

Histone methylation modification and diabetic kidney disease: Potential molecular mechanisms and therapeutic approaches (Review)

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Abstract. Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease and end-stage renal disease, and is characterized by persistent proteinuria and decreased glomerular filtration rate. Despite extensive efforts, the increasing incidence highlights the urgent need for more effective treatments. Histone methylation is a crucial epigenetic modification, and its alteration can destabilize chromatin structure, thereby regulating the transcriptional activity of specific genes. Histone methylation serves a substantial role in the onset and progression of various diseases. In patients with DKD, changes in histone methylation

are pivotal in mediating the interactions between genetic and environmental factors. Targeting these modifications shows promise in ameliorating renal histological manifestations, tissue fibrosis and proteinuria, and represents a novel therapeutic frontier with the potential to halt DKD progression. The present review focuses on the alterations in histone methylation during the development of DKD, systematically summarizes its impact on various renal parenchymal cells and underscores the potential of targeted histone methylation modifications in improving DKD outcomes.

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Abbreviations: AGE, advanced glycation end products; DKD, diabetic kidney disease; DZNep, 3-deazaneplanocin A; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; EndMT, endothelial-mesenchymal transformation; EZH2, enhancer of zeste homolog 2; G9a, euchromatic histone lysine methyltransferase 2; HKDM, histone lysine demethylase; HKMT, histone lysine methyltransferase; JmjC, jumonji C domain; LSD, lysine-specific demethylase; lncRNA, long non-coding RNA; MLL, mixed lineage leukemia; PTM, post-translational modification; SAM, S-adenosylmethionine; SET, su(var)3-9, enhancer-of-zeste and trithorax; WT1, Wilms tumor 1

Key words: DKD, epigenetics, histone methylation, transcriptional regulation, inhibitors

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1. Introduction

Diabetic kidney disease (DKD) is a prevalent microvascular complication, and the leading cause of mortality in individuals with diabetes (1). Approximately 30-40% of patients with diabetes develop DKD (2). It typically begins with microalbuminuria and, if not managed effectively, can progress to end-stage renal disease (3,4). Disease progression results in kidney failure, cardiovascular complications and premature mortality (5). Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, sodium-glucose cotransporter 2 inhibitors and mineralocorticoid receptor antagonists have been used to delay DKD progression (6-8). However, these treatments are not universally

effective (9,10). A 2021 study indicated that ~537 million adults worldwide were living with diabetes, and this number is projected to rise to 738 million by 2045. Of these individuals, nearly 90-95% have type 2 diabetes and approximately half are anticipated to develop DKD (11). Therefore, there is an urgent need to develop improved strategies for the prevention and treatment of DKD.

The pathogenesis of DKD is influenced by genetic and environmental factors. Specific genetic variants or predispositions can affect the susceptibility of an individual to DKD, and risk factors such as a high-sugar diet, high salt intake, obesity and physical inactivity contribute to the development of characteristic histological changes in the kidneys (12-14). These changes include podocyte depletion, tubular epithelial-mesenchymal transition (EMT), fibroblast activation, mesangial cell dysplasia and extracellular matrix (ECM) accumulation. Additionally, glomerular endothelial cells may undergo endothelial-mesenchymal transformation (EndMT), ultimately leading to irreversible renal fibrosis (15,16). Histone methylation of specific lysine or arginine residues is a critical post-translational modification (PTM) involved in these processes (17). The synergistic action of histone methylases and demethylases results in the addition or removal of methyl groups from specific sites on histones, leading to monomethylated (me1), dimethylated (me2) and trimethylated (me3) modifications (18,19). Although these changes only subtly alter the primary structure of histones, they can trigger chromatin remodeling, modify the accessibility of the underlying DNA sequences and regulate gene activation or silencing (20). Advanced glycation end products (AGEs) and various injury mediators produced by poor long-term glycemic control in patients with DKD have persistent effects on renal function by altering the distribution pattern of histone methylation in the kidneys (21). This highlights the pivotal role of histone methylation in mediating interactions between genes and environmental factors. By targeting these methylation modifications, it is possible to effectively improve the renal histological manifestations and prevent or reverse the progression of renal fibrosis and proteinuria in DKD, thereby offering a promising novel therapeutic strategy for prevention and treatment. Numerous studies have focused on the unique role of histone methylation modifications in DKD, emphasizing the importance of an improved understanding of the mechanisms underlying DKD and identifying novel treatment options (21-23).

The present review elucidates the mechanisms of histone methylation modifications and provides a comprehensive overview of the current understanding of histone methylation in patients with DKD. Furthermore, the present review systematically summarizes the alterations and impacts of histone methylases in various intrinsic renal cells of patients with DKD, including podocytes, renal tubule cells, fibroblasts, mesangial cells and glomerular endothelial cells, and discusses the therapeutic potential of inhibitors targeting histone methylation modifications as well as their prospective mechanistic implications.

2. Regulation of histone methylation constitutes a sophisticated, dynamic and precise network system

Histone methylation is a key epigenetic modification that influences various cellular processes, including gene expression,

DNA replication and repair, chromatin structure, and cell cycle control (24,25). Several histone residues are prone to methylation, notably at well-known sites, such as histone H3 lysine (H3K)4, H3K9, H3K27, H3K36, H3K79 and histone H4 lysine (H4K)20. This methylation process is dynamic and reversible, facilitated by the interplay between histone lysine methyltransferases (HKMTs or ‘writers’) and demethylases (HKDMs or ‘erasers’) (26). The methylation balance at these sites is maintained using S-adenosylmethionine (SAM) as the methyl donor (27,28).

HKMTs. Various types of HKMTs exist. All HKMTs except the DOT1 family possess conserved su(var)3-9, enhancer-of-zeste and trithorax (SET) domains, making them broadly similar from single-cell organisms to complex multicellular organisms (29). Each HKMT has a unique substrate specificity and catalytic function (Fig. 1). In humans, these classical HKMTs are categorized based on their catalytic sites: H3K4 methyltransferases, including mixed lineage leukemia (MLL) family complexes; H3K9 methyltransferases, including suppressor of variegation 3-9 homolog 1 and 2, SET domain bifurcated 1 and euchromatic HKMT2 (G9a); H3K27 methyltransferases, including enhancer of zeste homolog 2 (EZH2); H3K36 methyltransferases, including nuclear receptor binding SET domain protein 1-3; H3K79 methyltransferases, including disruptor of telomeric silencing 1-like; and H4K20 methyltransferases, including SET domain-containing protein 8 and suppressor of variegation 4-20 homolog 2 (26). Despite the complex recognition and binding mechanisms of HKMTs, HKMTs can transfer one, two or three methyl groups from the donor SAM to the ϵ -nitrogen of specific lysine side chains. While this enzymatic reaction induces only subtle changes in the primary structure of the modified polypeptide, it substantially affects the chromatin structure and DNA sequence accessibility, thereby influencing gene expression (27). Specifically, methylation of H3K4, H3K36 and H3K79 serves a pivotal role in transcriptional activation, whereas methylation of H3K9, H3K27 and H4K20 is typically associated with transcriptional inhibition (30). In addition, there are several non-classical lysine methylation sites on core histones (such as H3K23, H3K37 and H4K5) whose biological significance and regulatory pathways remain incompletely understood (31-33).

Histone lysine residues are not exclusive substrates of HKMTs. While numerous known histone methyltransferases are primarily involved in promoting lysine methylation on histones, they can also modify non-histone substrates (34). It is well-established that methylation of non-histone substrates is prevalent in cells. Various proteins, including transcription factors, cyclins, metabolic enzymes and DNA repair proteins, can be methylated at lysine residues. These changes impact the function, stability, interaction and intracellular localization of proteins, and serve a crucial role in the development of cancer, neurodegenerative diseases, metabolic disorders and numerous other diseases (35,36). Disease-specific methylation of non-histone substrates by a number of known histone methylases serves as a biomarker for these diseases and offers potential therapeutic targets (37,38).

