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Epigenetics in acute kidney injury

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Abstract

Purpose of review—Recent advances in epigenetics indicate the involvement of several epigenetic modifications in the pathogenesis of acute kidney injury (AKI). The purpose of this review is to summarize our understanding of recent advances in epigenetic regulation of AKI and provide mechanistic insight into the role of acetylation, methylation, and microRNA expression in the pathological processes of AKI.

Recent findings—Enhancement of protein acetylation by pharmacological inhibition of histone deacetylases (HDACs) leads to more severe tubular injury and impairment of renal structural and functional recovery. The changes in promoter DNA methylation occur in the kidney with ischemia/reperfusion. microRNA expression is associated with regulation of both renal injury and regeneration after AKI.

Summary—Recent studies on epigenetic regulation indicate that acetylation, methylation, and microRNA expression are critically implicated in the pathogenesis of AKI. Strategies targeting epigenetic processes may hold a therapeutic potential for patients with AKI.

Keywords

Epigenetics; acute kidney injury; acetylation; methylation; microRNA

Introduction

Acute kidney injury (AKI) characterized by a rapid decline in renal function is a serious disease with an unacceptably high mortality rate and no effective treatment beyond supportive care. The mortality of AKI has been estimated to be about 30–70% depending on the severity of injury [1]. The sequelae of AKI are severe and manifested by increased risk of short-term and long-term mortality, persistent chronic kidney disease (CKD) and accelerated likelihood of end-stage renal disease (ESRD) [2]. Although much progress has been made in understanding the cellular and molecular basis of AKI, there has been little

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Conflicts of interest

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improvement in its high mortality rate in the past several decades [2–4]. Therefore, exploring its pathogenesis to develop an effective treatment for AKI is urgently needed.

AKI can be induced by numerous insults, such as sepsis, ischemia/reperfusion (I/R), rhabdomyolysis, contrast media, or other nephrotoxins [5,6]. Studies have demonstrated that renal tubular cell death and tubulointerstitial inflammation are two important determinants of tissue damage and renal failure. The proximal straight tubule in the outer medulla of the kidney is particularly susceptible to I/R injury. After severe injury, some renal tubular cells die by apoptosis and necrosis and remaining surviving tubular cells undergo regeneration. During the regenerative process, renal epithelial cells dedifferentiate and then migrate and proliferate to replace lost cells, finally resulting in morphological and functional recovery of renal epithelium [7]. Animal studies have indicated that the kidney possesses a remarkable regenerative capacity after injury, its function can be completely resumed if the injury is mild [3]. Although the specific mechanism responsible for renal regeneration after AKI is incompletely understood, it has been recognized that some molecules such as vimentin, Pax-2 and neural cell adhesion molecule, which are expressed in metanephric mesenchyme but not in mature kidneys, are re-expressed in renal epithelial cells during recovery from acute injury [7,8]. This suggests that the process of renal restoration after AKI may recapitulate that of early kidney development.

Kidney development can be regulated by epigenetic modifications. Epigenetics refers to the modulation of gene expression via post-translational modification of protein complexes associated with DNA without changing DNA sequence, including acetylation, methylation, phosphorylation, ubiquitinylation, sumoylation, carbonylation and glycosylation as well as expression of microRNA (miRNA). Epigenetic information is encoded through covalent modification of histones and DNA. Chromatin, a complex of DNA and proteins inside the nuclei of eukaryotic cells, plays an important role in transcription, DNA replication and repair. The fundamental repeating units of chromatin is composed of the nucleosome, which is formed by a 146 base pairs of DNA wrapped around histone protein cores (two H2A/H2B dimers and a H3/H4 tetramer) [9]. Remodeling of chromatin between relatively ‘open’ and ‘closed’ forms has a crucial role in epigenetic modulation of gene expression [10]. Chromatin modifying enzymes can catalyze addition or removal of post-translational modifications, respectively. For example, histone deacetylases (HDACs) can remove acetyl groups from histone proteins and are required for growth and differentiation of the embryonic kidney and regulation of essential genes involved in these processes, including *Osr1*, *Eya1*, *Pax2/8*, *WT1*, *Gdnf*, *Wnt9b*, *Sfrp1/2*, and *Emx2* [11,12]. Pax2 can provide the DNA binding specificity for an MLL3/4 Trithorax like protein complex that promotes histone H3, lysine 4 methylation (H3K4me). Studies in mice indicated that reducing histone H3K4 methyltransferase activity could alter cellular phenotypes, leading to changes in gene expression patterns in podocytes [13].

