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REVIEW

The Role of Histone H3 Methylation in Acute Kidney Injury

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Abstract: Acute kidney injury (AKI) is a clinical syndrome in which kidney function declines sharply due to various reasons. Although the morbidity and mortality of AKI are high, the mechanism of occurrence and development of AKI has not been fully elucidated, and precise prevention and treatment measures are lacking. Epigenetics is a branch of genetics that provides a new perspective to explore the pathophysiology of AKI and renal repair. A large amount of literature shows that the methylation mechanism of H3 in histones is closely related to the development of kidney diseases. The sorting out of histone H3 methylation mechanism in AKI and kidney repair can help understand the pathophysiological process of the disease more deeply. It may also provide new ideas for diagnosing and treating of the disease.

Keywords: kidney, Acute kidney injury, histone methylation, epigenetic

Introduction

AKI is a clinical syndrome characterized by a rapid decline in renal function due to several reasons. It is manifested by a quick increase in serum creatinine, a decrease in urine output, or both.[1] AKI is a serious threat to human health. Its high treatment costs and many sequelae have caused a heavy economic burden on society: about 1.7 million people die from AKI annually in the world.[2,3] The main pathological features of AKI include sublethal and lethal damage of the renal tubular cells,[4] plasma membrane is the main damage site.[5] The kidney undergoes a repair response involving epithelial cell dedifferentiation, proliferation, and re-differentiation following an injury. However, during severe or persistent injury, the kidney resorts to maladaptive repair characterized by fibrosis, vascular sparing, tubular loss, glomerulosclerosis, and chronic inflammatory infiltration of the kidney.[6,7] The kidney undergoes pathological processes such as G2/M cell cycle arrest, cellular senescence, production of pro-fibrotic cytokines, activation of pericytes and interstitial myofibroblasts.[6,9] The events ultimately result in chronic kidney disease (CKD) and end-stage renal disease.[7,8] Here, epigenetic mechanisms such as histone modifications play essential roles in the pathology of AKI and kidney repair[10,11] (Figure 1). The regulatory mechanisms of AKI pathology and renal repair are complex. Studying the methylation of histone H3 amino acid residues can provide new perspectives for the disease.

Acute injury caused by cisplatin, folic acid, ischemia-reperfusion injury (IRI)and sepsis, and chronic kidney injury due to high glucose, Unilateral Ureteral Obstruction (UUO), subtotal nephrectomy (SNx), hyperuricemia, etc., affect the methylation level of histone H3 in the kidney. Intervention of methylation at this site can effectively modulate AKI prognosis.

Histone Methylation and Demethylation in Renal Injury

H3k27

The protein Enhancer of Zeste Homolog 2(EZH2) is a methyltransferase that catalyzes the trimethylation of the 27th amino acid (lysine) of the H3 histone (H3K27) and 3-deazaneplanocin A(3-DZNep) is an inhibitor of EZH2. Blocking EZH2 with 3-DZNep attenuates the renal tubular cell death in the proximal tubule cells after renal ischemia-reperfusion

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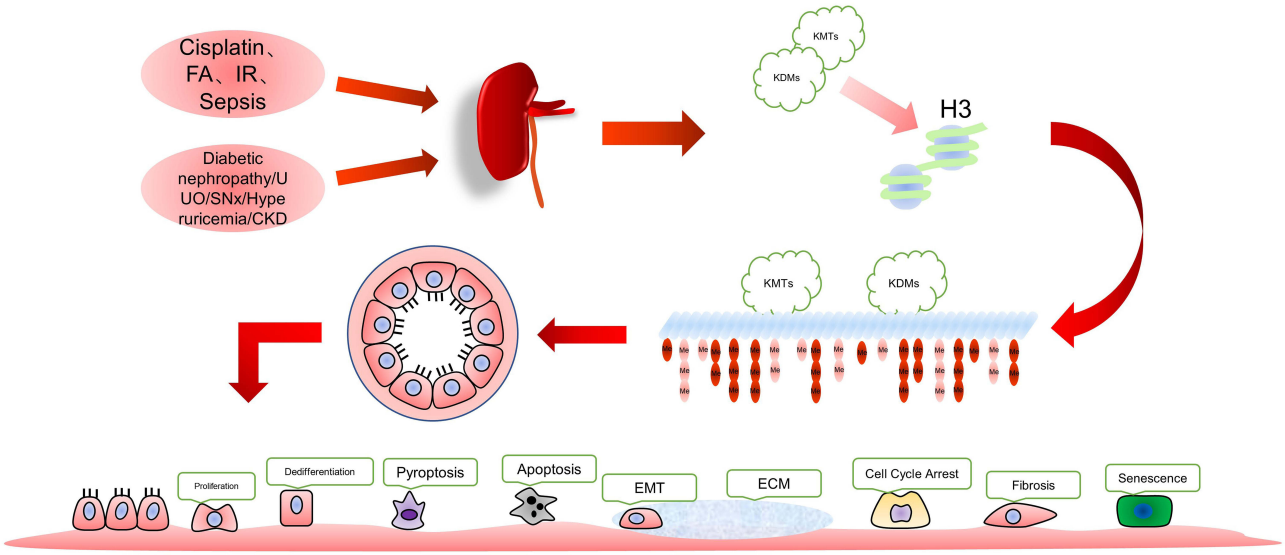

