsis, ischemia/reperfusion (I/R) or nephrotoxicity (i.e., radiocontrast agents, NSAIDs, etc.). Pathologically, AKI is characterized by the damage of renal tubules, vascular dysfunction, and a robust inflammatory response [4]. Despite the growing impact of AKI on the global burden of health, there is no satisfactory treatment for AKI. Thus, further

Karger@karger.com
www.karger.com/kdd

Correspondence to:
Shougang Zhuang, gangzhuang@hotmail.com

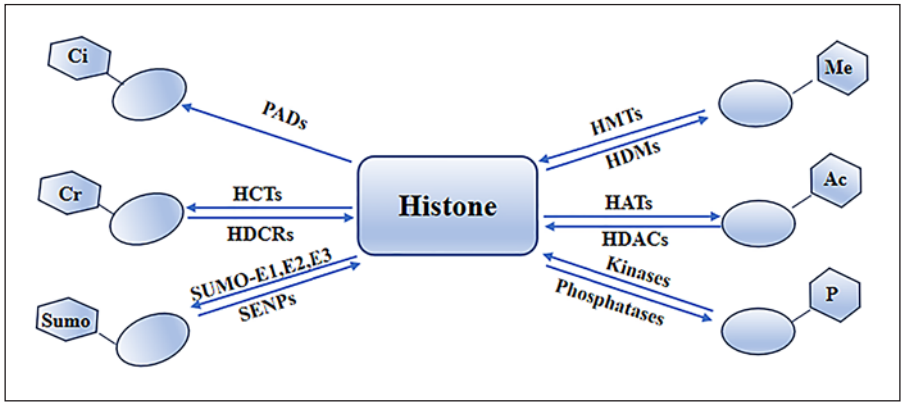

Fig. 1. Various types of histone modifications and their regulations in AKI. Histone methylation, acetylation, phosphorylation, crotonylation, and sumoylation are positively regulated by histone methyltransferases (HMTs), histone acetyltransferases (HATs), protein kinases, histone crotonyltransferases (HCTs), SUMO-specific activating (E1), conjugating (E2), and ligating (E3) enzymes (Sumo-E1, E2, E3), respectively, and negatively regulated by histone demethylases (HDMs), histone deacetylases (HDACs), protein phosphatases, decrotonylase (HDCR), and sentrin/SUMO-specific proteases (SENPs), respectively. Histone citrullination is catalyzed by peptidyl-arginine deiminase enzymes (PADs). Me, methylation; Ac, acetylation; P, phosphorylation; Ci, citrullination; Cr, crotonylation; Sumo, sumoylation.

understanding the mechanism underlying AKI would help to identify targets for the development of novel therapies to counter injury at the cellular level.

Emerging evidence indicates that epigenetic regulation contributes to the pathogenesis of AKI and is common to all insults. Epigenetics refers to heritable changes in gene expression that do not involve changes in the nucleotide sequence [5]. Several epigenetic mechanisms, including histone modifications, DNA methylation, and noncoding RNAs, can induce changes to a phenotype without changing the genotype. Among them, histone modification is an important epigenetic mechanism underlying AKI [6]. Post-translational modifications (PTMs) of histone proteins can alter chromatin structure and the docking sites for transcription regulators, leading to transcriptionally permissive or repressive states. Histones, including core histones (H2A, H2B, H3, and H4) and linker histones (H1 and H5), are highly conserved, basic, or positively charged proteins. They can associate with negatively charged DNA through electrostatic interactions and package it into highly condensed and ordered chromatin structure units called nucleosomes [7]. Histone modifications involve the covalent, PTMs of core histone proteins and include, but are not limited to, acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, citrullination, biotinylation, crotonylation, and ADP ribosylation. These modifications occur predominantly on the amino-terminal tails of the histones and are thought to change the structure of chromatin or provide docking sites for transcriptional regulators to either positively or negatively regulate gene expression [8]. In this article, we provide an overview of some major histone modifications that occur in AKI, including methylation, acetylation, phosphorylation, crotonylation, citrullination, and sumoylation (Fig. 1), and discuss their roles and mechanisms involved in various pathological processes of AKI, including cell death, inflammation, and repair/regeneration (Table 1).