HKDMs. Historically, histone methylation has been considered a permanent and stable modification (39). However, the

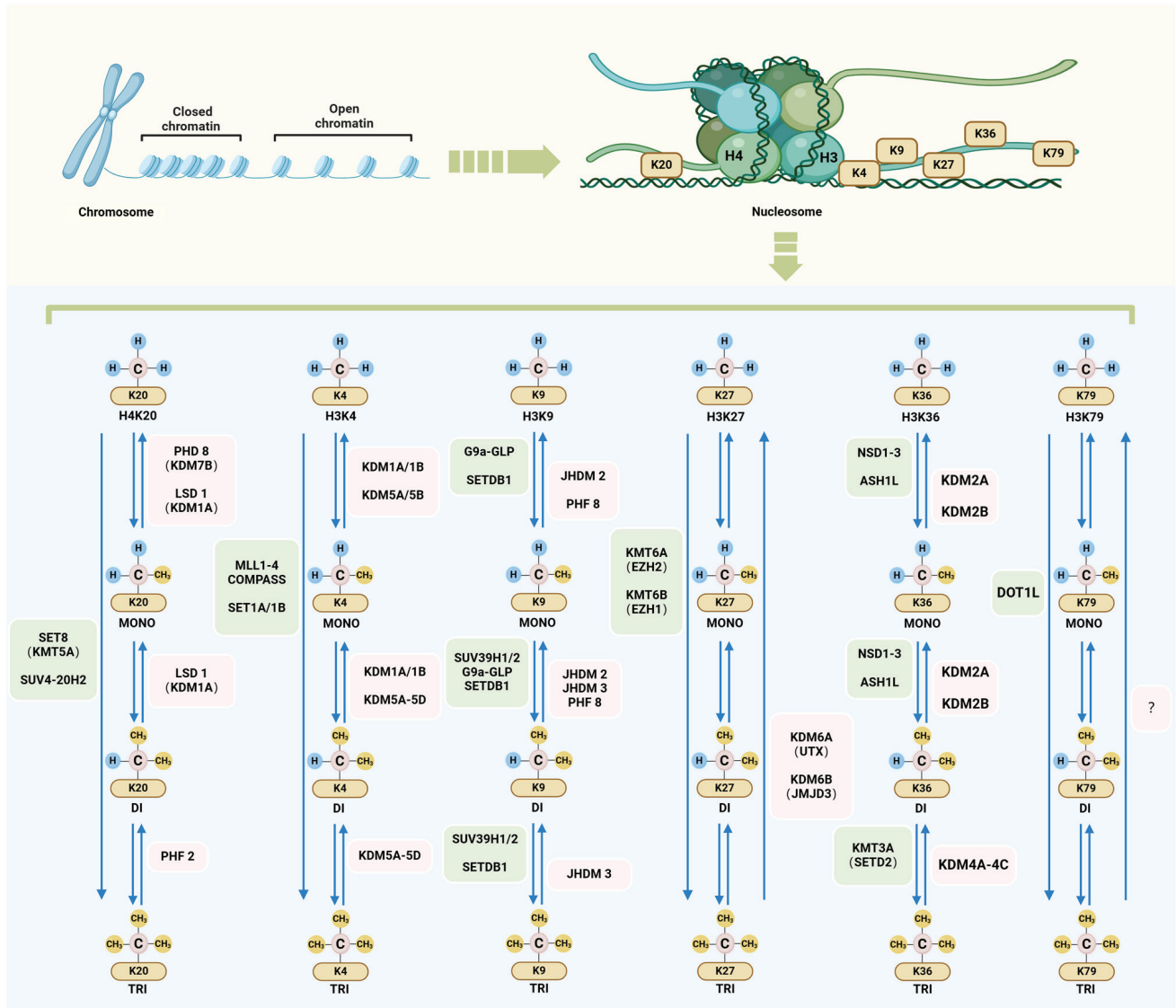


Figure 1. Histone methylase and histone demethylase are involved in the modification of classical histone lysine sites. ASH1L, absent, small, or homeotic discs 1-like; COMPASS, complex of proteins associated with Set1; DI, dimethylation; DOT1L, disruptor of telomeric silencing 1-like; EZH1/2, enhancer of zeste homolog 1/2; G9a, euchromatic histone lysine methyltransferase 2; GLP, G9a-like protein; H3K4, histone H3 lysine 4; H3K9, histone H3 lysine 9; H3K27, histone H3 lysine 27; H3K36, histone H3 lysine 36; H3K79, histone H3 lysine 79; H4K20, histone H4 lysine 20; JHDM, jumonji domain-containing histone demethylase; JMJD3, jumonji domain-containing protein-3; KDM1A/B, lysine-specific demethylase 1A/1B; KDM2A/B, lysine-specific demethylase 2A/2B; KDM5A-5D, lysine-specific demethylase 5A-5D; KDM6A/B, lysine-specific demethylase 6A/6B; KDM7B, lysine-specific demethylase 7B, KMT, lysine methyltransferase; KMT5A, lysine methyltransferase 5A; KMT6A/B, lysine methyltransferase 6A/B; LSD 1, lysine-specific demethylase 1; MLL1-4, mixed-lineage leukemia protein 1-4; MONO, monomethylation; NSD1-3, nuclear receptor-binding SET domain protein 1-3; PHD, plant homeodomain; PHF 2/8, plant homeodomain finger protein 2/8; SET, suppressor of variegation, enhancer of zeste, trithorax domain; SETDB1, SET domain bifurcated 1; SUV39H1/2, suppressor of variegation 3-9 homolog 1/2; SUV4-20H2, suppressor of variegation 4-20 homolog 2; TRI, trimethylation; UTX, ubiquitously transcribed tetratricopeptide repeat, X chromosome.

identification of lysine-specific demethylase (LSD)1 (also known as KDM1A) from the LSD family has revolutionized this perspective (40). HKDMs, including members of the LSD and jumonji C domain (JmjC) domain-containing families, can reverse changes in histone methylation (18). Specifically, the LSD family, which includes LSD1 and LSD2, removes mono- and dimethyl groups from histones H3K4 and H4K20 (41). Additionally, JmjC domain-containing families, which encompass subfamilies, such as lysine demethylase 2-6 (KDM2-6), serve substantial roles in histone demethylation (42). Although no H3K79 demethylases have been identified, studies have suggested that H3K79 methylation is reversible. Observations have indicated that H3K79 methylation levels changed

dynamically during the cell cycle, with a notable decrease after S phase, specifically in mammalian cell lines such as HeLa cells and mouse embryonic fibroblasts (43,44). These findings suggested the presence of histone demethylases in these cells.

Intricate regulatory network of histone methylation. The balance of histone methylation within cells is particularly vulnerable to external disruption. This can affect the function of essential proteins that add or remove methylation markers and can also change the levels of SAM, which influences the overall pattern of methylation modifications (18). SAM availability is critical as it is a vital methyl donor and a key intermediate in several metabolic pathways (45). Disturbances

in metabolic processes can impair SAM synthesis and availability, substantially affecting the expression and maintenance of histone methylation markers (46,47). Several proteins, known as co-factors, influence histone methylation by interacting with HKMTs or HKDMs. These interactions affect the localization, stability and enzymatic functions of HKMTs and HKDMs (48,49). For example, WD repeat domain 5 and ASH2 like histone lysine methyltransferase complex subunit (ASH2L), key components of the MLL complex, enhance H3K4 methylation by facilitating the recruitment of other MLL complex proteins to target sites, thereby affecting the progression of breast cancer and glioblastoma (50,51). In addition to proteins, non-coding RNAs serve a vital role in controlling histone methylation and substantially affect gene transcription by recruiting histone methyltransferases (52). The interplay among histone modifications has been the focus of epigenetic research. Histone modification crosstalk refers to the phenomenon in which the recognition or deposition of one epigenetic marker on a histone influences the distribution of another marker. This intricate crosstalk enhances the complexity and specificity of histone modification combinations, thereby enabling precise regulation of various biological processes, such as cell fate determination, development and disease states (53). A prime example of this cross-talk is the interaction between histone methylation and ubiquitination. Specifically, ubiquitination of lysine 14 on histone H3 is crucial for the initiation of H3K9 methylation (54). Similarly, existing histone acetylation and phosphorylation in gene promoter regions subtly influence the further development of histone methylation. For example, the dynamic interchange of acetylation and methylation of H3K27 regulates gene expression, with acetylation promoting transcriptional activation and methylation, leading to silencing (55). In cancer cells, deacetylated H3K27 can be specifically targeted for methylation by KDM6A (also known as ubiquitously transcribed tetratricopeptide repeat, X chromosome) after treatment with inhibitory drugs, resulting in the transcriptional suppression of *MYC*, *BCL2*, *CCND1* and other oncogenes (56). Additionally, a study showed that phosphorylation at threonine 11 on histone H3 hinders DOT1-catalyzed methylation at H3K79me3, thereby affecting the chromatin state and gene transcription activities vital for autophagy regulation and telomere silencing (57).