Numerous studies have shown that epigenetic processes are involved in the pathogenesis of AKI. In this article, we discuss recent advances in the epigenetics of AKI, with the focus on acetylation, methylation and change of miRNA expression.

Acetylation and acute kidney injury

The condensed repressive chromatin structure is partially dependent on the electrostatic interaction of the positive charge on histones and the negative charge on DNA [1]. Acetylation of the lysine residues at the N termini of histones removes the positive charges, thereby reducing the affinity of histones for the negatively charged DNA, subsequently altering the compact chromatin to a more relaxed structure for recruitment of activators or inhibitors of gene transcription. This relaxation can be reversed by HDAC activity. Acetylation and deacetylation are typically catalyzed by two groups of enzymes: histone acetyltransferases (HATs) and HDACs. HATs are enzymes that acetylate lysine amino acids of histone proteins by transferring an acetyl group from acetyl CoA to form ϵ -N-acetyllysine. Five families of HATs have been recognized: GNAT (Gcn5- related N-acetyltransferases), MYST (MOZ-Ybf2/Sas3-Sas2-Tip60), p300/CBP, nuclear hormone receptor coactivators, and TAF1 (formerly TAFII230 in human and TAFII250 in *Drosophila*) [14]. HDACs are a group of deacetylating enzymes that remove acetyl groups from ϵ -amino groups of lysine residues of histones as well as non-histones, causing the condensation of chromatin structure and thereby generally repressing gene expression [15,16]. There are four classes of HDACs: Class I HDACs (HDAC1, 2, 3 and 8); Class II HDACs (HDAC 4, 5, 6, 7, 9 and 10); Class III (SIRT1-7); Class IV (HDAC 11).

Studies have demonstrated that activation of HATs and HDACs is critically involved in renal regeneration after AKI. As mentioned above, proliferation of renal epithelial cells is a critical step during kidney regenerative process after AKI. In vitro and in vivo studies have shown that histone acetyltransferase binding to origin recognition complex-1 (HBO1) and Gene for Apoptosis and Differentiation-1 (JADE1) isoform JADE1S is required for epithelial cell proliferation [17]. JADE1 deficiency leads to degradation of HBO1 and prevents cell cycle progression in cultured renal epithelial cells. The JADE1S-HBO1 complex specifically marks the acetylation of histone H4 on lysines 5 and 12 and accumulates during epithelial cell regeneration, indicating a crucial role of JADE1S-HBO1 in kidney regeneration after IR-induced AKI [17]. Epigenetic modulation has also been shown to be involved in the pathogenesis of endotoxin hyper-responsiveness of cytokine production in AKI. In the unilateral renal I/R-induced mouse AKI model, lipopolysaccharide (LPS) triggers histone acetylation epigenetic pathways that interact at the TNF- α gene to generate endotoxin hyper-response in AKI [18].

Our recent studies indicated that inhibiting class I HDAC activity with a highly selective inhibitor MS-275, or silencing HDAC1, 3, or 8 with small interfering RNA (si-RNA) induced global histone H3 hyperacetylation, decreased cell proliferation, and reduced expression of cyclin D1 and proliferating cell nuclear antigen in cultured renal proximal tubular cells, suggesting an implication of class I HDACs in mediating renal tubular cell proliferation [19]*. Further in vivo studies showed that blockage of class I HDACs with MS-275 resulted in more severe tubular injury in the mouse model of AKI induced by folic acid or rhabdomyolysis, as evidenced by worsening renal dysfunction, increased NGAL expression, and enhanced apoptosis and caspase-3 activation [20]*. Blocking class I HDAC activity also impaired renal regeneration as indicated by decreased expression of renal Pax-2, vimentin and PCNA [20]. These data illustrated that class I HDACs activity is