Histone Acetylation in AKI

Histone acetylation, one of the most extensively studied forms of histone modification, involves the addition of a negatively charged acetyl group to the lysine of core histones by histone acetyltransferases (HATs). Acetylation of histone on lysine residues neutralizes the positive charges, thus destabilizing the histone-DNA interaction, subsequently changing the condensed chromatin to an open, loosely packed chromatin structure and consequently allowing access for the recruitment of activators or inhibitors of gene transcription [9, 10]. This process can be reversed by the action of histone deacetylases (HDACs). Thus, histone acetylation is a dynamic event that can be regulated by HATs and HDACs. Families of HATs include Gcn5-related N-acetyltransferases (GCN5, p300/CREB-binding protein [CBP]-associated factor [PCAF]), MYST (MOZ, Ybf2/Sas3), Sas2 and Tip60, co-

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Table 1. Histone modifications in AKI

Histone modifications	Models	Inhibitors	Mechanisms	Ref
Acetylation	Mouse model of I/R injury	Silence HDAC1	Enhance renal dysfunction and increase the expression of the inflammatory cytokines	16
	Mouse model of I/R injury	TSA (a pan-HDAC inhibitor)	Improve renal function	17
	Zebrafish larvae AKI induced by Gentamicin	m4PTB (a pan-HDAC inhibitor)	Increase survival and proliferation of renal tubular epithelial cells	18
	Mouse model of I/R injury		Accelerate recovery, reduce postinjury tubular atrophy and interstitial fibrosis, increase the regenerative capacity of actively cycling renal tubular cells	
	Human renal proximal tubular HK-2 cells; rat renal proximal tubular NRK-52E cells	TM-2-51 (a HDAC8 activator)	Inhibit mitochondrial fission and apoptosis	19
	Wistar rats of I/R injury	VPA (a pan-HDAC inhibitor)	Anti-inflammatory	20
	Mouse model of AKI induced by FA or rhabdomyolysis	MS-275 (a class I HDAC inhibitor)	Worsen renal dysfunction, increase NGAL expression, enhance apoptosis and caspase-3 activation, and impair renal regeneration	21
	Renal proximal tubular cells	MS-275 or silence HDAC1, 3, or 8	Decrease cell proliferation and reduce expression of cyclin D1 and PCNA	21
	Murine model of AKI induced by rhabdomyolysis	TA (a HDAC6 inhibitor)	Reduce Scr and BUN levels, attenuate renal tubular damage in injured kidneys, reduce number of apoptotic cells and inactivated caspase-3	22
	Murine model of cisplatin-induced AKI	TA	Lessen renal dysfunction, attenuate renal pathological changes, reduce expression of NGAL and Kim-1, decrease tubular cell apoptosis	23
	Cisplatin-induced renal tubular cells	TSA	Cytoprotective effects	24
	Mouse model with cisplatin-induced AKI	TSA	Suppress inflammation and tubular epithelial cell apoptosis	25
	Murine model of glycerol-induced AKI	23BB (a HDAC6 inhibitor)	Reduce tubular cell apoptosis	27
	Murine model of cisplatin-induced AKI	23BB	Reduce tubular cell apoptosis	28
	Cultured renal tubular cells	Silencing of PCAF	Reduce H3K18Ac and decrease inflammatory factors	30
	Murine model of LPS induced AKI	Romidepsin (FK228) (a HDAC 1/2 inhibitor)	Reduce the degree of renal injury and expression of CYP2E1, inhibit the oxidative stress	31
	Murine model of SA-AKI induced by LPS	TMP195 (a IIa HDAC inhibitor)	Mitigate renal tubular cell apoptosis and inflammation	32
	Cisplatin-induced nephrotoxicity	Resveratrol (a Sirt1 activator)	Attenuate structural and functional renal changes by reducing free radicals and inhibiting inflammatory cell infiltrates	34
	Septic AKI			35
	Murine model of cisplatin-induced AKI	SRT1720 (a Sirt1 activator)	Attenuate tubular cell injury through deacetylation of p53 and NF-κB p65 and preservation of peroxisome function	36
	Murine model of I/R injury	SRT1720	Attenuate renal injury	37
	Murine model of AKI induced by CLP and LPS	3-MA (the autophagy inhibitor); SIRT1 siRNA	Deduce the transcriptional activity of autophagic proteins in the nucleus	41
	Murine model of AKI induced by CLP	SRT1720; Ex527 (a Sirt1 inhibitor)	Down-regulate the stability of interaction between SIRT1 and HMGB1 and aggravate renal inflammation	43
	Murine model of AKI induced by CLP	SIRT3 deletion	Exacerbate kidney dysfunction, renal tubular cell injury, and apoptosis	44