3. Distinct function of histone methylation in the pathogenesis and progression of DKD

Substantial advancements in molecular biology and genomics have transformed medical research, moving beyond macroscopic phenotypic observations to explore changes in key epigenetic markers, such as histone methylation (58,59). These changes serve a critical role in disease pathogenesis and exert intricate molecular effects. Dysregulation of histone methylation has been linked to various diseases, including cancer, neurodegenerative disorders and developmental anomalies (60,61). Rapid and dynamic changes in histone methylation have been observed in patients with DKD. Research has shown an association between DKD severity and the levels of the active marker H3K4me2 and the inhibitory marker H3K27me3 (23,62). Further investigations have indicated that these methylation changes can trigger pathological processes

in DKD, such as cell dedifferentiation, inflammation, oxidative stress and fibrosis (63–66). Additionally, the response of different kidney cell types to histone methylation varies, leading to nonuniform pathological changes. This variability results from the diverse functions and microenvironmental differences between these cells (Fig. 2). In this section, the altered distribution patterns of histone methylation (Table I) and functional disparities in histone methylation in specific intrinsic renal cells under diabetic conditions are discussed.

Podocytes. Podocytes are specialized epithelial cells that form intricate networks of foot processes, essential for the glomerular filtration barrier. However, their proliferative capacity is limited, and once damaged, they cannot be repaired, making them particularly susceptible to DKD (67). These cells face multiple stressors, including mechanical, oxidative and immune challenges. Although normally adaptive to stress to maintain homeostasis, excessive stress may lead to substantial biological changes, such as structural disintegration and metabolic dysfunction, ultimately causing podocyte loss (68). In patients with DKD, podocytes disappear in response to hyperglycemia. Subsequently, surviving podocytes undergo changes in size and shape to compensate for the exposed basement membrane caused by podocyte loss. This morphological transition is accompanied by the activation of signaling pathways associated with podocyte dedifferentiation, leading to the transformation of the cell phenotype, such as diminished expression of cell-specific markers, aberrant organization of foot processes and impairment of cell-specific functionalities. Although these compensatory changes may temporarily delay the progression of proteinuria, they ultimately compromise podocyte damage resistance and structural integrity, thereby exacerbating the progression of DKD (69,70).

Podocyte dedifferentiation is regulated by a complex array of molecular mechanisms, primarily involving signaling pathways, such as the Wnt/ β -catenin, Notch and TGF- β /Smad signaling pathways (71). These pathways collectively govern cell fate (72). Histone methylation changes the transcriptional status of key factors in these signaling pathways, affecting podocyte differentiation and the occurrence of glomerular disease. In the promoter region of the podocyte-specific marker Wilms tumor 1 (WT1), jumonji domain-containing protein (JMDJ)3 (KDM6B), a demethylase from the JmjC family, mediates a reduction in transcriptional inhibitory marker H3K27me3 to maintain the normal expression of podocyte-specific markers (73). WT1 has an antagonistic effect on histone methyltransferase EZH2, which ameliorates podocytic injuries mediated by β -catenin in diabetic models, such as apoptosis and oxidative stress. This gene transcriptional de-inhibition occurs through reducing the enrichment of H3K27me3 in the promoter of the Wnt antagonist, secreted frizzled related protein 1, suggesting that podocytes possess compensatory mechanisms to adapt to epigenetic modifications caused by environmental changes (74). Elevated levels of AGEs, which are key mediators of metabolic memory, are associated with the epigenetic reactivation of the long-silenced Notch pathway in DKD (75). AGEs decrease the expression of nuclear inhibitor of protein phosphatase 1 (NIPPI), which is an upstream regulator of EZH2, disrupting the interaction between NIPPI and EZH2, and reducing

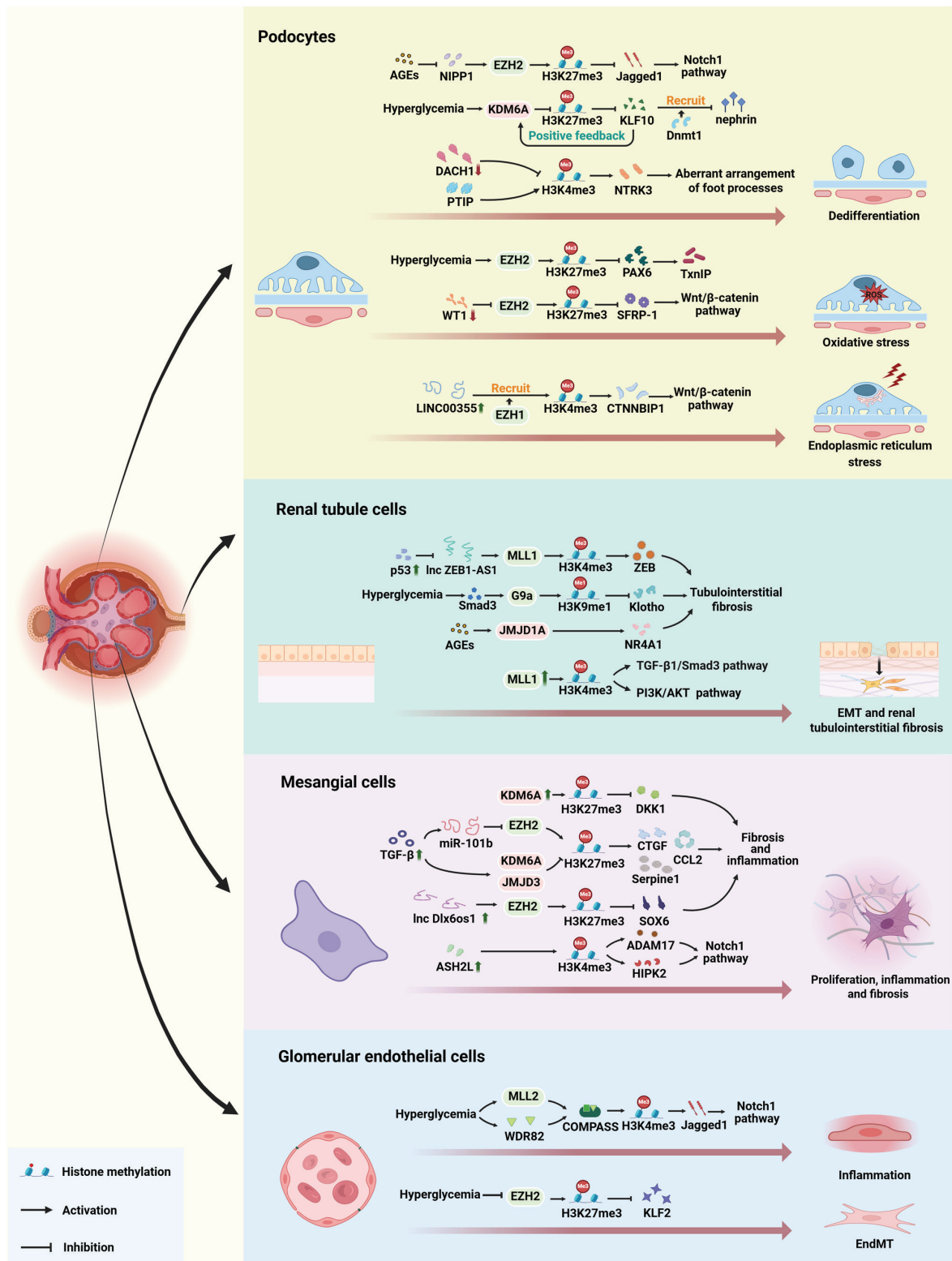


Figure 2. Mechanisms of injury induced by histone methylation disorders in diabetic nephropathy affect the major effector cells of the kidney. ADAM17, a disintegrin and metalloproteinase 17; AGEs, advanced glycation end products; ASH2L, ASH2 like histone lysine methyltransferase complex subunit; CCL2, C-C motif chemokine ligand 2; COMPASS, complex of proteins associated with Set1; CTGF, connective tissue growth factor; CTNNBIP1, catenin β interacting protein 1; DACH1, dachshund family transcription factor 1; DKK1, dickkopf WNT signaling pathway inhibitor 1; Dnmt1, DNA (cytosine-5)-methyltransferase 1; EMT, epithelial-mesenchymal transition; EndMT, endothelial-mesenchymal transformation; EZH1/2, enhancer of zeste homolog 1/2; G9a, euchromatic histone lysine methyltransferase 2; HIPK2, homeodomain interacting protein kinase 2; H3K4, histone H3 lysine 4; H3K9, histone H3 lysine 9; H3K27, histone H3 lysine 27; JMJD1A, jumonji domain containing 1A; KDM6A, lysine-specific demethylase 6A; KLF10, Kruppel like factor 10; KLF2, Kruppel like factor 2; Inc, long non-coding RNA; Inc Dlx6os1, long non-coding RNA Dlx6 opposite strand transcript 1; LINC00355, long intergenic non-protein coding RNA 355; Jagged1, jagged canonical Notch ligand 1; me3, trimethylated; miR-101b, microRNA 101b; MLL, mixed lineage leukemia protein; NIPPI1, nuclear inhibitor of protein phosphatase 1; NR4A1, nuclear receptor subfamily 4 group A member 1; NTRK3, neurotrophic receptor tyrosine kinase 3; PAX6, paired box 6; PTIP, PAX transactivation domain interacting protein; Serpine1, serpin family E member 1; SFRP-1, secreted frizzled related protein 1; TxnIP, thioredoxin interacting protein; WT1, Wilms tumor protein 1; WDR82, WD repeat domain 82; ZEB, zinc finger E-box binding homeobox; ZEB1-AS1, zinc finger E-box binding homeobox 1 antisense RNA 1.