acquired for renal repair and renal regeneration after AKI. The renoprotective effect of HDACs in kidney injury is consistent with the reports by other groups. Marumo et al. also found that ischemia/reperfusion of the mouse kidney induced a transient decrease in histone acetylation in the ischemic period, and subsequently down-regulation of HDAC5 during the recovery phase, resulting in histone re-acetylation and induction of bone morphogenetic protein-7 (BMP7) in proximal tubular cells [21]*. BMP7 is a key developmental factor in nephron formation during kidney development and is required for the proliferation and repair of the tubular cells after ischemia [22,23]. Thus, HDAC5 inhibition may serve as a potential therapeutic strategy for accelerating regeneration of the injured kidney. Furthermore, Hsing et al., showed that decreasing HDAC2 and HDAC5 expression levels is in parallel with increasing acetyl histone H3 and associated with the renoprotective effect of dexmedetomidine (DEX), and α 2-adrenoceptor agonist, in sepsis-induced AKI [24].

It should be noted that HDAC inhibition with phenylthiobutanoic acids (PTBAs), another class I HDAC inhibitor, has been reported to enhance renal recovery and attenuate renal fibrosis. This was demonstrated in animal models of ischemia/reperfusion and aristolochic acid induced AKI when M4PTB is administered at 24 hours after ischemic injury or 4 days after injection of aristolochic acid [25]. The effects of M4PTB seems to be in contrast to the observations made using MS-275, however, the anti-fibrotic effects were also observed when MS-275 was administered in an animal model of renal fibrosis induced by unilateral ureteral obstruction [26]. Thus, inhibition of renal fibrosis may be at least in part responsible for the beneficial effect of HDAC inhibitors in promoting renal regeneration and renal functional recovery.

In conclusion, protein acetylation plays an important role in the pathogenesis and regeneration of AKI. Future studies are needed to identify the specific HDAC isoforms and acetylated proteins involved in these processes of AKI.

Methylation and acute kidney injury

Methylation contributes to epigenetic inheritance and is carried out through either DNA methylation or protein methylation. DNA methylation refers to the addition of methyl groups (CH₃) from S-adenosyl methionine (SAM-CH₃) to the cytosine or adenine DNA nucleotides. It is catalyzed by a family of DNA methyltransferases. DNA methylation plays an important role in epigenetic gene modulation during development and diseases, including AKI. It was first reported by Pratt et al in 2006 that DNA methylation status was changed in the rat kidney after ischemia/reperfusion-induced AKI [27]*. Subsequently, aberrant DNA promoter hypermethylation was considered to be a biomarker of AKI. For example, kidney transplant recipients were significantly more likely to have aberrant hypermethylation of the calcitonin (CALCA) gene promoter in urine than healthy controls. Furthermore, there was a trend toward increased aberrant hypermethylation of urine CALCA in patients with biopsy-proven acute tubular necrosis versus acute rejection and slow or prompt graft function [28]. Plasma levels of unmethylated DNA corresponding to the Slc22a12 promoter region, a urate transporter specifically expressed in proximal tubular cells, were undetectable at baseline and were significantly elevated after acute kidney cortex necrosis [29]. Methylation of promoter kallikrein (KLK1) CpG in the kidney was higher in blood than urine DNA, while

KLK1 methylation in blood DNA was higher in established AKI than healthy controls, though KLK1 methylation in urine tended to be elevated in AKI, directionally consistent with earlier/incipient but not later/established changes in KLK1 excretion in AKI [30]. Huang et al. further showed that the global level of 5-hydroxymethylcytosine (5hmC) was reduced in mouse kidney insulted by ischemia reperfusion [31]. I/R injury also decreased the 5hmC enrichment at promoter regions of *Cxcl10* and *Ifngr2* genes, contributing to the increased levels of *Cxcl10* and *Ifngr2* mRNA in I/R-injured kidney [31]. These studies suggest the change of DNA methylation in acute renal injury. Further studies are needed to examine the relationship between cytosine methylation and AKI.