Histone modifications	Models	Inhibitors	Mechanisms	Ref
	Cisplatin-treated Sirt3 KO mice	SIRT3 deficiency	Increase renal tubular apoptosis and inflammation and aggravate renal injury	45
	Murine model of cisplatin-induced AKI	SIRT5 siRNA	Inhibit mitochondrial apoptotic, reduce mitochondrial fragmentation/fission, maintain mitochondrial homeostasis	48
	Murine model of I/R injury	SIRT6 deficiency	Exacerbate G2/M phase arrest and hypoxia-induced tubular epithelial cell damage	49
	Murine model of cisplatin-induced AKI	SIRT6	Attenuate renal injury by repressing the expression of ERK1/2 through deacetylating histone 3 at Lys9	50
	Murine models of AKI induced by I/R	SIRT7 deletion	Upregulate the phosphorylation of P65 and the action of NF-κB	51
	Murine models of AKI induced by cisplatin		Upregulate the NF-κB expression, decrease the expression of TNF-α	52
	Murine model of cisplatin-induced AKI	Curcumin (a HAT inhibitor)	Restore renal function, reduce lipid peroxidation, and enhance the levels of reduced glutathione and activities of superoxide dismutase and catalase	53
	Murine model of I/R injury	Curcumin	Reduce serum and tissue MDA, NO, and PC	54
Methylation	Murine models of AKI induced by I/R and FA	3-DZNep (a EZH2 inhibitor)	Improve renal function and decrease renal tubule damage	60
	Murine model of I/R injury	3-DZNep	Reduce renal dysfunction and tubular injury by regulating p38 signaling, apoptosis, and inflammation	61
	Cultured mTECs	3-DZNep	Inhibit cisplatin-induced activation of caspase-3, apoptosis, loss of cell viability	62
	Murine model of I/R injury	MM-102 (a MLL1 inhibitor)	Attenuate renal senescence, inflammation, and fibrosis	64
	Murine models of AKI induced by FA	PTIP deletion	Block mitosis in surviving tubular cells	63
Phosphorylation	Renal tubular cells	PD98059 (MAPK inhibitor) or 3-aminobenzamide (ADP-ribose polymerase inhibitor)	Promote renal tubular cell survival	70
Crotonylation	Renal tubular cell and mouse model of AKI induced by FA	Crotonate	Increase SIRT3 and PGC-1α expression, decrease CCL2 expression, and protect from AKI	76
Citrullination	Rabbit model of LPS-induced AKI	Cl-amidine (a pan-PAD inhibitor)	Attenuate AKI by histopathologic scoring and decrease creatinine and BUN levels	81
	Murine model of I/R injury	2-Chloroamidine or streptonigrin (a PAD4 inhibitor)	Reduce plasma creatinine, renal tubular necrosis, inflammation, and apoptosis	82
Sumoylation	Murine model of I/R injury and cisplatin	Ginkgolic acid (a sumoylation inhibitor)	Enhance apoptosis	85

m4PTB, methyl-4-phenylthio butanoate; VPA, valproic acid; PCNA, proliferating cell nuclear antigen; mTEC, mouse renal proximal tubular epithelial cell; PGC-1α, proliferator-activated receptor-gamma coactivator 1α; 3-MA, 3-methyladenine; CLP, cecal ligation and puncture.

activator p300/CBP, nuclear receptor coactivators (e.g., ACTR/SRC-1), and other HATs (TAFII250, TFIIIC, Rtt109, CLOCK). To date, 18 mammalian HDAC proteins have been identified, which, on the basis of their domain organization and sequence homology to yeast orthologues, are divided into four classes: class I HDACs (HDAC1, 2, 3, and 8); class II HDACs (HDAC4, 5, 6, 7, 9, and 10); class III HDACs (SIRT1–7); class IV HDAC (HDAC11). Class II HDACs have been further divided into class IIa HDACs (HDAC4, 5, 7, and 9) and class IIb HDACs (HDAC6 and 10) [11, 12].

A growing body of evidence suggests that AKI is associated with changes in histone acetylation. In the renal cortex, acetylated lysines are predominantly localized in the nuclei of renal tubular cells, and acetylation-positive tubules are apparently increased in the kidney subjected to I/R insult [13]. I/R enhances histone H3 acetylation levels in a time-dependent manner in the injured kidney. The extent of histone H3 acetylation is upregulated in post-ischemia kidneys, rising from 5% at baseline to 75% at 3 weeks [14]. A study showed that I/R of the mouse kidney induced a transient decrease in histone acetylation in proximal tubular cells. During reperfusion, H3 acetylation was restored and bone morphogenetic protein 7 was induced, at least in part owing to selective down-regulation of HDAC5 [15]. Another study in a mouse model of bilateral I/R injury reported an initial increase in acetylation of H3K14 followed by a decrease to the basal level. By contrast, H4K5Ac and H4K12Ac were reduced and then restored [16]. These studies demonstrate dynamic alterations in histone acetylation during the course of AKI.