Table I. Alterations in histone methylation profiles across diverse cell types in experimental models of diabetic nephropathy.

First author/s, year	Histone methylation	DKD	Model	Sample	(Refs.)
	Activating marks				
Zhang <i>et al</i> , 2023	H3K4me3	Increased in CTNNBIP1 promoter	db/db mice	Podocytes	(81)
Cao <i>et al</i> , 2021		Increased in NELL2/NTRK3/PAMP1/MYCL1 promoter	STZ mice	Podocytes	(80)
Wang <i>et al</i> , 2018		Decreased in ZEB promoter	STZ mice and db/db mice	Renal tubular epithelial cells	(95)
Zhong <i>et al</i> , 2024		Increased in HIPK2 promoter	db/db mice	Glomerular mesangial cells	(117)
Pandya Thakkar <i>et al</i> , 2022		Increased in Jagged1 and Jagged2 promoter	ob/ob mice	Glomerular endothelial cells	(130)
Takizawa <i>et al</i> , 2013		Increased in Serpine1 promoter	STZ mice	Primary mouse endothelial cells	(126)
	Repressive marks				
Irifuku <i>et al</i> , 2016	H3K9me1	Increased in Klotho promoter	UUO mice	Renal tubular epithelial cells	(96)
An <i>et al</i> , 2023	H3K27me2	Increased in EMT-associated genes	UUO mice	Fibroblasts and macrophages	(106)
Lin <i>et al</i> , 2019	H3K27me3	Decreased in KLF10 promoter	Mouse podocytes under high glucose conditions	Podocytes	(77)
Siddiqi <i>et al</i> , 2016		Decreased in PAX6 promoter	STZ mice	Podocytes	(66)
Majumder <i>et al</i> , 2018		Decreased in Jagged1 promoter	db/db mice and adriamycin mice	Podocytes	(64)
Chen <i>et al</i> , 2022		Increased in SOX6 promoter	db/db mice	Glomerular mesangial cells	(118)
Chen <i>et al</i> , 2019		Decreased in inflammatory genes	db/db mice	Glomerular mesangial cells	(120)

DKD, diabetic kidney disease; EMT, epithelial-mesenchymal transition; H3K4, histone H3 lysine 4; H3K9, histone H3 lysine 9; H3K27, histone H3 lysine 27; me1, monomethylated; me2, dimethylated; me3, trimethylated; STZ, streptozocin; UUO, unilateral ureteral obstruction.

H3K27me3 levels in podocytes (76). Majumder *et al* (64) observed that decreased H3K27me3, due to downregulation of methylase EZH2 or upregulation of demethylase KDM6A, leads to the de-repression of Jagged1, thereby activating the Notch1 pathway. This promotes podocyte dedifferentiation and susceptibility to damage, and contributes to renal function deterioration (64). However, RNA sequencing analysis in another study revealed no substantial alterations in *Jagged1* and other *Notch* receptor mRNA levels in podocytes over-expressing KDM6A. KDM6A expression was upregulated under high-glucose conditions, but not under hypertensive conditions. Loss of H3K27me3 led to transcriptional de-repression of Kruppel like factor 10 (KLF10), enhancing the feedback loop between KDM6A and KLF10, and maintaining high expression levels of KLF10 under diabetic conditions. Increased KLF10 expression recruited DNMT1 to the nephrin promoter, inhibited nephrin expression

and contributed to podocyte dysfunction. Upregulation of KLF10 expression also suppressed the expression of other podocyte-specific genes, such as *WT1*, *Podocin* and *Synaptopodin* (77).

In patients with diabetic nephropathy, alterations in H3K4 methylation in podocytes are also observed. Paired box transactivation domain interacting protein (PTIP)-dependent H3K4 methylation is crucial for maintaining differentiation and cell type-specific transcriptional programs in mature podocytes. In normal podocytes, PTIP is recruited to target gene promoters by PAX or dachshund family transcription factor 1 (DACH1), with each binding mode exerting opposing effects on methylase activity. Specifically, when PTIP is recruited by PAX, it promotes methylase activity, while recruitment by DACH1 inhibits methylase activity (78-80). This balance shapes the H3K4 methylation landscape in the podocytes. In DKD mice, reduced DACH1 expression leads

to transcriptional de-repression of multiple downstream target genes (80). Abnormal expression of the H3K4me3 downstream gene *NTRK3* results in an aberrant foot process arrangement and impaired podocyte function (22).

In addition to inducing cellular dedifferentiation, histone methylation also induces oxidative stress in podocytes. Low EZH2 expression decreases H3K27me3 levels and triggers PAX6 expression in podocytes with high glucose levels. The enrichment of PAX6 in the gene promoter promotes the expression of the antioxidant inhibitor, thioredoxin interacting protein, thereby enhancing oxidative stress in podocytes (66). Additionally, non-coding RNA LINC00355 elevates H3K4me3 levels by recruiting histone methylase EZH1 to the catenin β interacting protein 1 promoter, activating the β -catenin signaling pathway, and promoting endoplasmic reticulum stress-induced podocellular injury (81).

Renal tubular epithelial cells and fibroblasts. Tubular epithelial cells and the tubular interstitium constitute >90% of the renal cortex and serve pivotal roles in maintaining fluid and electrolyte balance, excretion of metabolic waste and regulation of blood pressure (82). Given their high energy demand and reliance on aerobic metabolism, tubular epithelial cells are particularly susceptible to diabetes-related metabolic disorders (83,84). Structural alterations in the diabetic renal tubules, including atrophy, interstitial fibrosis and peritubular capillary thinning, are closely linked to decreased renal function (85). Tubular atrophy and interstitial fibrosis form the basis of DKD renal fibrosis and contribute substantially to the decline in renal function (86). TGF- β 1 is a well-established pathogenic factor in fibrotic diseases affecting multiple organs and serves a pivotal role in the onset and progression of DKD (87-90). In progressive renal fibrosis associated with DKD, there is substantial upregulation of TGF- β 1 synthesis and secretion, along with Smad3 phosphorylation. This triggers a cascade of core responses, including EMT, fibroblast activation and abnormal ECM deposition (37,91). Modification of histone methylation serves as a key epigenetic regulatory mechanism in this process by modulating the expression of genes related to fibrosis (92).

H3K4 methylation and gene transcription activation mediated by histone methylase MLL1 are essential for the activation of TGF- β /Smad3 and AKT signaling pathways, upregulation of Snail and downregulation of E-cadherin (93). Tao *et al* (63) reported that epigenetic inhibitors targeting methylase EZH2 effectively attenuated kidney injury and fibrosis by modulating the TGF- β /Smad3 signaling pathway via regulation of Smad7. Smad7 is an essential inhibitory factor for fibrosis, which suppresses the activation of the TGF- β 1/Smad3 pathway by inhibiting Smad3 phosphorylation (94). In diabetic nephropathy, elevated p53 levels inhibit the expression of the zinc finger E-box binding homeobox 1 antisense RNA 1 (*ZEB1-AS1*) long non-coding RNA (lncRNA), thereby regulating the binding of methylase MLL1 to the ZEB promoter. This leads to the downregulation of H3K4me3 and the inhibition of ZEB expression, contributing to the development of renal fibrosis (95). Furthermore, various methylation and demethylation events in renal tubules can serve as downstream targets of fibrosis-related signaling pathways. Irifuku *et al* (96) demonstrated that TGF- β 1/Smad3 upregulates G9a, leading to

H3K9 methylation, which facilitates the induction of fibrosis markers and suppresses Klotho expression. Another study on chronic kidney disease revealed that hypoxia-inducible factor (HIF)1 α /HIF1 β -induced activation of JMJD1A, a histone demethylase opposing G9a, exerts a negative regulatory effect on the expression of renal fibrosis-related factors (97). However, whether the upregulation of HIF1 α /HIF1 β in DKD results in similar methylation changes remains unclear. Additionally, elevated levels of AGEs in a mouse of diabetic nephropathy can upregulate the expression of JMJD1A, leading to an increase in nuclear receptor subfamily 4 group A member 1 levels and ultimately inhibiting the fibrotic process of renal tubular epithelial cells (98). Notably, H3K9 has garnered attention as a mediator linking the TGF- β 1/Smad3 signaling pathway to Klotho (96). However, another study indicated that the age-related decreased expression of Klotho results from the transcriptional suppression of key factors in the serum/glucocorticoid regulated kinase 1/FOXO3 signaling pathway driven by H3K27me3 (99). Further exploration is warranted to determine whether H3K9 methylation upstream of Klotho specifically promotes fibrosis in DKD.

