REVIEW ARTICLE

Epigenetics of kidney diseases.

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Abstract

Epigenetics has been recently recognized as an essential mechanism for pathogenesis in many diseases, including kidney diseases. Epigenetic modifications are inherited nuclear characteristics, or molecular changes that can affect gene expression without altering DNA sequences, including DNA methylation, histone modification, and non-coding RNAs. The kidney has an intricate structure and its origin is very complex despite sharing the same DNA. Indeed, epigenetic modulation of the kidney is diverse; furthermore, the extracellular environment after birth may affect various aspects of renal epigenetic modification. Epigenetic modifications in patients with acute kidney injury (AKI) or chronic kidney disease (CKD) are actively undergoing investigation. However, there have been few reports relating epigenetic changes to mineral homeostasis and CKD–mineral and bone disorder (CKD-MBD), particularly in the text of parathyroid diseases.
In this review, we describe epigenetic modification and subsequently discuss the roles and mechanisms of epigenetic modification in the pathogeneses of AKI, AKI-to-CKD transition, CKD, and CKD–MBD.

Key Words
Acute kidney injury, Chronic kidney disease, Chronic kidney disease–mineral and bone disorder, Epigenetics, Calcium-sensing receptor, Vitamin D receptor

1. Epigenetic modification

Epigenetics is a discipline that was advocated by Conrad Hal Waddington[1-3], which is now attracting great attention. Epigenetic modifications are inherited nuclear characteristics, or molecular changes that can affect gene expression without altering DNA sequences. Waddington emphasized that just one cell, a fertilized egg, differentiated into cell lineages via unidirectional differentiations[4]. The epigenome differs among cell types and integrates various information regarding the functional identity of each cell type during development or disease[5]. Thus, epigenetic modifications contribute to embryogenesis[6], and cell differentiation; moreover, they affect the incidence of diseases, such as imprinting disorders[7-10], cancer, neurological disease[11-14], autoimmune disorders[15, 16], and various lifestyle-related diseases[17, 18].

The most common epigenetic modifications are DNA methylation, histone modification, and non-coding RNA-associated gene silencing (Figure 1). These modifications influence gene expression; thus, epigenetics promotes biological adaptation by permitting functional variability in response to environmental changes[19-21], such as diet, inflammation, metabolic changes and toxins[21-24]. Notably, epigenetic changes may be reversible[25, 26]. Accordingly, investigation of the epigenome contributes to the elucidation of mechanisms of numerous diseases as well as the development of innovative therapeutic targets, including kidney diseases.

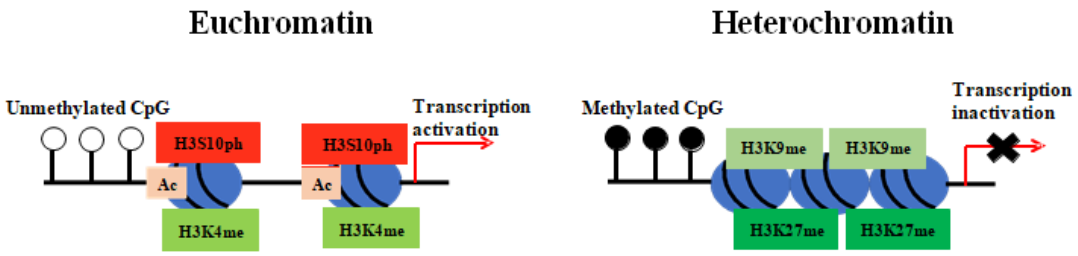

Figure 1: Model for the regulation of epigenetic modifications. Schematic representation of euchromatin and heterochromatin as accessible or condensed nucleosome fibers that are acetylated (Ac), phosphorylated (ph), or methylated (me). Typical transcriptional control by histone modification is complex; for example, active histone markers include the methylation of H3K4, H3K36, H3K79, and H3R3; acetylation of H2AK15, H2BK12, H2BK15, H4K5, H4K8, H4K12, H4K16, H3K9, H3K14, and H3K18; ubiquitination of H2BK123; and phosphorylation of H3S10. Inactive histone markers include the methylation of H3K9, H3K27, and H3R8; ubiquitination of H2AK119; and phosphorylation of H2AS1. In addition, there are complicated histone modifications, such as dimethylated lysine and trimethylated lysine.