Different from acetylation correlated with an “open” chromatin state and the activation of gene expression, histone methylation change transcription though creating docking sites for chromatin modifiers and have more diverse outcomes—active, poised, or repressive status of chromatin and transcriptional marks. The known methylated sites consist of six lysine residues (K4, K9, K23, K27, K36, K56 and K79) in H3, K20 in H4, K26 in H1, and four arginine (R) residues (R2, R8, R17, R26) in H3, R3 in H4, and R11 and R29 in H2A. Generally, methylation at H3K4, H3K36 and H3K79 is associated with the activation of gene transcription, while methylation at H3K9, H3K27 and H4K20 is related to the repression of gene transcription [32]. Methylation of histone lysine or arginine residues is modulated by methyltransferases and demethylases. Histone methyltransferases include two major types, lysine-specific (KMT) and arginine-specific (RMT). Lysine-specific demethylases (LSD or KDM) include six LSD families, from KDM1 to KDM6.

There are few studies exploring the role of histone methylation in AKI. It was reported that histone 3 lysine 4 trimethylation (H3K4m3) levels at the first and last exons of the *TNF- α* gene were higher in post-ischemic kidneys, compared with contralateral kidneys [33]. Increased levels of H3K4m3 at exon 1 of the *HMG-CoA* reductase (*HMGCR*) gene contributes to an upregulation of *HMGCR* activity in patients with AKI [34]. Increased H3K4m3 at exons of monocyte chemoattractant-1 (*MCP-1*) and *TNF- α* gene corresponds to increases in the recruitment of RNA polymerase II to the *TNF- α* and *MCP-1* genes in three highly divergent models of acute renal injury (LPS-preconditioning, maleate nephrotoxicity, and unilateral ureteral obstruction) [35]. Currently, it remains unclear whether modulation of histone methylation would alter the pathogenesis and regenerative responses after AKI.

Nevertheless, emerging evidence indicates that histone methylation is involved in the regulation of cell differentiation and proliferation. For example, LSD1, which demethylates histone H3 on Lys4 or Lys9 (H3K4/K9), is necessary for decommissioning enhancers during the differentiation of mouse embryonic stem cells (ESC) so as to allow the transition of ESC to new cell states [36]. The interaction of H3K27me3, H3K36me3, H3K4me1/2/3 or H3K9me3, with Polycomb group proteins is essential to preserve stemness and regulate differentiation of epidermal stem cells [37]. Moreover, accumulation of histone methylation by administration of trans-2-phenylcyclopropylamine (2-PCPA), a LSD1 inhibitor, was shown to suppress proliferation of neuromast cells and to enhance cellular apoptosis within neuromasts during zebrafish development [38], suggesting that LSD1 contributes to growth and survival of neuromasts. As survival, proliferation and differentiation of epithelial tubular cells are critical steps of renal regeneration during AKI, histone methylation might also

involve in these processes. Further studies are needed to address the role of histone methylation in AKI by utilizing pharmacological and genetic approaches.

miRNA and acute kidney injury

miRNA are a family of endogenous, short non-coding RNA molecules that regulate gene expression at the post-transcriptional level, thus implicating themselves in diverse cellular processes including development, cell differentiation and proliferation, cell cycle, and apoptosis and metabolism [39–41]. It has been demonstrated that miRNAs are involved in the pathogenesis of kidney diseases, including AKI. The significance of miRNA in AKI was first revealed in a mouse model in which proximal tube-specific Dicer, a critical enzyme for miRNA production, was knocked out, where over 80% miRNAs were depleted [42]**. Down regulation of miRNA in the renal cortex was shown a remarkable renal protective effect as evidenced by better renal function, less tissue damage, lower tubular apoptosis and improved survival compared to their wild-type littermates during acute renal I/R injury [42]. Consistent with these observations, further studies also showed that miRNA containing microvesicles protected the kidney against ischemic AKI [43].