Fibroblasts serve a pivotal role in ECM protein synthesis in fibrotic kidneys (100,101). Fibroblasts are multifaceted and include resident fibroblasts, mesenchymal stem cell-like cells, epithelial cells, endothelial cells and myeloid fibroblasts (102). During the progression of renal fibrosis, injured renal tubule cells and infiltrating inflammatory cells release diverse profibrotic mediators that target fibroblast precursors and induce fibroblast activation (103). The TGF- β /Smad3 signaling pathway regulates fibroblast activation in patients with DKD (91). TGF- β 1 induces the redistribution of H3K9me3 within fibroblast nuclei, leading to increased α -smooth muscle actin expression (104). Additionally, increased methylase EZH2 expression has been identified in damaged kidneys and renal interstitial fibroblasts, and serves as a crucial regulatory factor in the progression of renal fibrosis. EZH2-mediated histone hypermethylation facilitates the activation of the TGF- β /Smad3, EGFR and platelet derived growth factor receptor pathways, resulting in the upregulation of pro-fibrotic genes, such as collagen I and the deposition of ECM proteins. The activation of renal fibroblasts and the subsequent development of renal interstitial fibrosis are critical events in the pathogenesis of chronic kidney disease (105). JMJD3-mediated histone demethylation activates genes by removing inhibitory H3K27me3 from the target gene promoter, thereby promoting myeloid fibroblast activation and accumulation in the kidney (106). Notably, the specific loss of JMJD3 in myeloid fibroblasts exerts an inhibitory effect on fibrosis similar to that of overall JMJD3 deficiency (106).

Mesangial cells. Mesangial cells exert multiple functions in maintaining glomerular function and structure (107). Within the glomeruli, mesangial cells, along with their associated mesangial matrix, form a stalk that holds together multiple capillary loops. Mesangial cells serve a crucial role in regulating the contraction and expansion of the capillaries to ensure a normal glomerular filtration rate. Outside the glomeruli, mesangial cells are integral to regulating blood pressure and fluid volume through their secretion of renin (108,109). Additionally, these cells serve as the primary producers

of glomerular matrix (110). In DKD, mesangial cells are primarily responsible for glomerular hypertrophy and sclerosis. Heightened activation of mesangial cells is observed in the kidneys of patients with DKD, which is characterized by increased proliferative activity and excessive production of type IV collagen and fibronectin, both of which are pivotal components that contribute to fibrosis and sclerosis (111-113). In addition, mesangial cells exhibit reduced responsiveness to angiotensin II (114). At the molecular level, mesangial cells undergo epigenetic and transcriptional changes, leading to the expression of various growth factors, fibrotic elements, complement components and other pro-inflammatory mediators, which collectively drive the progression of glomerular fibrosis and sclerosis (115).

Similar to podocytes, abnormal histone methylation has been demonstrated to mediate aberrant activation of the Notch1 signaling pathway in mesangial cells in a diabetic nephrotic model. Zhong *et al* (116,117) identified ASH2L, a crucial component of the MLL methyltransferase complex, as a pivotal 'transcriptional igniter'. The enrichment of ASH2L-mediated H3K4me3 in the promoter region of the gene substantially enhanced the expression of a disintegrin and metalloproteinase 17 (ADAM17) and homeodomain interacting protein kinase 2 (HIPK2) as co-factors. Subsequently, ADAM17 and HIPK2 facilitate the expression and nuclear translocation of Notch intracellular domain 1 in the mesangial cells of diabetic mice, ultimately leading to the activation of the Notch1 signaling pathway, which is implicated in the pathogenesis of DKD fibrosis and inflammation (116,117). Furthermore, high expression levels of the Dlx6 opposite strand transcript 1 (Dlx6os1) lncRNA are observed in diabetic mesangial cells. Dlx6os1 recruits methylase EZH2 to inhibit gene expression via EZH2-mediated H3K27 methylation within the SOX6 promoter region, thereby accelerating hyperglycemic mesangial cell proliferation, fibrosis and the release of inflammatory cytokines (118). KDM6A, a histone H3K27 demethylase, serves a crucial role in regulating inflammation in cultured mesangial cells and db/db mouse kidneys. Dickkopf WNT signaling pathway inhibitor 1 expression is modulated by H3K27me3, and its upregulation effectively mitigates TGF- β 1-induced fibrosis (119). Furthermore, KDM6A interacts with p53, leading to DNA damage (120). Notably, H3K27me3 is also influenced by TGF- β , and the increased TGF- β levels in diabetic conditions result in decreased methylase EZH2 expression, and increased demethylase KDM6A and demethylase JMJD3 expression. This promotes profibrotic and inflammatory gene activation in rat mesangial cells through H3K27me3 depletion of genes such as connective tissue growth factor, Serpine1 and C-C motif chemokine ligand 2 (121).

Glomerular endothelial cells. Glomerular endothelial cells are specialized vascular cells that form the glomerular filtration membrane and act as primary barriers to circulating substances in the blood (122). Glomerular endothelial cells are particularly susceptible to hyperglycemia-induced damage, leading to endothelial cell dysfunction in DKD, which is a critical pathological change in the early stages (123). This dysfunction results in increased permeability, apoptosis and loss of glomerular endothelial cell fenestration, resulting in substantial plasma protein wastage (124).

Although the mechanisms underlying glomerular endothelial cell dysfunction are not fully understood, histone methylation modifications are involved in processes such as cellular inflammation and EndMT. For instance, elevated blood glucose levels induce increased H3K27me3 levels in endothelial cells by promoting the nuclear localization of methylase EZH2 and assembly of the H3K27 methylase complex 2, leading to endothelial inflammation through the downregulation of Kruppel like factor 2 (125). Furthermore, high glucose-induced H3K4me3 triggers the transcriptional activity of Serpine1, a downstream NF- κ B gene, resulting in increased expression of plasminogen activator inhibitor-1, a crucial protein encoded by Serpine1, ultimately leading to endothelial dysfunction (126). Huang *et al* (127) revealed that methylase lysine methyltransferase (KMT)5A interacts with its co-factor, cAMP response element-binding protein, to cooperatively regulate protein tyrosine phosphatase 1B expression, influencing P65 phosphorylation and inflammatory factor levels, thereby contributing to the development of DKD. These findings underscore the substantial role of high glucose-driven histone methylation in DKD. Additionally, various histone methylases have been identified as crucial epigenetic regulators of EndMT in endothelial cells (128). For example, inflammatory stimuli and hypoxia induce endothelial identity and functional disorders, which are tightly controlled by the histone demethylase JMJD2B through the modulation of H3K9me3 levels (129). Further studies are required to determine whether similar effects occur in renal endothelial cells under high-glucose conditions.

Histone methylation serves a role in regulating the differentiation and plasticity of endothelial cells in DKD. Similar to that in podocytes, histone methylation contributes to the reactivation of the Notch1 signaling pathway in endothelial cells. This regulatory mechanism involves the deposition of H3K4me3, rather than the ablation of H3K27me3 markers. High glucose exposure results in the accumulation of H3K4me3 in endothelial cells, driven by increased expression of MLL2 and WD repeat domain 82, two crucial protein subunits of H3K4 methyltransferase complex. Aberrant elevation of H3K4me3 in the promoters of Jagged1 and Jagged2 leads to the acquisition of mesenchymal properties in endothelial cells through hyperactivation of the Notch signaling pathway (130). Studies have elucidated the unique role of bivalent chromosomes composed of H3K27 and H3K4 linkages in ontogeny and cell phenotype maintenance, suggesting that the phenotype of terminally differentiated cells is partially sustained through interactions between active H3K4me3 and inhibitory H3K27me3 markers (131,132). H3K27 methylation is a well-established marker of transcriptional silencing and is crucial for maintaining stable differentiated states (133,134). The abundant deposition of H3K4 in gene promoters often leads to the activation of gene transcription. H3K4me3 histone methylation co-mediated by the methylase MLL3/4 and its co-factor PTIP is necessary for the maintenance or re-establishment of cell epithelial phenotypes (135). H3K4me3, a marker of gene activation, and inhibitory H3K27me3, a marker of gene repression, together form bivalent chromatin in the kidney (136). However, their influence on the occurrence and progression of DKD via crosstalk remains debatable. Therefore, it is prudent to consider the roles of H3K27, H3K4 and bivalent chromatin when studying histone methylation during phenotypic changes

Table II. Targets and impacts of inhibitors associated with histone methylation modification.