2. Epigenetics of AKI

AKI has received increasing attention due to the high incidence of adverse events, such as mortality rates and the risk of chronic kidney disease (CKD)[27,28]. The involvement of epigenetics in AKI has recently attracted great interest[29, 30], such that the number of reports regarding epigenetics of AKI has increased.

Regarding the role of DNA methylation in AKI, using a mouse ischemia-reperfusion renal injury (IRI) model, Huang reported that the global level of 5-hydroxymethylcytosine was reduced in the injured kidney; however, the 5-methylcytosine level did not significantly change. Furthermore, Huang showed decreased expression of *Tet1* and *Tet2* genes but not *Tet3*[31]. Guo showed that the DNA methylation inhibitor 5-aza-2'-deoxycytidine increased the number of apoptotic cells in a rat kidney proximal tubular cell line upon exposure to cisplatin[32]. These reports indicated that DNA methylation plays an essential role in AKI.

Regarding the role of histone modification in AKI, chromatin immunoprecipitation with sequencing (ChIP-seq) enable the determination of the gene expression profile in target tissues. Nangaku reported that gene expression is intricately regulated by DNA methylation; histone modification; chromosome conformation changes; and ncRNA in various types of diseases, including kidney disease[33]. Marumo demonstrated that reduction of histone deacetylases 5 (HDAC5) contributed to histone re-acetylation; furthermore, BMP7, a renoprotective factor, induced the onset of the recovery phase in the mouse IRI model[34]. Ruiz-Andres demonstrated that histone lysine crotonylation increased during AKI; this increased crotonylation may positively impact the onset of AKI owing to the altered gene expression of peroxisome-proliferator-activated receptor gamma coactivator-1α (PGC-1α) and sirtuin-3[35]. Naturally, the investigation of the modulators of histone modification as a therapeutic target has made progress. Obstruction (blocking) class I HDAC activity and inhibition of HDAC6, a class IIb HDAC, are protective against AKI[36-38]. Therefore, histone modification appears to have an important role in AKI.

In regards to the role of ncRNA in AKI, many reports have shown relationships between AKI and each of the following: miRNAs, lncRNAs, and circular RNAs (cirRNAs)[39]. Using various mouse models (IRI, cisplatin-induced AKI, contrast-induced AKI, and miRNA knockout) and in human studies using blood samples and urine samples of AKI patients with AKI, many miRNAs such as miR-10a, miR-21, miR-24, and miR-217, have been identified related to AKI[40-45]. Few studies have addressed the roles of lncRNAs in AKI[46-48]. Based on these results, ncRNAs have the

potential to serve as diagnostic and therapeutic tools.

3. Epigenetics of AKI-to-CKD transition

Previously AKI was considered a transient event for patients who recovered from the acute phase of AKI and regained complete kidney function on a long-term basis. However, recent epidemiological studies and meta-analyses have shown that apparent recovery from AKI can lead to CKD, including end-stage kidney disease[28]. If aberrant repair mechanisms and/or injury-induced stimuli persist, AKI can progress to CKD, characterized by fibrosis and inadequate organ remodeling[48]. Histological features include glomerulosclerosis, vascular sclerosis and tubulointerstitial fibrosis regardless of etiology; this fibrosis exacerbates the aberrant renal function through capillary rarefaction and tissue hypoxia[49]. Nangaku demonstrated the importance of hypoxia associated with the mechanism of AKI-to-CKD transition[50]. Hypoxia-inducible factor (HIF), a master regulator of adaptive responses against hypoxia, is important in the transcriptional regulation of target genes (e.g., erythropoietin, vascular endothelial growth factor, glucose transporters, and CCAAT/enhancer-binding protein δ). Furthermore, Nangaku showed epigenetic changes in AKI-to-CKD transition, namely hypoxic memory; these include decreased dimethylation of lysine 9 (H3K9me2), caused by increased KDM3A; increased H3K27me3, caused by decreased KDM6B; and increased lncRNA DARS-AS1[50]. Zager has also showed that postischemic inflammation, ongoing lipid accumulation (lipotoxicity), and increasing histone acetylation at proinflammatory/profibrotic genes may sustain the injured state; based on those results, he concluded that AKI can trigger CKD[51]. Notably, there have been several reports regarding the epigenetic regulation of fibrosis. In the kidney fibrosis model of unilateral ureteral obstruction (UUO), Hewitson showed that global kidney H3K9me3 and H3K9Ac were increased[52]. In a similar mouse model, Zhou demonstrated that the expression of enhancer of zeste homolog 2 (EZH2)—a methyltransferase that induces H3K27me3—was increased and suggested that the inhibition of *EZH2* could be a therapeutic target for the treatment of CKD[53].