The role and mechanisms of histone acetylation in different models of AKI have been extensively studied. I/R injury can induce the expression of activating transcription factor 3 (ATF3), a transcriptional repressor in the kidney. ATF3 exerts its protective effects by down-regulating the expression of inflammatory cytokines, such as interleukin-6 and IL-12B. Mechanistically, ATF3 can recruit HDAC1 to ATF/NF-κB-binding sites and curtail the production of inflammatory cytokine genes, thereby preventing damaging inflammatory responses after renal I/R injury, while silencing of HDAC1 can enhance renal dysfunction and increase the expression of the inflammatory cytokines [17]. In I/R-induced renal injury, administration of the pan-HDAC inhibitor trichostatin A (TSA) prior to kidney ischemic damage improved renal function in the early phase after unilateral renal I/R injury and is associated with a substantial reduction of renal fibrosis [18]. Hukriede et al. [19] found that the HADC inhibitor methyl-4-phenylthio butanoate increased survival and proliferation of renal tubular epithelial cells in zebrafish larvae. In mice, treatment with methyl-4-phenylthio butanoate at 24–48 h after inducing AKI also accelerated recovery, reduced postinjury tubular atrophy and interstitial fibrosis, and increased the regenerative capacity of actively cycling renal tubular cells by decreasing the number of cells in G2/M arrest. Unlike most class I HDACs, HDAC8 protects against IR-induced AKI. This is evidenced by the observation that treatment with HDAC8 activator TM-2-51 reduces mitochondrial fission and renal tubular cell death by reducing expression of dynamin-related protein 1, a key factor required for mitochondrial fission [20]. Moreover, valproic acid, a pan-HDAC inhibitor, prevented kidney dysfunction and structural injury after kidney IRI by reducing kidney inflammatory cell infiltration and the expression of some proinflammatory cytokines (i.e., TNF-α and MCP-1) [21].

Histone acetylation is also involved in several other forms of AKI. In mouse models of AKI induced by folic acid (FA) or rhabdomyolysis, blocking class I HDAC with a highly selective inhibitor, MS-275, resulted in more severe tubular injury and worsening renal dysfunction, increased neutrophil gelatinase-associated lipocalin (NGAL) expression, enhanced apoptosis and caspase-3 activation, and impaired renal regeneration [22]. In cultured renal proximal tubular cells, inhibiting class I HDAC activity with MS-275, or silencing HDAC1, 3, or 8 with small interfering RNA induced global histone H3 hyperacetylation, decreased cell proliferation, and reduced expression of cyclin D1 and proliferating cell nuclear antigen. These data illustrated that class I HDAC activity is required for renal repair and renal tissue regeneration after AKI [22].

In contrast to class I HDACs, a HDACIIb isoform, HDAC6, plays a role in potentiating AKI. In a murine model of glycerol injection, mice developed severe acute tubular injury. Administration of tubastatin A (TA), a highly selective inhibitor of HDAC6, significantly reduced serum creatinine (Scr) and blood urea nitrogen (BUN) levels, as well as attenuated renal tubular damage in injured kidneys. HDAC6 inhibition also decreased expression of NGAL, reduced number of apoptotic cells, and inactivated caspase-3 after AKI [23]. Similar findings have also been made in a murine model of cisplatin-induced AKI [24] in which blocking HDAC6 with TA lessened renal dysfunction, attenuated renal pathological changes, reduced expression of NGAL and Kim-1, and decreased tubular cell apoptosis. In cultured human epithelial cells, TA or HDAC6 siRNA treatment also inhib-

ited cisplatin-induced apoptosis [24]. Moreover, other researchers found that the HDAC inhibitor TSA exerts a cytoprotective effect in mice against cisplatin-induced apoptosis of renal tubular cells as well [25]. TSA treatment was associated with upregulation of a novel anti-inflammatory and anti-apoptotic protein called activated microglia/macrophage WAP domain protein in tubular epithelial cells [26]. Dong et al. further demonstrated that the effects of TSA and suberoylanilide hydroxamic acid on renal tubular cells exposed to cisplatin are dose dependent: they are toxic at high-micromolar concentrations, but at concentrations <1 μmol/L, they are protective against cell death. [27].