So far, a number of specific miRNAs including miRNA-24, miRNA-494, miRNA-21 and miRNA-127 have been demonstrated to play roles in AKI. Expression of miRNA-24 was upregulated in the mouse kidney after I/R injury and in patients after kidney transplantation [44]. Overexpression of miRNA-24 induced apoptotic responses and altered functional parameters, while silencing of miRNA-24 ameliorated apoptosis and rescued functional parameters during hypoxic conditions in renal endothelial and tubular epithelial cells [44]. In vivo study also showed that silencing of miRNA-24 in mice before I/R injury resulted in a significant improvement in survival and kidney function, a reduction of apoptosis, improved histologic tubular epithelial injury, and less infiltration of inflammatory cells [44]. These results indicate that miRNA-24 promotes renal ischemic injury by stimulating apoptosis in endothelial and tubular epithelial cells, suggesting that inhibition of miRNA-24 might be a promising therapeutic option in the treatment of patients with ischemic AKI.

miRNA-494 was also upregulated in the kidney tissues after I/R injury, which significantly attenuated the level of activating transcription factor 3 (ATF3) and promoted inflammatory mediators, including IL-6, monocyte chemotactic protein-1 (MCP-1), and P-selectin, and NF- κ B dependent proinflammatory response, exacerbating apoptosis and further decreasing renal function [45]. Urinary levels of miRNA-494 increased significantly before the rise in serum in this I/R model and in patients with AKI than normal controls [45]. Therefore, upregulation of miRNA-494 contributes to inflammatory or adhesion molecule-induced kidney injury after I/R injury by inhibiting expression of ATF3. Furthermore, miRNA-494 may be a specific and noninvasive biomarker for AKI.

In vitro, knockdown of miRNA-21 in tubular epithelial cells resulted in increased cell death, whereas its overexpression prevented cell death [46]. In vivo studies also indicate that preconditioning-induced upregulation of miRNA-21 protects against renal I/R injury by the targeted genes such as the proapoptotic gene programmed cell death 4 and interactions between miRNA-21 and hypoxia-inducible factor (HIF) [47]. This suggests a protecting role

of miRNA-21 in AKI. Another species of miRNA, miRNA-127, which is a critical regulator of cell-cell and cell-matrix adhesion, protects proximal tubule cells against renal I/R injury through HIF-1 and by targeting Kinesin Family Member 3B (KIF3B), with important implications in cell endocytosis [48]. A very recent study has further shown that under hypoxic and ischemic conditions, miRNA-687 can be induced via HIF-1 and upon induction, miRNA-687 represses PTEN and then facilitate cell cycle activation for tubular cell proliferation and kidney repair [49]**. These studies indicate that miRNA can target both renal injury and regenerative processes in AKI and suggest that regulation of miRNA expression holds a therapeutic potential for treatment of ischemic renal injury.

Other histone modifications and acute kidney injury

In addition to histone modifications, histone phosphorylation and sumoylation have also been reported to be involved in the process of AKI. Histone phosphorylation can occur on serine, threonine and tyrosine residues and involve in DNA damage repair, transcription regulation, and chromatin compaction [50]. Available evidence indicates that histone phosphorylation plays a role in a cross-talk with other histone modifications, including acetylation [51] and methylation [52]. 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 [50]. As EGF and EGF receptor have been shown to be critically implicated in renal regeneration after AKI [53,54], it is speculated that this modification may also affect renal repair and renal functional recovery.

Sumoylation is a form of post-translational modification by which small ubiquitin-like modifiers (SUMO) are covalently attached to target proteins to regulate their properties. A study by Dong and colleagues indicated that a dynamic change of renal protein sumoylation occurred in ischemic and cisplatin nephrotoxic AKI in mice and that inhibition of sumoylation with ginkgolic acid (GA), a pharmacological inhibitor of sumoylation, enhanced apoptosis during cisplatin incubation. This suggests a cytoprotective role of sumoylation in kidney tubular cells after injury [55].

Although other histone modifications, such as ubiquitinylation, ADP ribosylation, deamination, carbonylation and glycosylation have also been reported in diverse diseases [56–60], there is no available information on their modifications and implications in AKI.