There have been a few reports of epigenetic silencing via miRs in kidney fibrosis[54]. Some miRs have specific roles in fibrosis; miR-21 and -130 have profibrotic activity, whereas miR-29 has anti-fibrotic activity; notably, miR-192 has both profibrotic and anti-fibrotic activities[55-58].

There is some evidence that DNA methyltrasnsferase inhibitors may be beneficial in the treatment of renal fibrosis. TGF-β1 caused hypermethylation of *RASAL1* through increased

Dnmt1expression in fibrotic kidney, leading to Ras hyperactivity and proliferation[59]. Hydralazine, a demethylating agent, led to RASAL1 promoter demethylation and renal fibrosis attenuation[60]. These findings were confirmed in *COL4A3*-deficient Aloport mice as well as murine models of diabetic nephropathy, UUO, subtotal nephrectomy, and folic acid nephropathy[61]. However, in the IRI model mouse, the hypermethylation of *RASAL1* could not be confirmed[60]. Accordingly, hypermethylation of *RASAL1* in the kidney may be important in the process of AKI-to-CKD transition to irreversible fibrosis. Importantly, TGF-β1 has been shown to promote the differentiation of erythropoietin-secreting pericytes into myofibroblasts as well as to support *erythropoietin* hypermethylation in experimental kidney fibrosis; this change was prevented by low-dose 5-aza[62]. Therefore, specific demethylation therapy may prevent AKI-to-CKD transition[32, 63].

4. Epigenetics of CKD

Several groups have identified associations between CKD and epigenetic modulation[64]. Ingrosso demonstrated global hypomethylation in peripheral mononuclear cells in a group of male hemodialysis patients with hyperhomocysteinemia compared with mononuclear cells from control subjects[25]. However, with respect to different stages of CKD (stage 2–4), there were no significant correlations between global DNA methylation levels and homocysteinosis or arteriosclerosis[65]. Epigenetic regulation occurs in stage-specific and tissue-specific manners[5]; thus, these aspects should be considered when investigating epigenetic modifications. Smyth showed that 23 genes have differential methylation patterns in CKD patients compared to their patterns in controls[66]. These genes included several strong biologic candidates for CKD, such as *CUX1*, *ELMO1*, *FKBP5*, *INHBA-AS1*, *PTPRN2*, and *PRKAG2*. These genes have been implicated in pathways involving kidney development, extracellular matrix accumulation, cell growth, cell differentiation, apoptosis, hypertension, and type 1 diabetes mellitus. These results suggest that the CKD environment causes the particular DNA methylation changes in specific genes related to its pathophysiology. In addition, diabetes mellitus and obesity, both strongly associated with CKD and risk factors for the onset of CKD, involve differential methylation patterns[67], therefore, further studies regarding causes of CKD are necessary to clearly understand DNA methylation in CKD.

Regarding the role of histone modification in CKD, Van Beneden showed that valproic acid, a class I HDAC inhibitor, abrogated the reduction in glomerular acetylation and halted glomerulosclerosis through podocyte detachment, epithelial to mesenchymal

transition, apoptosis, and proliferation in mice with adriamycin-induced nephropathy[68]. Furthermore, H3K4me in podocytes was found to have an important role in CKD[69]; H3S10ph in proximal tubular epithelial cells prevented regeneration and proliferation in CKD[70]; and histone H3.3 and histone cell cycle regulation defective homolog A (HIRA) were implicated in TGF-β1-induced renal fibrosis[71]. These findings suggest that changes in histone modification may be a common mechanism in the process of CKD; thus, they may provide therapeutic targets for treatment of CKD.