Recently, Yan et al. [28], showed that administration of 23BB, another HDAC6 inhibitor, significantly alleviated rhabdomyolysis-induced AKI, reduced Scr and BUN levels, as well as attenuated renal tubular damage. 23BB also decreased the number of TUNEL-positive tubular cells, suppressed BAX, BAK, cleaved caspase-3 levels, and preserved Bcl-2 expression, indicating that 23BB has a potent renoprotective effect by suppressing renal tubular cell apoptosis. Moreover, 23BB protected the kidney by reducing endoplasmic reticulum stress-mediated apoptosis in tubular epithelial cells. Finally, 23BB attenuated acute kidney dysfunction and renal tubular damage in cisplatin-induced AKI [29]. Collectively, these data provide strong evidence that HDAC6 inhibition is protective against AKI induced by rhabdomyolysis or cisplatin, and suggest that HDAC6 may be a potential therapeutic target for AKI treatment.

Lipopolysaccharide (LPS) is an important cause of sepsis-induced AKI [30]. In a mouse model of septic AKI, upregulation of PCAF was associated with increased acetylation of histones, such as H3K18Ac, and expression of inflammatory genes. Silencing of PCAF in cultured renal tubular cells significantly reduced H3K18Ac, resulting in decreased expression of inflammatory factors. These results suggest that induction of H3K18Ac contributes to the upregulation of inflammatory genes in septic AKI [31]. Some researchers confirmed that in a mouse model of AKI induced by LPS, romidepsin (FK228), an inhibitor of HDAC1 and HDAC2, could reduce the levels of BUN, Scr, and cystatin C. Histologic examination of the mouse kidneys showed that treatment with FK228 reduced the degree of renal injury and expression of CYP2E1, a membrane protein, while acetylation of H3 was upregulated [32]. In other experiments, LPS increased HDAC2, HDAC5, TNF-α, and MCP-1 expression but decreased BMP-7 expression in kidney tubular epithelial cells in mice that underwent cecal ligation and puncture. Our studies also indicated that administration of the selective class IIa HDAC inhibitor TMP195 significantly reduced increases in Scr and BUN levels and renal damage in a murine LPS model of septic AKI. This was coincident with reduced expression of HDAC4, a major isoform of class IIa HDACs, and elevated histone H3 acetylation. TMP195 exerts a powerful renoprotective effect by mitigating renal tubular cell apoptosis and inflammation [33].

In addition to HDAC inhibitors, the effects of HDAC SIRT activators in AKI have been investigated. It was shown that Sirt1 overexpression in kidney tubules ameliorates cisplatin-induced AKI by inhibiting apoptotic cell death and oxidative stress [34]. Resveratrol, a naturally occurring Sirt1 activator, protects against renal tubule injury in experimental models of cisplatin-induced nephrotoxicity and septic AKI [35, 36]. However, given that resveratrol is not Sirt1-specific activator, SRT1720, a potent and specific activator of Sirt1, was studied in an animal model of cisplatin-induced AKI. The study showed that SRT1720 significantly attenuated acute renal failure and histopathological alterations in cisplatin-treated mice through suppression of apoptotic cell death, oxidative stress, and inflammation [37]. Administration of SRT1720 to mice with IRI also induced proliferation of renal tubular cells and attenuated renal injury [38]. Furthermore, resveratrol and SRT1720 enhanced resistance to apoptosis induced by oxidative stress in primary cultured mouse renal medullary interstitial cells [39]. The therapeutic effects of Sirt1 activation were associated with deacetylation of p53 and NF-κB p65 and preservation of peroxisome function [37, 40, 41]. In cecal ligation and puncture- and LPS-induced septic mouse models, the expression of SIRT1 was decreased and p53 was translocated from the nucleus to the cytoplasm, resulting in reduced transcriptional activity of autophagic proteins in the nucleus [42]. However, activation of SIRT1 could partially restore p53-induced autophagy and boost beclin-dependent autophagy [41, 42]. In addition, SIRT1 is involved in the pathogenesis of septic AKI by regulating high-mobility group (HMGB1) [43]. During septic AKI, the interaction between SIRT1 and HMGB1 was disrupted, with more HMGB1 releasing to the extracellular space, promoting renal inflammatory responses [44]. Therefore, the upregulation of SIRT1 has important therapeutic implications in septic AKI.

In sepsis-induced AKI models, SIRT3 expression protects against mitochondrial damage in the kidney by reducing oxidative stress and inflammatory cytokines [45], whereas SIRT3 deficiency increases renal tubular apoptosis and inflammation and aggravates renal injury [46].