Figure 1 Various factors modulate renal cell changes by altering the methylation status of histone H3.

injury or FA(folic acid)-induced injury in experimental mice.[12] Later studies have shown that EZH2 inhibition inactivates p38, decreasing the level of active caspase-3 and pro-inflammatory molecules and reducing cell apoptosis.[13] Cisplatin, a chemotherapy drug, is one of the common causes of AKI. Animal studies or cell experiments have confirmed the following: 1. Cisplatin mediates the increased expression of the trimethylated form of histone H3 protein at the 27th amino acid (lysine) (H3K27me3) in the kidney cells. 2. 3-DZNep demonstrates a protective effect on the renal tubular cells in response to the damage induced by cisplatin. 3. The basal concentration of EZH2 has a protective effect on the kidney cells.[14] Interestingly, cisplatin did not mediate the up regulation of EZH2 in renal cells in vitro, and 3-DZNep did not change the EZH2 level in the cells after the intervention. However, in animal experiments, cisplatin administration increased EZH2, and 3-DZNep dependently inhibited EZH2 expression. Thus, the protective effect of 3-DZNep on the cisplatin-mediated renal injury was not achieved by EZH2 and/or H3K27 trimethylation.[14] At the same time, 3-DZNep treatment did not activate ERK1/2, p38 and JNK1/2. Instead, it inhibited cisplatin-induced renal tubular epithelial cell (RTEC) apoptosis and AKI through an E-cadherin dependent mechanism.[14] E-cadherin is the main component of the tubular adhesion protein. It maintains intercellular contact and cell polarity in epithelial tissue, and has a protective effect on cisplatin-induced AKI.[15] H3K27me3 and H3K9me3 participate in regulating its expression regulation.[16,17] According to evidence, 3-DZNep inhibits H3K27me3 and reduces the levels of H3K9 me3, H3K36 me3 and H3K4 me3.[18] Thus, in cisplatin- induced AKI, H3K9 me3 play a crucial role in regulating the mechanism of 3-DZNep on the repair of E-cadherin. Concerning cisplatin-related AKI, new in vitro studies on the NRK-52E cells (rat RTECs) have demonstrated that EZH2 inhibition increases the transcription by reducing H3K27 me3 in the DEPTOR promoter region. This event further inhibits the activities of mTORC1 and mTORC2, down-regulates the expression of the apoptosis inhibitory genes, and finally leads to renal tubular cell apoptosis. Meanwhile, the inhibition of EZH2 aggravates cisplatin-induced renal tubular cell injury by inactivating the mTOR complex.[19] The mechanism of H3K27 me3 in cisplatin-related AKI has been investigated further. New studies indicated that EZH2 inhibition reduces NOX4, attenuates ROS-mediated pyrolysis and protects the kidneys by regulating oxidative stress.[20] These studies provide new ideas for understanding the mechanism of EZH2 in AKI.

H3k4

In sepsis induced AKI, the level of H3K4 me3 decreases in kidneys, and the effects of anti-anxiety, sedation and analgesia are improved. α Dexmedetomidine (DEX), an α_2-adrenergic receptor agonist, inhibits the histone demethylase KDM5A, increasing the level of H3K4 me3 and protecting renal function. Thus, DEX inhibits histone deacetylase (histone deacetylase, HDAC) by participating in apparent acetylation. Further, DEX modulates AKI through histone

methylation.[21] DEX also improves renal IRI (ischemia-reperfusion injury) and its inflammatory responses by inhibiting the activation of T cells and the level of inflammatory factors.[13,22] However, the relationship between the level of histone methylation and the levels of immune cells and inflammatory factors is not yet clear. The exploration of this aspect may illuminate the role of epigenetics in kidney disease. In addition, methylation of H3K4 regulates the HMG-CoA reductase activity during AKI and abnormal cholesterol metabolism.[23,24] Table 1 shows the changes and roles of histone methylation targets in injury.