5. Epigenetics of CKD–MBD

Epigenetics of CKD-MBD is more complex than AKI, AKI-to-CKD transition, and CKD because there are four intricate main axes that involve complex interactions, namely kidney, intestine, bone, and parathyroid gland. Furthermore, epigenetic modifications of these organs may differ depending on the origins of CKD. Epigenetic modifications in patients with AKI and CKD are actively undergoing investigation; however, few reports are available concerning epigenetic changes to mineral homeostasis and CKD–MBD.

The parathyroid gland plays a crucial role in mineral homeostasis, particularly when there is the loss of kidney function. However, it is difficult to elucidate the maintenance mechanisms and pathogenesis of parathyroid diseases because the parathyroid glands in animal models are too small and stable cell lines of parathyroid glands are not provided due to difficulties in operatively extracting the normal human parathyroid glands as control samples.

Klotho, which is mainly expressed in parathyroid glands, kidney, and pituitary glands and considerably important for mineral homeostasis, functions as an essential subunit of the high-affinity receptor for fibroblast growth hormone 23 (FGF23). There have been a few reports regarding epigenetic changes of Klotho in CKD; however, Klotho is not a mineral regulator, but functions as a multifunctional protein through inhibition of multiple signaling pathways (TGF-β1, Wnt, and insulin/insulin-like growth factor-1). Klotho deficiency is associated with the progression of renal fibrosis as well as secondary hyperparathyroidism (SHPT), vascular calcification, and cardiac hypertrophy[72-75]. Various reports have shown that CKD causes the epigenetic changes in Klotho expression, thereby inducing renal fibrosis. Sun reported that hypermethylation of *Klotho* in renal tubules induced uremic toxin associated with renal fibrosis[76]; Irifuku then demonstrated that TGF-β1 induced G9a, an H3K9 methyltransferase with an important role in the progression of renal fibrosis, which reduced klotho expression through H3K9me[77]. There is no

report of epigenetic modification in Klotho gene as a mineral regulator.

However, several studies have reported the epigenetic changes in parathyroid diseases. Parathyroid cancers are rare malignancies and have shown a prevalence of 0.005% in all cancers. Approximately 90% of parathyroid cancers are hormonally hypersecreting parathyroid hormone (PTH). Somatic inactivating mutations of the *HRPT2/CDC73* and *MEN1* genes are identified in parathyroid cancers[78, 79]; moreover, recent reports showed the epigenetic change of parathyroid cancers. Parathyroid cancers showed hypermethylation of the promoter region of genes such as *CDKN2B/p15*, *CDKN2A/p16*, *SFRPs*, *RASSSF1*, *HIC1* and *APC*[80]. The H3K27 methyltransferase EZH2 is overexpressed in parathyroid cancers[81]; thus, global H3K27me3 status may be obtained. Furthermore, miRNA expressions, such as miR-517c and -372-3p, have been identified in parathyroid cancers[82].

Pseudohypoparathyroidism type 1B (PHP1B) is a imprinting disorder characterized by renal resistance to PTH, namely decreased or absent urinary phosphate excretion and cAMP responses to PTH injection. The pathogenesis of PHP1B is complex. One of the causes is DNA methylation changes involves the region of the *GNAS* gene, including the loss of methylation at the A/B, GANS-AS1, and XLαs differentially methylation regions (DMRs) and gain of methylation at the NESP55 DMR[83]. Elli showed that epimutation in PHP1B patients occurred in early post-zygotic phases and that the partial GNAS imprinting defects were mosaics[84].

Thus, as mentioned above, there are some epigenetic disorders in parathyroid glands; therefore, epigenetic modifications occur in secondary hyperparathyroidism (SHPT) caused by CKD. Calcium-sensing receptor (CaSR) and vitamin D receptor (VDR) expression levels in PTGs are characteristically decreased in the progression of SHPT. Although many regulatory factors are involved in mineral homeostasis, CaSR and VDR are regarded as major determinants of parathyroid function in CKD. However, the underlying mechanism remains largely unknown. Lewin previously reported no change in *CaSR* and *VDR* methylation in SHPT rats[85]. However, Lewin used melting curve analysis and the severity of SHPT in those CKD rats was moderate; we investigated the methylation status of *CaSR* and *VDR* genes in the parathyroid glands using more severe SHPT rat model and quantitative analysis of DNA methylation using real-time PCR (qAMP). CKD rats fed a normal phosphate diet or high phosphate diet and in sham-operated rats fed a normal phosphate diet or high phosphate diet; the CKD model comprised two-step 5/6 nephrectomy rats. The results showed that although *CaSR* and *VDR* hypermethylation occurred in the

PTGs of CKD rats fed a high phosphate diet, the extent of hypermethylation was insufficient to support clear relationship between hypermethylation and down-regulation of gene expression because of the low percentage of methylation. Consequently, we concluded that mechanisms other than DNA hypermethylation were responsible for the reduction in mRNA and protein levels of CaSR and VDR in the PTGs of CKD rats fed a high phosphate diet[86].