First author/s, year	Inhibitor	Target	Histone	Action	(Refs.)
	Small molecule inhibitors				
Majumder <i>et al</i> , 2018	GSK-J4	UTX/KDM6A	H3K27	GSK-J4 mitigates the progression of adriamycin or diabetes-induced glomerular disease and accompanied by safeguarding against podocyte differentiation.	(64)
Hung <i>et al</i> , 2022				GSK-J4 ameliorates glomerular morphological abnormalities, mesangial matrix accumulation, inflammation and fibrosis in diabetic mice.	(119)
An <i>et al</i> , 2023		JMJD3/KDM6B	H3K27	GSK-J4 effectively mitigates renal fibrosis, suppresses bone marrow fibroblast activation and impedes M2 macrophage polarization in obstructed kidneys.	(106)
Majumder <i>et al</i> , 2018	EPZ-6438/ tazemetostat	EZH2	H3K27	EPZ-6438 facilitates postmitotic podocyte dedifferentiation and expedites glomerular disease progression.	(64)
Siddiqi <i>et al</i> , 2016	DZNep	EZH2	H3K27	DZNep induces the suppression of PAX6 expression, instigates intracellular oxidative stress and impairs podocyte function.	(66)
Irifuku <i>et al</i> , 2016	BIX 01294	G9a	H3K9	BIX 01294 effectively hinders TGF- β 1-induced fibrotic alterations and mitigates the downregulation of Klotho.	(96)
Zou <i>et al</i> , 2023	MI-503	MLL1-menin interaction	H3K4	MI-503 exerts antifibrotic effects through the downregulation of TGF- β 1, Snail and Twist expression, dephosphorylation of Smad3 and AKT, inhibition of epithelial-mesenchymal transition, and inactivation of interstitial fibroblasts.	(93)
	Natural products				
Tao <i>et al</i> , 2022	GNA	EZH2	H3K27	GNA modulates the TGF- β /Smad3 signaling pathway, thereby ameliorating renal fibrosis mediated by Smad7.	(63)
Sasaki <i>et al</i> , 2016	Sinefugin	SET7/9	H3K4	Sinefugin can effectively ameliorate renal fibrosis by suppressing the expression of intermediate mesenchymal markers and extracellular matrix proteins in the kidney.	(158)

DZNep, 3-deazaneplanocin A; GNA, gambogenic acid; H3K4, histone H3 lysine 4; H3K9, histone H3 lysine 9; H3K27, histone H3 lysine 27; PAX6, paired box 6.

and functional transformations, particularly those associated with the Notch1 signaling pathway.

4. Therapeutic approaches aimed at modulating histone methylation in the context of DKD

Histone methylation affects gene expression, which is critical for the progression of DKD, marking a key event in the pathological timeline (38). Most of these modifications are reversible

and regulated by intricate networks, indicating the potential of histone methylation as a reliable biomarker and effective therapeutic target for the treatment of DKD (137,138). However, compared with that of classical PTMs such as acetylation, drug development targeting histone methylation is still in its early stages, particularly for DKD treatment (139,140). Therefore, the present review provides a comprehensive overview of existing histone methylase inhibitors and the potential therapeutic approaches investigated in experimental studies (Table II).

A series of small-molecule inhibitors targeting histone methylation have emerged, and show promise for managing various pathological processes in DKD. Specific HKMTs and HKDMs, including EZH2, KDM6A and G9a, are abnormally expressed in several intrinsic renal cells in DKD (138,141). The strategic use of targeted therapies, particularly histone methyltransferase inhibitors, has effectively reduced sugar-induced renal cell damage in animal models and *in vitro*, substantially slowing DKD progression (141). In 2020, The Food and Drug Administration first approved the KMT inhibitor tazemetostat for clinical use, although its application is currently limited to the treatment of hematological malignancies and solid tumors (142). This approval prompted researchers to explore the potential of histone methyltransferase inhibitors in the treatment of other diseases, including DKD, malignant rhabdoid tumors and ovarian cancer, highlighting their promise as novel therapeutic strategies (64,143,144). 3-Deazaneplanocin A (DZNep) is a well-known inhibitor of histone methyltransferase, initially identified for its potential in antiviral research. Its primary mechanism involves the reduction of H3K27me3 modification by inhibiting methylase EZH2 activity, leading to the activation of gene expression (66). DZNep has been widely utilized to explore its potential as an antitumor agent, as EZH2 expression is upregulated in a variety of cancer types, including lung cancer, breast cancer and glioblastoma, and is closely associated with the development and progression of tumors (145-148). However, due to the indirect inhibition of EZH2, primarily by increasing S-adenosyl-L-homocysteine levels, DZNep lacks specificity as a drug candidate (149). EPZ-6438/tazemetostat is a potent and highly selective inhibitor of EZH2 methyltransferase, which is currently undergoing advanced stage testing (150). In a study on DKD, EPZ-6438 effectively inhibited podocyte dedifferentiation and mitigated podocyte damage under adverse conditions (64). GSK-J4, a leading H3K27 demethylase inhibitor, exerts a potent dual inhibitory effect on JMJD3 and KDM6A (151). GSK-J4 effectively mitigates the pathological changes in various intrinsic renal cells associated with DKD, thereby attenuating the progression of glomerular disease, mesangial matrix accumulation, kidney inflammation and fibrosis (64,106,119). A range of inhibitors targeting the histone H3K9 methylase G9a have been developed, with BIX-01294 being a particularly potent and well-tolerated inhibitor of G9a. This compound has been widely used in relevant research because of its superior efficacy and reduced toxicity compared with earlier small-molecule inhibitors (152-154). During the process of renal fibrosis, BIX-01294 effectively suppresses the EMT of tubule cells and attenuates the TGF- β 1-induced down-regulation of Klotho (96). The aforementioned series of small molecule drugs primarily function as inhibitors by suppressing the activity of key enzymes involved in histone methylation. Disruption of the interactions between core enzymes and other co-factors within the histone methylase complex also affects the distribution and extent of histone methylation in cells (18). Menin serves as a crucial scaffold protein in the methylase MLL1 complex of proteins associated with Set1, and the interactions between MLL and menin are essential for maintaining H3K4 methylation levels and the expression of MLL target genes under specific pathological conditions (155,156). MI-503 exerts a substantial anti-fibrotic effect through targeted inhibition of the MLL-menin interaction (93).

Compared with small-molecule inhibitors, natural products exhibit greater selectivity, fewer side effects and enhanced biological activity in drug development, making them a preferred source for the identification and development of novel therapeutic agents (157). A limited number of natural products are available for treating histone methylation in DKD, with a primary focus on addressing renal fibrosis (158). Gambogic acid, an active constituent derived from the traditional medicinal plant *Garcinia*, has been extensively investigated for its anti-tumor, anti-inflammatory and anti-fibrotic properties (159-161). Tao *et al* (63) demonstrated that gambogic acid modulates the TGF- β /Smad 3 signaling pathway through Smad 7 mediation, leading to amelioration of renal fibrosis. Sinefungin, a naturally occurring nucleoside analog, was initially recognized for its antiparasitic efficacy (63). Subsequent research has revealed its potential as a methylase SET7/9 inhibitor, leading to improved renal fibrosis through the inhibition of H3K4me1 (158).

The application of histone methylation inhibitors has shown promising results in experimental studies. However, their therapeutic efficacies have certain limitations: i) Histone methylation is prevalent *in vivo* (27), and the lack of precise therapeutic targets may affect normal cell function during treatment; ii) the regulatory mechanism of histone methylation is not entirely independent, and its establishment process is influenced by metabolic mediators, co-factors and existing epigenetic modifications (18), which implies that targeting a histone methyl residue or related enzyme may lead to unpredictable effects, and the aggressive use of histone methylation modification inhibitors could potentially pose unintended risks because of a lack of understanding of the protein; and iii) discrepancies in histone methylation in patients with DKD and experimental models may be attributed to variations in genome structure and gene expression patterns across different species (62). This implies that animal models inadequately replicate the histone methylation process in patients with DKD. Therefore, it is crucial to expand the currently limited histone methylation database of human kidney samples to develop effective therapeutic strategies for DKD.