In addition to regulating the stage of kidney injury, changes in histone methylation levels also participate in post-injury repair processes. The regulation of the methylation level of histone H3 can improve the repair, which provides new thinking for blocking pathological processes such as fibrosis caused by incomplete repair. In addition to H3K27 and H3K4, H3K79, H3K9, and H3K36 are also involved.

Histone Methylation and Demethylation in Kidney Repair

H3k27

In the pathological process of kidney repair, H3K27me demonstrates similar effects in different kidney cells. In renal fibroblasts from UUO-treated mice and humans with CKD, EZH2 and H3K27 me3 are highly expressed. Moreover, inhibiting the increase in EZH2 and H3K27 me3 reduces the activation of the renal fibroblasts induced by TGFβ-1 and reduces the kidney fibrosis progress after UUO injury.[25] When the specific Jumonji domain-containing protein-3 (JMJD3) (a lysine-specific demethylase of H3K27 me3) is inhibited, the renal interstitial fibroblasts are activated and renal fibrosis after UUO and SNx is aggravated.[26] Thus, the H3K27 me3 level increase in the kidney after UUO injury, promoting fibrosis after incomplete repair. New studies show that H3K27 me3 regulates the dedifferentiation of the glomerular podocytes in kidney injury caused by diabetic nephropathy, adriamycin kidney and SNx, and protects the kidneys. The loss of H3K27 me3 promotes the dedifferentiation of podocytes after mitosis and accelerates glomerular disease. Moreover, the inhibition of lysine-specific demethylase may help improve the progression of glomerular disease.[27] Subsequent studies confirmed that the H3K27me demethylase KDM6B regulates in vitro podocyte differentiation. The podocytes in the glomeruli of patients with renal disease exhibited increased KDM6B content and decreased H3K27me3 levels,[28] consistent with the previous results. EZH2 inhibition promotes kidney oxidative stress and fibrosis induced by high glucose.[29] In the pathology of UUO injury, inhibition of EZH2 minimizes renal fibrosis by reducing renal tubular cell arrest in the G2/M phase and epithelial-mesenchymal transition (EMT).[25,30] Moreover, EZH2 is inhibited by TGF-β through miR-101b.[31] In the pathology of CKD induced by hyper uric acid, EZH2 blockade reduces the activation and proliferation of renal interstitial fibroblasts, renal tubular cell damage, apoptosis, and renal interstitial fibroblast activation and extracellular matrix (ECM) deposition.[32] The upregulation of aging-related H3K27

Table 1 Changes and Roles of Histone Methylation Targets in Injury

Kidney Histone Modification Sites	Model	Changes in Methylation Levels	Intervention and Its Targets and Effects On Targets	Change in Target Methylation (±) After Intervention and its Effect on the Kidney	References
H3K27me3	IRI/ FA(Mouse)	↑	3-DZNeP EZH2 (↓)	↓ Protection	[12]
	Cisplatin(Mouse)	↑	3-DZNeP EZH2 (↓)	↓ Protection	[14]
	Cisplatin(mTECs)	↑	3-DZNeP EZH2 (→)	→ Protection	[14]
	Cisplatin(NRK-52E)	↑	3-DZNeP EZH2 (↓)	↓ Protection	[19]
H3K4me3	LPS(Mouse)	↓	DEX KDM5A (↓)	↑ Protection	[21]

Abbreviations: mTECs, mouse renal proximal tubular epithelial cells; LPS, lipopolysaccharide; DEX, dexmedetomidine; IRI, ischemia-reperfusion injury; ↑, up; ↓, down; →, No change.

me3 in elderly mice, is primarily due to reduced JMJD3 expression in aging kidneys. Klotho is a one-way transmembrane protein highly expressed in the kidney, H3K27me3 directly binds to the Klotho promoter and inhibits Klotho gene expression.[33] It prevents and alleviates damage, promotes recovery, and inhibits fibrosis to reduce repair after kidney damage through exogenous supplementation or stimulation of endogenous Klotho recovery.[34] Briefly, in repair after kidney damage induced by factors such as folic acid, cisplatin, UUO, SNx, high glucose and aging, the presence of H3K27me3 promotes fibrosis and deteriorates the disease; inhibiting H3K27me3 has a protective effect on the kidneys. However, sepsis is one of the critical causes of AKI, and the role of trimethylation at H3K27 in kidney repair after AKI has not been elucidated.