Further studies are needed to clarify the precise mechanism concerning CKD-MBD in PTGs as well as kidney, bone, and intestine.

Conflict of interest All the authors have declared no competing interest.

References

1. Waddington CH. The epigenotype. Endeavour 1942; 1: 18-20.
2. Waddington CH. Genetic assimilations of the bithorax phenotype. Evolution 1956; 10: 1-13
3. Waddington CH. Ultrastructure aspects of cellular differentiation. Symp Soc Exp Biol. 1963; 17: 85-97.
4. Goldberg AD, Allis D, Bernstein E, Epigenetics: A landscape takes shape. Cell 2007; 128: 635-638.
5. Rivera CM, Ren B, Mapping human epigenomes. Cell 2013; 155: 39-55.
6. Guo H, Zhu P, Qiao J, The DNA methylation landscape of human early embryos. Nature 2014; 511: 606-610.
7. Weksberg R, Smith AC, Sadowski P, Beckwith-Wiedemann syndrome demonstrates a role for epigenetic control of normal development. Hum Mol Genet. 2003; 1: R61-R68.
8. Hitchins MP, Stanier P, Moore GE, Silver-Rusesell syndrome: a dissection of the genetic aetiology and candidate chromosomal regions. J Med Genet. 2001; 38: 810-819.
9. Kamnasaran D, Cox DW, Current status of human chromosome 14. J Med Genet. 2002; 39: 81-90.
10. Nicholls RD, Knepper JL, Genome organization, function, and imprinting in Parader-Willi and Angelman syndromes. Annu Rev Genomics Hum Genet. 2001; 2: 153-175.
11. Feinberg AP, Vogelstein B, Hypomethylation distinguishes gene of some human cancers from their normal counterparts. Nature 1983; 301: 89-92.
12. Sharma S, Kelly TK, Jones PA, Epigenetics in cancer. Carcinogenesis 2010; 31: 27-36.
13. Jones PA, Baylin SB, The fundamental role of epigenetic events in cancer. Nat Rev Genet. 2002; 3: 415-428.
14. Saito Y, Jones PA, Epigenetic activation of tumor suppressor microRNAs in human cancer cells. Cell Cycle 2006; 5: 2220-2222.
15. Maciejewska-Rodrigues H, Karouzakis E, Jungel A, Epigenetics and rheumatoid arthritis: the role of SENP1 in the regulation of MMP-1 expression. J Autoimmun. 2010; 35: 15-22.
16. Zhang Z, Song L, Sullivan KE, Global H4 acethylation analysis by ChIP-chip in systemic lupus erythematousus monocytes. Genes Immun. 2010; 11: 124-133.
17. Mutskov V, Felsenfeld G, The human insulin gene is part of a large open chromatin domain specific for human islets. Proc Natl Acad Sci U S A. 2009; 106: 17419-17424.
18. Mu S, Schimosawa T, Fujita T, Epigenetic modulation of renal β-adrenergic-WNK4 pathway in salt-sensitive hypertension. Nat Med. 2011; 17: 573-580