5. Conclusions

The present review provides a comprehensive overview of the pathological effects of histone methylation modification disorders in various intrinsic renal cells during the onset and progression of DKD, as well as potential therapeutic strategies involving related inhibitors. Aberrant histone methylation, particularly altered H3K27 and H3K4 methylation levels in podocytes, renal tubular epithelial cells, interstitial cells and glomerular cells in patients with DKD, is closely associated with proteinuria and decreased glomerular filtration rate. Conversely, research on H3K36, H3K79 and H4K20 has been limited, highlighting a substantial gap in the epigenetic theory of DKD. Studies have demonstrated the efficacy of histone methylation modification inhibitors in ameliorating glomerular injury and mitigating renal fibrosis in the management of DKD, while reducing proteinuria and preserving renal function. These findings have attracted considerable attention from the scientific community. However, further research is needed to determine how to effectively utilize these drugs while minimizing their adverse effects. In conclusion,

additional mechanistic studies are required to refine the profile of histone methylation in specific intrinsic renal cells in DKD and develop inhibitors with higher specificity and favorable pharmacokinetics.

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Authors' contributions

PQ, LL and QJ contributed to acquisition, analysis and interpretation of data, and drafted the manuscript. DL, YQ and YZ revised the manuscript. QS, SR and ZL performed editing and proofreading. LP and TL contributed to conception and design, and critically revised the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Thomas MC, Brownlee M, Susztak K, Sharma K, Jandeleit-Dahm KA, Zoungas S, Rossing P, Groop PH and Cooper ME: Diabetic kidney disease. *Nat Rev Dis Primers* 1: 15018, 2015.
2. Johansen KL, Chertow GM, Foley RN, Gilbertson DT, Herzog CA, Ishani A, Israni AK, Ku E, Kurella Tamura M, Li S, *et al*: US renal data system 2020 annual data report: Epidemiology of kidney disease in the United States. *Am J Kidney Dis* 77 (4 Suppl 1): A7-A8, 2021.
3. Anders HJ, Huber TB, Isermann B and Schiffer M: CKD in diabetes: Diabetic kidney disease versus nondiabetic kidney disease. *Nat Rev Nephrol* 14: 361-377, 2018.
4. Thomas MC, Weekes AJ, Broadley OJ, Cooper ME and Mathew TH: The burden of chronic kidney disease in Australian patients with type 2 diabetes (the NEFRON study). *Med J Aust* 185: 140-144, 2006.
5. Scilletta S, Di Marco M, Miano N, Filippello A, Di Mauro S, Scamporrino A, Musmeci M, Coppolino G, Di Giacomo Barbagallo F, Bosco G, *et al*: Update on diabetic kidney disease (DKD): Focus on Non-Albuminuric DKD and cardiovascular risk. *Biomolecules* 13: 752, 2023.
6. Parving HH, Hommel E, Jensen BR and Hansen HP: Long-term beneficial effect of ACE inhibition on diabetic nephropathy in normotensive type 1 diabetic patients. *Kidney Int* 60: 228-234, 2001.
7. Zou H, Zhou B and Xu G: SGLT2 inhibitors: A novel choice for the combination therapy in diabetic kidney disease. *Cardiovasc Diabetol* 16: 65, 2017.
8. Barrera-Chimal J, Lima-Posada I, Bakris GL and Jaisser F: Mineralocorticoid receptor antagonists in diabetic kidney disease-mechanistic and therapeutic effects. *Nat Rev Nephrol* 18: 56-70, 2022.
9. Zhang R, Wang Q, Li Y, Li Q, Zhou X, Chen X and Dong Z: A new perspective on proteinuria and drug therapy for diabetic kidney disease. *Front Pharmacol* 15: 1349022, 2024.
10. Wang N and Zhang C: Recent advances in the management of diabetic kidney disease: Slowing progression. *Int J Mol Sci* 25: 3086, 2024.
11. Forst T, Mathieu C, Giorgino F, Wheeler DC, Papanas N, Schmieder RE, Halabi A, Schnell O, Streckbein M and Tuttle KR: New strategies to improve clinical outcomes for diabetic kidney disease. *BMC Med* 20: 337, 2022.
12. Regele F, Jelenics K, Shiffman D, Paré G, McQueen MJ, Mann JF and Oberbauer R: Genome-wide studies to identify risk factors for kidney disease with a focus on patients with diabetes. *Nephrol Dial Transplant* 30 (Suppl 4): iv26-iv34, 2015.
13. Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP and Hawthorne VM: Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *N Engl J Med* 321: 1074-1079, 1989.
14. Cefalu WT, Buse JB, Tuomilehto J, Fleming GA, Ferrannini E, Gerstein HC, Bennett PH, Ramachandran A, Raz I, Rosenstock J and Kahn SE: Update and next steps for real-world translation of interventions for type 2 diabetes prevention: Reflections from a diabetes care editors' expert forum. *Diabetes Care* 39: 1186-1201, 2016.
15. Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, Ferrario F, Fogo AB, Haas M, de Heer E, *et al*: Pathologic classification of diabetic nephropathy. *J Am Soc Nephrol* 21: 556-563, 2010.
16. Caramori ML, Parks A and Mauer M: Renal lesions predict progression of diabetic nephropathy in type 1 diabetes. *J Am Soc Nephrol* 24: 1175-1181, 2013.
17. Mohandes S, Doke T, Hu H, Mukhi D, Dhillon P and Susztak K: Molecular pathways that drive diabetic kidney disease. *J Clin Invest* 133: e165654, 2023.
18. Li Y, Ge K, Li T, Cai R and Chen Y: The engagement of histone lysine methyltransferases with nucleosomes: Structural basis, regulatory mechanisms, and therapeutic implications. *Protein Cell* 14: 165-179, 2023.
19. Greer EL and Shi Y: Histone methylation: A dynamic mark in health, disease and inheritance. *Nat Rev Genet* 13: 343-357, 2012.
20. Millán-Zambrano G, Burton A, Bannister AJ and Schneider R: Histone post-translational modifications-cause and consequence of genome function. *Nat Rev Genet* 23: 563-580, 2022.
21. Keating ST, van Diepen JA, Riksen NP and El-Osta A: Epigenetics in diabetic nephropathy, immunity and metabolism. *Diabetologia* 61: 6-20, 2018.
22. Lefevre GM, Patel SR, Kim D, Tessarollo L and Dressler GR: Altering a histone H3K4 methylation pathway in glomerular podocytes promotes a chronic disease phenotype. *PLoS Genet* 6: e1001142, 2010.
23. Sayyed SG, Gaikwad AB, Lichtnekert J, Kulkarni O, Eulberg D, Klusmann S, Tikoo K and Anders HJ: Progressive glomerulosclerosis in type 2 diabetes is associated with renal histone H3K9 and H3K23 acetylation, H3K4 dimethylation and phosphorylation at serine 10. *Nephrol Dial Transplant* 25: 1811-1817, 2010.
24. Husmann D and Gozani O: Histone lysine methyltransferases in biology and disease. *Nat Struct Mol Biol* 26: 880-889, 2019.
25. Martin C and Zhang Y: The diverse functions of histone lysine methylation. *Nat Rev Mol Cell Biol* 6: 838-849, 2005.
26. Hyun K, Jeon J, Park K and Kim J: Writing, erasing and reading histone lysine methylations. *Exp Mol Med* 49: e324, 2017.
27. Gong F and Miller KM: Histone methylation and the DNA damage response. *Mutat Res Rev Mutat Res* 780: 37-47, 2019.