H3k79

Disruptor of telomeric silencing 1-like (DOT1L) protein is the methyltransferase of H3K79.[35] It regulates cell cycle and cell senescence,[36,37] and increases the expression of the senescence-associated secretory phenotype (SASP).[37] Deleting the DOT1L protein by gene editing increases the renal collecting duct intercalated cell/primary cell ratio and urine volume and decreases urinary osmolality, but electrolyte metabolism remains normal in the mice.[38] The targeted destruction of DOT1L, the progenitor cell of the nephron, leads to congenital renal dysplasia. The kidney with a DOT1L mutation exhibits the phenotype of congenital nephron defect and cystic dysplasia nephropathy, indicating the role of DOT1L in the maintenance and differentiation of the progenitor cells into epithelial nephrons.[39] A study on the repair after kidney injury found that the G2/M phase tubular epithelial cell cycle arrest mediates renal fibrosis after injury.[9] Inhibition of DOT1L can blocks renal interstitial fibroblast activation and EMT along with the injury-induced inhibition of the G2/M phase cell cycle arrest. Additionally, blockade of DOT1L reduces the expression of Snail, Twist and Notch1; and inhibits injury to the kidney. Inhibition of DOT1L also inactivates several pro-fibrotic signaling molecules like Smad3, epidermal growth factor receptor, platelet-derived growth factor receptor, signal transducer and activator of transcription 3, protein kinase B, and NF-κB. At the same time, DOT1L inhibition increases the expression of PTEN (phosphatase and tensin homolog) and prevents the reduction in the renoprotective factors Klotho and Smad7.[40] In addition to the above methods, inhibition of DOT1L alleviates oxidative stress by blocking the PI3K/AKT pathway, reducing renal ischemia-reperfusion injury and post-injury fibrosis.[41] In conclusion, Dot1L is indispensable for kidney growth and development, but its inhibition in adult mice ameliorates fibrosis after kidney injury.

H3k4

The absence of H3K4 methylation has no negative impact on the kidney development and function in terms of growth and regeneration in young mice. However, the lack of H3K4 methylation results in the appearance of pathophysiological changes similar to chronic kidney disease in the kidney of old mice; these include podocyte death, reduction, interstitial fibrosis, and proteinuria.[42] The methylation of histone H3K4 is also related to the regeneration of RTECs: the renal function of the mice without H3K4 methylation is normal. However, after injury, the renal tubular repair and regeneration ability is severely damaged, mainly causing fibrosis and scars repair.[43] In fibrosis, TGF-β1 increases the methylation of H3K4 at the p21 promoter by up-regulating the H3K4 methyltransferase SET domain-containing lysine methyltransferase7/9 (SET7/9). TGF-β1 also promotes its gene expression and increases ECM gene expression.[44,45] H3k4me1 was up-regulated in UUO injury, which has been observed in rat RTECS and renal interstitial fibroblasts as well as in vivo experiments in mice. Inhibiting SET7/9 and reducing H3K4me1 alleviates renal fibrosis. The SET7/9 expression is affected by TGF β1 -Smad3 pathway regulation; correspondingly, SET7/9 expression positively correlates with the degree of interstitial fibrosis in human kidney biopsy specimens from patients with IgA nephropathy and membranous nephropathy.[46] The histone H3K4 me3 is highly expressed in the nuclei of podocytes, mesangial cells, and endothelial cells of patients with membranous nephropathy.[47] To investigate the role of this target methylation in podocytes, mice were treated with lipopolysaccharide. The histone H3K4 me3 increased in the podocytes; there was an increase in podocyte swelling, serum creatinine, and urine albumin. The inhibition of H3K4 methyltransferase reduces H3K4-me3 restores the up-regulation of cathepsin L, decreases the synaptopod in protein and the podocyte swelling induced by lipopolysaccharide.[47] Briefly, the presence of a certain amount of H3K4 methylation positively affects kidney repair after injury, but increased H3K4 methylation after injury participates in promoting kidney fibrosis.