19. Boland MJ, Nazor KL, Loring JF, Epigenetic regulation of pluripotency and differentiation. Circ Res. 2014; 115: 311-324.
20. Trerotola M, Relli V, Alberti S, Epigenetic inheritance and the missing heritability. Hum Genom. 2015; 28, 9-17.
21. Bunkar N, Pathak N, Mishra PK, A key paradigm in reproductive health. Clin Exp Repord Med. 2016; 43: 59-81.
22. Perna AF, Ingrosso D, De Santo NG, Mebrane protein damage and methylation reactions in chronic renal failure. Kidney Int. 1996; 50: 358-366.
23. Robertson KD, Wolffe AP, DNA methylation in health and disease. Nat Rev Genet. 2000; 1: 11-19.
24. Luch A, Nature and nurture-lessons from chemical carcinogenesis. Nat Rev Cancer 2005; 5: 113-125.
25. Ingrosso D, Cimmino A, De Santo NG, Folate treatment and unbalanced methylation and changes of allelic expression induced by hyperhomocysteinaemia in patients with uraemia. Lancet 2003; 361: 1693-1699.
26. Ptak C, Petronis A, Epigenetics and complex disease: From etiology to new therapeutics. Annu Rev Pharmacol Toxicol. 2008; 48: 257-276.
27. Ympa YP, Sakr Y, Vincent JL, Has mortality from acute renal failure decreased? A systematic review of the literature. Am J Med. 2005; 118: 827-832.
28. Basile DP, Nangaku M, Ronco C, Progression after AKI: understanding maladaptive repair processes to predict and identify therapeutic treatments. J Am Soc Nephrol. 2016; 27: 687-697.
29. Fontecha-Barriuso M, Ortiz A, Sanz AB, Targeting epigenetic DNA and histone modifications to treat kidney disease. Nephrol Dial Transplant. 2018; 1-12.
30. Allison SJ, Genetic engineering: Trans-epigenetic modulation of target genes in acute kidney injury. Nat Rev Nephrol. 2018; 14: 72.
31. Huang N, Tan L, Qang H, Reduction of DNA hydroxymethylation in the mouse kidney insulted by ischemia reperfusion. Biochem Biophys Res Commun. 2012; 422: 697-702.
32. Guo C, Pei L, Dong Z, DNA methylation protects against cisplatin-induced kidney injury by regulating specific genes, including interferon regulatory factor 8. Kidney Int. 2017; 92: 1194-1205.
33. Mimura I, Kanki Y, Nangaku M, Revolution of nephrology research by deep sequencing: ChIP-seq and RNA-seq. Kidney Int. 2014; 85: 31-38.
34. Marumo T, Hishikawa K, Fujita T, Epigenetic regulation of BMP7 in the regenerative response to ischemia. J Am Soc Nephrol. 2008; 19: 1311-1320.
35. Ruiz-Andres O, Ortiz A, Sanz AB,

Histone lysine crotonylation during acute kidney injury in mice. Dis Model Mech. 2016; 9: 633-645.

36. Tan J, Yan Y, Zhao TC, Class I HDAC activity is required for renal protection and regeneration after acute kidney injury. Am J Physiol Renal Physiol. 2014; 307: F303-F316.
37. Shi Y, Xu L, Tang J, Inhibition of HDAC6 protects against rhabdomyolysis-induced acute kidney injury. Am J Physiol Renal Physiol. 2017; 312: F502-F515.
38. Tang J, Shi Y, Liu N, Blockade of histone deacetylase 6 protect against cisplatin-induced acute kidney injury. Clin Sci (Lond). 2018; 132: 339-359.
39. Brandenburger T, Salgado Somoza A, Lorenzen JM, Noncoding RNAs in acute kidney injury. Kidney Int. 2018; 94: 870-881.
40. Bellinger MA, Bean JS, Rader MA, Concordant changes of plasma and kidney microRNA in the early stage of acute kidney injury: time course in a mouse model of bilateral renal ischemia-reperfusion. PLoS One 2014; 9: e93297.
41. Saikumar J, Hoffman D, Kim TM, Expression, circulation, and excretion profile of microRNA-21, -155, and -18a following acute kidney injury. Toxicol Sci. 2012; 129: 256-267.
42. Wilflingseder J, Sunzenauer J, Toronyi E, Molecular pathogenesis of post-transplant acute kidney injury: assessment of whole-genome mRNA and miRNA profiles. PLoS One 2014; 9: e104164.
43. Lorenzen JM, Kaucsar T, Schauerte C, MicroRNA-24 antagonism prevents renal ischemia reperfusion injury. J Am Soc Nephrol. 2014; 25: 2717-2729.
44. Aguado-Fraile E, Ramos E, Conde E, A pilot study identifying a set of microRNAs as precise diagnostic biomarkers of acute kidney injury. PLoS One. 2015; 10: e0127175.
45. Chun N, Coca SG, He JC, A protective role for microRNA-688 in acute kidney injury. J Clin Invest. 2018; pli: 124923. Doi: 10.1172/JCI124923.
46. Lin J, Zhang X, Xue C, The long noncoding RNA landscape in hypoxic and inflammatory renal epithelial injury. Am J Physiol Renal Physiol. 2015; 309: F901-F913.
47. Köllong SC, Seeger H, Kistler A, Malat1 is dispensable for renal ischemia-reperfusion injury. Sci Rep. 2018; 8: 3438.
48. Yu TM, Palanisamy K, Sun KT, RANTES mediates kidney ischemia reperfusion injury through a possible role of HIF-1α and LncRNA PRINS. Sci Rep. 2016; 6: 18424.
49. Darby IA, Hewitson TD, Hypoxia in tissue repair and fibrosis. Cell Tissue Res. 2016; 365: 553-562.
50. Nangaku M, Hirakawa Y, Tanaka T, Epigenetic changes in the acute kidney