Decreased SIRT3 expression is associated with increased severity of renal injury [47]. Recent studies suggest that SIRT3 can regulate fatty acid oxidation by deacetylating liver kinase B1 and activating AMP-activated protein kinase to reduce cisplatin-induced AKI in mice [48]. In addition to SIRT3, SIRT5 exerts anti-apoptotic effects in cisplatin-induced AKI by reducing mitochondrial fragmentation/fission and maintaining mitochondrial homeostasis [49]. SIRT6 expression was down-regulated in the kidneys of mice following IR injury, and SIRT6 overexpression inhibited G2/M phase arrest and attenuated hypoxia-induced tubular epithelial cell damage [50]. SIRT6 can also attenuate cisplatin-induced kidney injury by repressing the expression of ERK1/2 through histone 3 deacetylation at Lys9, thus inhibiting NF-κB and p53 signaling, and by reducing oxidative stress and apoptosis by activating the SIRT6/Nrf-2 pathway [51]. In contrast, knockdown of SIRT7 facilitates the recovery of cisplatin and IR-induced AKI by reducing NF-κBp65 phosphorylation and release of various proinflammatory factors [52, 53]. Thus, unlike most members of the SIRT family, SIRT7 inhibition is beneficial to prevent AKI. In rats, administration of curcumin (an inhibitor of the HAT) showed renoprotective effects in various AKI models, including cisplatin-induced nephrotoxicity, I/R injury, and LPS-induced AKI [54–56].

Together, inhibition of HDACs seems to protect the kidney in multiple forms of AKI. In contrast, activation of SIRT1, SIRT3, SIRT5, and SIRT6 exerts renoprotective effects. The diverse functional role of HDACs in AKI is associated with the expression/activation of different renal protective or/and pro-apoptotic molecules. Future studies are needed to determine the role of individual HDAC isoforms in AKI and detail mechanisms using genetic approaches and develop isoform-selective HDAC inhibitors for research and therapeutic use.

Histone Methylation in AKI

Histone methylation involves the addition of a methyl group to a basic amino acid on core histones. It can change transcription by creating docking sites for chromatin modifiers with diverse outcomes depending on whether it leaves the chromatin in the active, poised, or repressive state. Histone methylation commonly occurs in specific lysine and arginine residues at the amino terminal of the histone core. Lysine can be monomethylated, dimethylated, or trimethylated on its ε-amine group, while arginine can be monomethylated, or symmetrically or asymmetrically dimethylated, on its guanidyl group [57]. Histone H3 lysine residues (K4, K9, K23, K27, K36, K56, and K79), K20 in H4, K26 in H1, and arginine (R) residues (R2, R8, R17, and R26) in H3 along with R11, R12 in H2A, and R3 in H4 are the known methylation sites [57]. Modifications of both histone tails and residues within the core play a role in gene expression [58].

Histone methyltransferases are a class of enzymes that catalyze the methylation of lysine or arginine residues of histones. So far, more than 50 human lysine methyltransferases (KMTs) have been reported. These enzymes have high selectivity for the histone lysine residue they target and are classified into two types: KMTs and arginine methyltransferases. KMTs are further divided into two families: SET domain-containing KMTs, which include Su(var)3–9, enhancer of zeste homolog, trithorax, and non-SET domain-containing KMTs, such as the DOT1-like proteins [59, 60]. Among the arginine methyltransferases, there are three types of methylation patterns based on different arginine-binding pockets. Histone methylation plays important roles in many biological processes, including cell cycle regulation, stress response, development, and differentiation.

Enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase that trimethylates histone H3 at lysine 27 (H3K27me3). The expression of EZH2 and H3K27me3 is upregulated in murine kidneys following I/R and FA injury [61]. Inhibition of EZH2 by 3-deazaneplanocin (3-DZNep) improves renal function and decreases renal tubule damage in these two models. Inhibiting EZH2 with either 3-DZNep or its specific siRNA also promotes survival of renal epithelial cells in culture following oxidant injury [61]. In the I/R-induced AKI model, EZH2 inhibition also reduces renal dysfunction and tubular injury by regulating p38 signaling, apoptosis, and inflammation [62]. In another study, cultured mouse renal proximal tubular epithelial cells exposed to cisplatin resulted in cleavage of caspase-3, decreased cell viability, and increased H3K27me3, whereas expression levels of EZH2 were not affected. Treatment with 3-DZNeP significantly inhibited cisplatin-induced activation of caspase-3, apoptosis, loss of cell viability but did not alter levels of EZH2 and H3K27me3 in cultured mouse renal proximal tubular epithelial cells [63]. As such, further studies are needed to address the role and mechanism of EZH2 in AKI by utilizing genetic approaches.