H3k9

The role of methylation of H3K9 in kidney repair completely various among different research groups. Initial studies reported a TGF-β1-induced reduction in the H3K9me2/3 level of ECM-related gene promoters in RMC.[44] However, subsequent studies identified TGF-β1-induced upregulation of H3K9 methyltransferase G9a expression via Smad3 in the kidney of mice after UUO. Also, TGF-β1 inhibits H3K9 methyltransferase G9a reduces H3K9 me1, and inhibits renal fibrosis. Other reports indicated that the G9a immunostaining region positively correlates with H3K9me1 levels and fibrosis markers in human kidney biopsies.[48] The study also showed that H3K9me1, which reduces the Klotho promoter region, retains klotho expression.[48] This observation, provides a new perspective on the apparent regulation of Klotho protein expression. New research shows that G9a inhibits the transcription of the histone deacetylase SIRT1 through H3K9 me2.[49] Moreover, SIRT1 is regulated by Klotho expression.[50,51] Few studies have dealt with H3K9 methylation, and the contradictory of these studies are not well explanation. More in-depth studies may prompt additional information for the analysis of kidney repair after injury.

H3k36

Few studies have investigated the role of H3K36 in kidney repair. The lysine methyltransferase SET and MYND domain protein 2 (SMYD2) mediates the methyltransferase H3K36 me3. The inhibition of this protein prevents renal fibrosis and inhibits the activation and proliferation of renal interstitial fibroblasts. SMYD2 inhibition also hinders the transformation of epithelial cells to the fibrogenic phenotype, and prevents the down-regulation of the renal protective factor Smad7 under in vivo and in vitro conditions.[52] The role of H3K36 methylation in kidney repair needs further exploration.

Among the drugs used in the clinical treatment of kidney diseases, traditional Chinese medicine prescription QianyangYuyin granules are found to regulate the level of H3K4me3, inhibit the proliferation of kidney epithelial cells, and prevent kidney damage caused by hypertension.[53] Table 2 shows the changes and roles of histone methylation targets in post-injury repair.

Table 2 Changes and Roles of Histone Methylation Targets in Post-Injury Repair

Kidney Histone Modification Sites	Model	Changes in Methylation Levels	Intervention and its Targets and Effects on Targets	Change of Target Methylation (±) After Intervention and its Effect on Kidney	References
H3K27me3	High Glucose(Rat Podocytes)	↓	3-DZNeP EZH2 (↓)	↓ Damage	[29]
	Nephrotic syndrome(HPC)	↓	GSK-J4 KDM6B (↓)	↓ Not yet clear	[28]
	UUO(Mouse) CKD(Humanity/ NRK-49F)	↑	3-DZNeP/GSK126 EZH2 (↓)	↓ Protection	[25]
	UUO/ SNx(Mouse) TGFβ1(NRK-49F/mTECs)	↑	GSK-J4 JMJD3 (↓)	↑ Damage	[26]
	Adriamycin /SNx/ BKS-db (Mouse)	↓	GSK-J4 JMJD3 (↓)	↑ Protection	[27]
	Old mouse(Mouse)	↑	EED226 PRC2 (↓)	↑ Protection	[33]
	Streptozotocin(Rat/ Mouse) High sugar(MC)	↓	TGF-β EZH2 (↓) /Jmjd3, Utx (↑)	↑ Protection	[31]
	Uric acid(Mouse) Uric acid(NRK-49F/HK2)	↑	3-DZNeP EZH2 (↓)	↓ Protection	[32]
H3K79me2	0.5%FBS(NRK-49F/ RPTCs) UUO(Mouse)	↑	EPZ5676 DOT1L (↓)	↓ Protection	[40]
	H/R(HK-2) IRI(Rat)	?	EPZ004777 DOT1L (↓)	? Protection	[41]

(*Continued*)

Table 2 (Continued).