injury-to-chronic kidney disease transition. Nephron 2017; 137: 256-259.

51. Zager RA, Johnson AC, Becker K, Acute unilateral ischemic renal injury induces progressive renal inflammation, lipid accumulation, histone modification, and ``end-stage`` kidney disease. Am J Physiol Renal Physiol. 2011; 301: F1334-F1345.
52. Hewitson TD, Holt SG, Smith ER, Epigenetic modifications to H3K9 in renal tubulointerstitial cells after unilateral ureteric obstruction and TGF-β1 stimulation. Front Pharmocol. 2017; 8: 307.
53. Zhou X, Zang X, Zhuang S, Enhancer of zeste homolog 2 inhibition attenuates renal fibrosis by maintaining smad7 and phosphatase and tensin homolog expression. J Am Soc Nephrol. 2016; 27: 2092-2108.
54. Gomez IG, Nakagawa N, Duffield JS, MicroRNAs as novel therapeutic targets to treat kidney injury and fibrosis. Am J Physiol Renal Physiol. 2016; 310: F931-F944.
55. Chung AC, Meng X, Lan HY, miR-192 mediates TGF-beta/smad3-driven renal fibrosis. J Am Soc Nephrol. 2010; 21: 1317-1325.
56. Denby L, Ramadas V, McClure J, miR-21 and miR-214 are consistently modulated during renal injury in rodet models. Am J Physiol Renal Physiol. 2011; 179: 661-672.
57. Meng XM, Nikolic-Paterson DJ, Lan HY, TGF-beta: the master regulator of fibrosis. Nat Rev Nephrol. 2016; 12: 325-338.
58. Bai X, Tian J, Li X, MicroRNA-130b improves renal tubulointerstitial fibrosis via repression of snail-induced epithelial-mesenchymal transition in diabetic nephropathy. Sci Rep. 2016; 6: 20475.
59. Bechtel W, McGoohan S, Zeisberg M, Methylation determine fibroblast activation and fibrogenesis in the kidney. Nat Med. 2010; 16: 544-550.
60. Tampe B, Steinle U, Zeisberg M, Low-dose hydralazine prevents fibrosis in a murine model of acute kidney injury-to-chronic kidney disease progression. Kidney Int. 2017; 91: 157-176.
61. Tampe B, Tampe D, Zeisberg M, Tet3-mediated hydroxymethylation of epigenetically silenced genes contributes to bone morphogenic protein 7-induced reversal of kidney fibrosis. J Am Soc Nephrol. 2014; 25: 905-912.
62. Chang YT, Yang CC, Lin SL, DNA methyltransferase inhibition restores erythropoietin production in fibrotic murine kidneys. J Clin Invest. 2016; 126: 721-731.
63. Tikoo K, Ali Y, Gupta C, 5-azacitidine prevents cisplatin induced nephrotoxicity and potentiates anticancer activity of cisplatin by involving inhibition of metallothionein,

pAKT and DNMT1 expression in chemical induced cancer rats. Toxicol Lett. 2009; 191: 158-166.