A recent study showed that renal epithelial cell regeneration is dependent on histone H3K4 methylation. Depletion of the Paxip1 gene in mature renal proximal tubules, an essential protein in the mixed lineage leukemia

protein 3/4 complex, led to failed regeneration of damaged tubules and renal fibrosis in a murine model of AKI [64]. This suggests that mixed lineage leukemia protein 3/4-mediated H3K4 methylation is required for renal tubule regeneration and preventing renal fibrosis following AKI. In contrast, Shimoda et al. [65] showed that inhibition of MLL1, another H3K4 methyltransferase, by interrupting the MLL1/WDR5 complex with MM-102 attenuates renal senescence, inflammation, and fibrosis in mice with I/R injury. In addition, deletion of PTIP, a cofactor of MLL-mediated H3K4 methylation, leads to decreased expression of H3K4me2/3 in proximal renal tubules and interrupts the repair of renal tubules after AKI [64]. Mechanistically, PTIP deficiency suppresses proximal tubular SOX9 gene activation following injury and prevents surviving tubular cells from entering mitosis for repair [64, 66]. These data suggest that H3K4 methyltransferases may exert a different role based on their interaction with other proteins. Genetic approaches are required to further investigate the role of individual H3K4 methyltransferases in AKI.

Although many human HMS that have been identified so far, only EZH2 and MLL families have been studied in AKI. Currently, expression patterns and functional roles of other HMS in the pathogenesis of AKI remain largely unknown and need further exploration.

Histone Phosphorylation in AKI

Histone phosphorylation is another form of histone modification that changes the chromatin structure. There are 16 histone residues known to be phosphorylated in mammals [67]. Histone phosphorylation is involved in all aspects of chromatin function including transcription activation and repression, chromatin condensation, and DNA repair. Emerging evidence suggests that histone phosphorylation plays a role in cross-talk with other histone modifications (e.g., acetylation) [68]. Given that histone phosphorylation is catalyzed by kinases that are components of the signaling cascade, this post-transcriptional modification is likely to play a key role in linking signal transduction pathways to chromatin.

Studies demonstrate that phosphorylation of serines 10 and 28 of H3 and serine 32 of H2B is associated with regulation of epidermal growth factor (EGF)-responsive gene transcription [69]. As EGF and EGF receptor have been shown to be critically implicated in renal regeneration after AKI [70], it is speculated that this modification may also affect renal repair and renal functional recovery. A study demonstrated that histone H3 phosphorylation induced chromatin condensation and promoted the damage and death of renal proximal tubular cells in response to oxidative stress [71]. Prevention of H3 phosphorylation by the selective mitogen-activated protein kinase 1 inhibitor PD98059 or by the inhibition of poly (ADP-ribose) polymerase with 3-aminobenzamide promoted renal tubular cell survival [71]. Phosphorylation of the histone H2A variant H2AX at serine 139, indicative of double-strand DNA damage, has been linked to AKI in various models, including cisplatin-induced AKI and renal IRI [72–74]. Obviously, relative to other types of PTMs, less studies are conducted on the role and mechanism of histone phosphorylation in AKI. Further investigations are required to provide more information on the relationship between histone phosphorylation and AKI.

Histone Crotonylation in AKI

Histone crotonylation involves the addition of a crotonyl group to lysine residues on core histones by the actions of histone crotonyl transferases. The crotonyl group added to histones can be removed by histone decrotonylases, such as Sirt1, Sirt2, and Sirt3. Lysine crotonylation is a recently identified post-transcriptional modification. Histone crotonylation can neutralize the positive charge of lysine residues and stimulate transcription [75].

Constitutive histone crotonylation is present in different healthy tissues, including the kidney [76], and increased histone crotonylation has been described in kidney tissues in models of AKI induced by FA and cisplatin [77]. In murine tubular cells stimulated with the cytokine TWEAK, a mediator of kidney injury [78], and in kidneys from mice with AKI, histone crotonylation was increased and associated with decreased SIRT3 and proliferator-activated receptor-gamma coactivator 1α expression and increased expression of the chemokine-encoding Ccl2 gene [77]. In this context, administration of crotonate by increasing the substrate promotes histone crotonylation, increases kidney SIRT3 and proliferator-activated receptor-gamma coactivator 1α expression in vivo and in cultured cells, thereby decreasing CCL2 expression and protecting from AKI [77]. Thus, increased histone crotonylation level might have a beneficial effect on ameliorating AKI.