Kidney Histone Modification Sites	Model	Changes in Methylation Levels	Intervention and its Targets and Effects on Targets	Change of Target Methylation (±) After Intervention and its Effect on Kidney	References
H3K4me1/2/3and H3K9me2/3	High sugar (30 mM) (Rat MC)	↑ (H3K4me1/2/3) ↓ (H3K9me2/3)	TGF-β1 SET7/9(H3K4me1↑)	H3K4me1↑ Damage	[44]
H3K4me1	UUO(Mouse) 0.5% FBS(NRK-52E/NRK-49F)	↑	Sinaifungin SET7/9 (↓)	↓ Protection	[46]
H3K4me2/3	PTIP deletion in glomerular podocytes (Mouse)	↑	PTIP deletion H3K4 Me (↓)	↑ Damage	[42]
H3K4me3	LPS(Mouse)	↑	MLL3 shRNA H3K4 Me (↓)	↓ Protection	[47]
	Folic acid(Mouse)	?	PTIP deletion H3K4 Me (↓)	↓ Damage	[43]
	Hypertension(Rat) Ang II(HEK293T)	↓	Qianyang Yuyin Granules NNMT (↓)	↑ Protection	[53]
H3K9me1/2	UUO(Mouse) TGF-β1(NRK-49F/ NRK-52E)	↑	BIX01294/ siRNA G9a (↓)	↓ Protection	[48]
H3K9me2	IRI(Mouse) HR(HK-2)	↑	BIX01294 G9a (↓)	↓ Protection	[49]
H3K36me3	UUO(Mouse) TGF-β1(Renal interstitial fibroblasts)	↑	AZ505/ siRNA SMYD2 (↓)	↓ Protection	[52]
H4R3Me2a	UUO(Mouse) TGF-β 1(NRK-49F)	↑	AMI-1/siRNA PRMT1 (↓)	↓ Protection	[54]

Abbreviations: HPC, human podocyte cells; UUO, unilateral ureteral obstruction; IRI, ischemia-reperfusion injury; mTECs, mouse renal tubular epithelial cells; SNx, 5/6 surgical nephrectomy; PTIP, Pax transactivation-domain interacting protein; Me, methyltransferase; Diabetic mice, BKS- Leprem2Cd479/Nju (BKS-DB/Nju); MC, mesangial cell; NRK-52E, Rat renal tubular epithelial cell line; RPTCs, renal proximal tubular cells; NRK-49F, Rat renal interstitial fibroblast cell line; H/R, Hypoxia/reoxygenation; HEK293T, Human embryonic kidney cells 293; GSK-J4, KDM6B/JMJD3 inhibitor; 3-DZNep/GSK126, EZH2 inhibitor; G9a, Key enzymes of H3K9 methylation; SMYD2, SET and MYND domain protein 2; Ang II, Angiotensin II; ↑, up; ↓, down; →, No change; ?, not clarified.

Conclusion

Epigenetics is an emerging discipline that provides new ideas for understanding AKI and kidney repair. Histone H3 methylation is an essential regulatory point, and its research has produced many new results. A certain amount of methylation of amino acid residues on histone H3 is critical for healthy kidney development. However, methylation levels are generally elevated in sepsis-induced-kidney injury and injury due to other reasons. Studies support the observation that inhibition of methylation attenuates AKI and impedes renal fibrosis resulting from incomplete repair after injury. In addition to affecting the repair after kidney injury through the traditional fibrosis pathway, H3 methylation also participates in the process of kidney repair by regulating the expression of Klotho. Thus, histone methylation controls the cellular aging pathological process. Some studies support that histone methylation regulates inflammatory factor levels, and sepsis is one of the common causes of AKI in clinical practice. However, few studies discuss sepsis-induced AKI and repair after renal injury. The lack of such studies could be due to the complex injury mechanism of the animal model of sepsis kidney injury, the relative difficulty of modeling and the high mortality of animals after modeling.

Currently, effective treatments do not exist for AKI; only supportive treatment is available. In addition, efficient prevention and treatment options for various problems in renal repair are not available. With an increasing number of studies on AKI, the injury process of AKI and the aspect of post-injury fibrosis are explained using the epigenetic theory. The experiments have proved that AKI pathology can be improved. Histone methylation plays a vital role in the normal

development of the kidney, and the intervention drugs or resources in these experiments have not reached the stage of clinical application. At the same time, drugs presently used in the clinic are used to treat kidney diseases by regulating the methylation of histones[21,53]. These observations enhance our belief that the research on histone methylation in AKI and kidney repair will help provide therapy for kidney diseases. Numerous histone methylation targets are available, and the mechanism is complex, which provides new ideas for an in-depth understanding of disease progression and the development of new therapeutic strategies. Further, many mechanisms are unclear, and several aspects need exploration.

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Disclosure

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