64. Hayashi K, Itoh H, Transcription factors and epigenetic modulation: its therapeutic implication in chronic kidney disease. Arch Immunol Ther Exp (Warsz). 2015; 63: 193-196.
65. Nanayakkara PW, Kiefte-de Jong JC, Smulders YM, Association between global leukocyte DNA methylation, renak function, carotid intima-media thickness and plasma homocysteine in patients with stage 2-4 chronic kidney disease. Nephrol Dial Transplant. 2008; 23: 2586-5892.
66. Smyth LJ, McKay GJ, McKnight AJ, DNA hypermethylation and DNA hypomethylation is present at different loci in chronic kidney disease. Epigenetics 2014; 9: 366-376.
67. Larkin BP, Glastras SJ, Saad S, DNA methylation and the potential role of demethylating agents in prevention of progressive chronic kidney disease. FASEB J. 2018; 32: 5215-5226.
68. Van beneden K, Geers C, Van Den Branden C, Valproric acid attenuates proteinuria and kidney injury. J Am Soc Nephrol. 2011; 22: 1863-1875.
69. Lefvre GM, Patel SR, Dressler GR, Altering a histone H3K4 methylation pathway in glomerular podocytes promotes a chronic kidney disease phenotype. PLoS Genet. 2010; 6: e1001142.
70. Yang L, Shah JV, Bonentre JV, Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. Nat Med. 2010; 16: 535-543.
71. Shindo T, Doi S, Masaki T, TGF-β1 promotes expression of fibrosis-related genes through the induction of histone variant H3.3 and histone chaperone HIRA. Sci Rep. 2018; 8: 14060.
72. Liu H, Fergusson MM, Castilho RM, Augmented Wnt signaling in a mammalian model of accelerated aging. Science 2007; 317: 803-806.
73. Wolf I, Levanon-Cohen S, Bose S, Klotho: a tumor suppressor and an modulator of the IGF-1 and FGF pathways in human breast cancer. Oncogene 2008; 27: 7094-7105.
74. Doi S, Zou Y, Togao O, Klotho inhibits transforming growth factor-β1 (TGF-β1) signaling and suppresses renal fibrosis and cancer metastasis in mice. J Biol Chem. 2011; 286: 8655-8665.
75. Hu MC, Kuro-o M, Moe OW, Secreted klotho and chronic kidney disease. Adv Exp Med Biol. 2012; 728: 126-157.
76. Sun CY, Chang SC, Wu MS, Suppression of Klotho expression by protein-bound uremic toxins is associated with increased DNA methyltransferase expression and DNA hypermethylation. Kidney Int. 2012; 81: 640-650.
77. Irifuku T, Doi S, Masaki T, Inhibition of

H3K9 histone methyltransferase G9a attenuates renal fibrosis and retains klotho expression. Kidney Int. 2016; 89: 147-157.

78. Thakker RV, Genetics of parathyroid tumors. J Intern Med. 2016; 280: 574-583.
79. Chandrasekharappa SC, Guru SC, Marx SJ, Positional cloning of the gene for multiple endocrine neoplasia type 1. Science 1997; 276: 404-407.
80. Daniel FI, Cherubini K, Salum FG, The role of epigenetic transcription repression and DNA methyltransferase in cancer. Cancer 2011; 117: 677-687.
81. Svedlund J, Barazeghi E, Westin G, The histone methyltransferase EZH2, an oncogene common to benign and malignant parathyroid tumors. Endocr Relat Cancer. 2014; 21: 231-239.
82. Verdelli C, Corbetta S, Epigenetics alterations in parathyroid cancers. Int J Mol Sci. 2017; 18: E310.
83. Thran S, Bastepe M, GNAS spectrum of disorders. Curr Osteoporos Rep. 2015; 13: 146-158.
84. Elli FM, Bordogna P, Mantovani G, Mosaicism for GNAS methylation defects associated with psudohypoparathyroidism type 1B arose in early post-zygotic phases. Clin Epigenetics. 2018; 10: 16.
85. Hofman-Bang J, Gravesen E, Lewin E, Epigenetic methylation of parathyroid CaR and VDR promoters in experimental secondary hyperparathyroidism. Int J Nephrol. 2012; 2012: 123576.
86. Uchiyama T, Tatsumi N, Okabe M, Hypermethylation of the CaSR and VDR genes in the parathyroid glands in chronic kidney disease rats with high-phosphate diet. Hum Cell. 2016; 29: 155-161.