Histone Citrullination in AKI

Citrullination, as first described in 1958 by Rogers and Simmonds, is a post-translation modification in which an arginine amino acid is converted to a citrulline amino acid. This process depends on catalytic enzymes such as peptidyl-arginine deiminase enzymes (PADs). This modification leads to a charge shift, which affects the protein structure, protein-protein interactions, and hydrogen bond formation. The irreversible citrullination reaction is not limited to specific proteins, cells, or tissues. It can target a wide range of proteins in the cell membrane, cytoplasm, nucleus, and mitochondria [79]. At present, there are five known PAD isoenzymes (PAD1, PAD2, PAD3, PAD4, and PAD6), which are calcium-dependent proteins responsible for citrullination or the post-translational conversion of arginine to citrulline on histones [80]. PAD4 is the only PAD enzyme localized in the nucleus and is the only PAD protein detected in the kidney [81]. PAD4-mediated post-translational protein citrullination has been implicated in several inflammatory autoimmune diseases. Siddiqui et al. [82] evaluated the impact of Cl-amidine (a pan-PAD inhibitor) on AKI in a model of LPS-induced endotoxic shock in rabbits. They found that Cl-amidine treatment attenuated AKI, as evidenced by less damages of kidney tissue, and decreased Scr and BUN levels compared with control animals by 12 h after onset of sepsis. Some researchers found renal I/R injury in mice increased PAD4 activity as well as PAD4 expression in the mouse kidney. After 30 min of renal I/R, vehicle-treated mice developed severe AKI with large increase of Scr. In contrast, mice pretreated with PAD4 inhibitors 2-chloroamidine or streptonigrin significantly reduced renal I/R injury with significantly decreased Scr, renal tubular necrosis, inflammation, and apoptosis. Finally, cultured mouse kidney proximal tubules treated with recombinant PAD4 had significantly increased proinflammatory chemokine expression compared with vehicle-treated cells. Taken together, PAD4 plays a critical role in renal I/R injury by increasing renal tubular inflammatory responses and neutrophil infiltration after renal I/R [83].

In addition, it was found that the expression level of PAD4 mRNA in the kidney was sex dependent [84]. In male kidneys, circulating citH3 levels increased after IR injury, with elevated citH3-DNA interactions mediated by PAD4 and eventual release of large amounts of neutrophil extracellular trap; whereas in female kidneys, citH3 was found to remain accumulated in the cytoplasm of epithelial cells, with decreased levels of circulating citH3 and reduced neutrophil extracellular trap formation [85]. Therefore, it is reasonable to speculate that estrogen alleviates the renal damage posed by IR in women by reducing neutrophil infiltration through modulation of PAD4.

Histone Sumoylation in AKI

Sumoylation is a form of post-translational modification by which small ubiquitin-like modifiers (SUMOs) are covalently attached to target proteins to regulate their properties. It is catalyzed by SUMO-specific activating (E1), conjugating (E2), and ligating (E3) enzymes while SUMO proteins are removed from substrates by members of the SUMO1/sentrin-specific peptidase family. A study by Dong et al. [86] indicated that a dynamic change of renal protein sumoylation occurred in ischemia/reperfusion and cisplatin-induced AKI in mice and that inhibition of sumoylation with ginkgolic acid, a selective inhibitor of sumoylation, enhanced apoptosis during cisplatin incubation. This suggests a cytoprotective role for sumoylation in kidney tubular cells after injury.

Other Histone Modifications in AKI

Other histone modifications include ubiquitylation, adenosine diphosphate ribosylation, deimination, and proline isomerization. More is known about these modifications in yeast rather than mammals. There is no information available about alterations in these modifications in AKI.

Conclusions and Perspectives

AKI is a serious clinical problem. At present, there are no effective therapies to ameliorate injury, accelerate recovery, and prevent postinjury fibrosis after AKI. Given gene expression and signal transduction during AKI are affected by histone modifications, histone modifications are an interesting field to be explored for identifying novel therapeutic targets for AKI treatment. Despite numerous studies have determined the role and mechanism of various types of histone modifications in AKI, more information is needed to elucidate the role of individual modifications and their coordinate regulation in AKI. Further studies are also needed to search for more specific modulators, inhibitors, or activators of different

types of histone modification and establish the utility of pharmacologic targeting of histone modification as a potential novel therapy for AKI.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

Jun Wang, Fengchen Shen, and Feng Liu prepared the manuscript; Shougang Zhuang edited the manuscript. All the authors approved the final version of the manuscript.

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