Conclusion and Perspective

Although progress has been made in understanding the molecular basis of AKI, the therapeutic treatment for AKI is still limited to supportive care and renal replacement therapy in the event of no return of function. Recent advances in understanding epigenetic regulation allow us to explore epigenetic therapies for this disease. Increasing evidence indicates that the pathogenesis of AKI, in particular renal regenerative processes, is subjected to at least three types of epigenetic regulations (acetylation, methylation, and miRNA) (Table 1). Epigenetic modifiers are also aberrantly expressed during AKI, which might be a promising biomarker for AKI. However, the underlying mechanism by which epigenetic regulation contributes to AKI initiation and progression remains incompletely understood. Thus, further dissection of epigenetic regulations on these processes would

provide the cellular and molecular basis for epigenetic therapy in AKI. While those aforementioned epigenetic mechanisms are linked to the pathogenesis of AKI, it also remains unknown concerning the cross-talk among various epigenetic regulations in AKI. Clearly, a cross-talk between miRNA and methylation and acetylation exists in cancers. It has been shown that expression of some miRNAs such as let-7a, miRNA-9, miRNA-34a, miRNA-124, miRNA-137, miRNA-148 and miRNA-203 can be modulated by DNA methylation and histone modifications [61–65]. Conversely, DNA methylation and histone acetylation are also controlled by a subset of miRNAs [66]. N-terminal acetylation of H4 was discovered as a novel regulator of arginine methylation and this cross-talk regulated Ribosomal DNA silencing [67]. The integrative network between these three epigenetic pathways appears to establish an acetylation-methylation-miRNA regulatory loop intertwined with the transcriptional and post-transcriptional pathways which opens new doors for a potential cross-talk events and chromatin signaling networks [66]. Future studies are needed to identify the specific proteins targeted by epigenetic regulation and the molecular basis by which the epigenetic modifiers are regulated during AKI. A better understanding of the role of epigenetics in AKI will lead to development of new drugs and specific treatment strategies.

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Key points

- Epigenetic modifications including acetylation, methylation, and miRNA expression occur in the kidney after acute injury.
- Increases acetylation is associated with damage of renal tubular cells and disruption of renal regenerative processes after AKI.
- AKI is associated with changes in DNA methylation, and aberrant DNA promoter hypermethylation can be considered to be a biomarker of AKI.
- miRNA can target both renal injury and regenerative processes in AKI depending on which miRNA is involved.

Table 1

Effects and mechanisms of epigenetic regulation in AKI

Epigenetic regulation	Effects	Mechanisms
Acetylation	Regulates epithelial cell regeneration in AKI	<ul style="list-style-type: none"> • Interacts with JADE1S-HBO1 complex [17] • Interacts at the TNF-α gene to generate endotoxin hyper-response in AKI [18]. • Regulates activation of EGFR/STAT3 and EGFR/Akt pathway during AKI [19,20]. • Induces bone morphogenetic protein-7 (BMP7) in proximal tubular cells [21].
Methylation	Aberrant DNA promoter hypermethylation was considered to be a biomarker of AKI	<ul style="list-style-type: none"> • Aberrant hypermethylation of the calcitonin gene promoter is higher in urine than healthy controls [28]. • KLK1 methylation in blood DNA is higher in established AKI than healthy controls [30]. • Increases in the recruitment of RNA polymerase II to the TNF-α and MCP-1 genes during AKI [35].
MicroRNA	Aggravate or protect against renal ischemic injury	<ul style="list-style-type: none"> • miRNA-24 promotes renal ischemic injury by stimulating apoptosis in endothelial and tubular epithelial cells and facilitating infiltration of inflammatory cells in I/R injury kidney [44]. • miRNA-494 inhibits expression of ATF3 and promotes inflammatory mediators, including IL-6, MCP-1 and P-selectin, exacerbating apoptosis and decreasing renal function in the kidney after I/R injury [45]. • Upregulation of miRNA-21 protects against renal I/R injury by the targeted genes such as the proapoptotic gene programmed cell death 4 and interactions between miRNA-21 and hypoxia-inducible factor (HIF) [47]. • miRNA-687 represses PTEN and then facilitates cell cycle activation for tubular cell proliferation and kidney repair under hypoxic and ischemic conditions [49]. • miRNA-127 protects proximal tubule cells against renal I/R injury through • HIF-1 and by targeting Kinesin Family Member 3B (KIF3B) [48].