28. Black JC, Van Rechem C and Whetstine JR: Histone lysine methylation dynamics: Establishment, regulation, and biological impact. *Mol Cell* 48: 491-507, 2012.
29. Mohan M, Herz HM and Shilatifard A: SnapShot: Histone lysine methylase complexes. *Cell* 149: 498-498.e1, 2012.
30. Højfeldt JW, Agger K and Helin K: Histone lysine demethylases as targets for anticancer therapy. *Nat Rev Drug Discov* 12: 917-930, 2013.
31. Schwartz-Orbach L, Zhang C, Sidoli S, Amin R, Kaur D, Zhebrun A, Ni J and Gu SG: *Caenorhabditis elegans* nuclear RNAi factor SET-32 deposits the transgenerational histone modification, H3K23me3. *Elife* 9: e54309, 2020.
32. Shen Y, Mevius DEHF, Caliandro R, Carrozzini B, Roh Y, Kim J, Kim S, Ha SC, Morishita M and di Luccio E: Set7 Is a H3K37 methyltransferase in *Schizosaccharomyces pombe* and is required for proper gametogenesis. *Structure* 27: 631-638.e8, 2019.
33. Zong Y, Weiss N, Wang K, Pagano AE, Heissel S, Perveen S and Huang J: Development of complementary photo-arginine/lysine to promote discovery of Arg/Lys hPTMs Interactomes. *Adv Sci (Weinh)* 11: e2307526, 2024.
34. Feng X, Wang AH, Juan AH, Ko KD, Jiang K, Riparini G, Ciuffoli V, Kaba A, Lopez C, Naz F, *et al*: Polycomb Ezh1 maintains murine muscle stem cell quiescence through non-canonical regulation of Notch signaling. *Dev Cell* 58: 1052-1070.e10, 2023.
35. Wang Z and Liu H: Roles of lysine methylation in glucose and lipid metabolism: Functions, regulatory mechanisms, and therapeutic implications. *Biomolecules* 14: 862, 2024.
36. Aziz N, Hong YH, Kim HG, Kim JH and Cho JY: Tumor-suppressive functions of protein lysine methyltransferases. *Exp Mol Med* 55: 2475-2497, 2023.
37. Liu BC, Tang TT, Lv LL and Lan HY: Renal tubule injury: A driving force toward chronic kidney disease. *Kidney Int* 93: 568-579, 2018.
38. Cheng Y, Chen Y, Wang G, Liu P, Xie G, Jing H, Chen H, Fan Y, Wang M and Zhou J: Protein methylation in diabetic kidney disease. *Front Med (Lausanne)* 9: 736006, 2022.
39. Allis CD, Bowen JK, Abraham GN, Glover CV and Gorovsky MA: Proteolytic processing of histone H3 in chromatin: A physiologically regulated event in *Tetrahymena* micronuclei. *Cell* 20: 55-64, 1980.
40. Shi Y, Lan F, Matson C, Mulligan P, Whetstine JR, Cole PA, Casero RA and Shi Y: Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell* 119: 941-953, 2004.
41. Di Nisio E, Manzini V, Licursi V and Negri R: To Erase or not to erase: non-canonical catalytic functions and non-catalytic functions of members of histone lysine demethylase families. *Int J Mol Sci* 25: 6900, 2024.
42. Yang J, Hu Y, Zhang B, Liang X and Li X: The JMJD family histone demethylases in crosstalk between inflammation and cancer. *Front Immunol* 13: 881396, 2022.
43. Kim W, Kim R, Park G, Park JW and Kim JE: Deficiency of H3K79 histone methyltransferase Dot1-like protein (DOT1L) inhibits cell proliferation. *J Biol Chem* 287: 5588-5599, 2012.
44. Feng Q, Wang H, Ng HH, Erdjument-Bromage H, Tempst P, Struhl K and Zhang Y: Methylation of H3-lysine 79 is mediated by a new family of HMTases without a SET domain. *Curr Biol* 12: 1052-1058, 2002.
45. Lee YH, Ren D, Jeon B and Liu HW: S-Adenosylmethionine: More than just a methyl donor. *Nat Prod Rep* 40: 1521-1549, 2023.
46. Gou D, Liu R, Shan X, Deng H, Chen C, Xiang J, Liu Y, Gao Q, Li Z, Huang A, *et al*: Gluconeogenic enzyme PCK1 supports S-adenosylmethionine biosynthesis and promotes H3K9me3 modification to suppress hepatocellular carcinoma progression. *J Clin Invest* 133: e161713, 2023.
47. Lim CY, Lin HT, Kumsta C, Lu TC, Wang FY, Kang YH, Hansen M, Ching TT and Hsu AL: SAMS-1 coordinates HLH-30/TFEB and PHA-4/FOXO activities through histone methylation to mediate dietary restriction-induced autophagy and longevity. *Autophagy* 19: 224-240, 2023.
48. Cenik BK and Shilatifard A: COMPASS and SWI/SNF complexes in development and disease. *Nat Rev Genet* 22: 38-58, 2021.
49. Xue H, Yao T, Cao M, Zhu G, Li Y, Yuan G, Chen Y, Lei M and Huang J: Structural basis of nucleosome recognition and modification by MLL methyltransferases. *Nature* 573: 445-449, 2019.
50. Mitchell K, Sprowls SA, Arora S, Shakya S, Silver DJ, Goins CM, Wallace L, Roversi G, Schafer RE, Kay K, *et al*: WDR5 represents a therapeutically exploitable target for cancer stem cells in glioblastoma. *Genes Dev* 37: 86-102, 2023.
51. Zhao Z, Rendleman EJ, Szczepanski AP, Morgan MA, Wang L and Shilatifard A: CARM1-mediated methylation of ASXL2 impairs tumor-suppressive function of MLL3/COMPASS. *Sci Adv* 8: eadd3339, 2022.
52. Lu J, Huang Y, Zhang X, Xu Y and Nie S: Noncoding RNAs involved in DNA methylation and histone methylation, and acetylation in diabetic vascular complications. *Pharmacol Res* 170: 105520, 2021.
53. Lee JS, Smith E and Shilatifard A: The language of histone crosstalk. *Cell* 142: 682-685, 2010.
54. Stirpe A, Guidotti N, Northall SJ, Kilic S, Hainard A, Vadas O, Fierz B and Schalch T: SUV39 SET domains mediate crosstalk of heterochromatic histone marks. *Elife* 10: e62682, 2021.
55. Segelle A, Núñez-Álvarez Y, Oldfield AJ, Webb KM, Voigt P and Luco RF: Histone marks regulate the epithelial-to-mesenchymal transition via alternative splicing. *Cell Rep* 38: 110357, 2022.
56. Hogg SJ, Motorna O, Cluse LA, Johanson TM, Coughlan HD, Raviram R, Myers RM, Costacurta M, Todorovski I, Pijpers L, *et al*: Targeting histone acetylation dynamics and oncogenic transcription by catalytic P300/CBP inhibition. *Mol Cell* 81: 2183-2200.e13, 2021.
57. He F, Yu Q, Wang M, Wang R, Gong X, Ge F, Yu X and Li S: SESAME-catalyzed H3T11 phosphorylation inhibits Dot1-catalyzed H3K79me3 to regulate autophagy and telomere silencing. *Nat Commun* 13: 7526, 2022.
58. Metzker ML: Sequencing technologies-the next generation. *Nat Rev Genet* 11: 31-46, 2010.
59. Pulecio J, Verma N, Mejía-Ramírez E, Huangfu D and Raya A: CRISPR/Cas9-Based engineering of the epigenome. *Cell Stem Cell* 21: 431-447, 2017.
60. Peng X, Peng Q and Zhong L: Targeting H3K36 methyltransferases NSDs: A promising strategy for tumor targeted therapy. *Signal Transduct Target Ther* 6: 220, 2021.
61. Basavarajappa BS and Subbanna S: Histone methylation regulation in neurodegenerative disorders. *Int J Mol Sci* 22: 4654, 2021.
62. Komers R, Mar D, Denisenko O, Xu B, Oyama TT and Bomsztyk K: Epigenetic changes in renal genes dysregulated in mouse and rat models of type 1 diabetes. *Lab Invest* 93: 543-552, 2013.
63. Tao S, Yang L, Wu C, Hu Y, Guo F, Ren Q, Ma L and Fu P: Gambogenic acid alleviates kidney fibrosis via epigenetic inhibition of EZH2 to regulate Smad7-dependent mechanism. *Phytomedicine* 106: 154390, 2022.
64. Majumder S, Thieme K, Batchu SN, Alghamdi TA, Bowskill BB, Kabir MG, Liu Y, Advani SL, White KE, Geldenhuys L, *et al*: Shifts in podocyte histone H3K27me3 regulate mouse and human glomerular disease. *J Clin Invest* 128: 483-499, 2018.
65. Paneni F, Costantino S, Battista R, Castello L, Capretti G, Chiandotto S, Scavone G, Villano A, Pitocco D, Lanza G, *et al*: Adverse epigenetic signatures by histone methyltransferase Set7 contribute to vascular dysfunction in patients with type 2 diabetes mellitus. *Circ Cardiovasc Genet* 8: 150-158, 2015.
66. Siddiqi FS, Majumder S, Thai K, Abdalla M, Hu P, Advani SL, White KE, Bowskill BB, Guarna G, Dos Santos CC, *et al*: The histone methyltransferase enzyme enhancer of zeste homolog 2 protects against podocyte oxidative stress and renal injury in diabetes. *J Am Soc Nephrol* 27: 2021-2034, 2016.
67. Pavenstädt H, Kriz W and Kretzler M: Cell biology of the glomerular podocyte. *Physiol Rev* 83: 253-307, 2003.
68. Nagata M: Podocyte injury and its consequences. *Kidney Int* 89: 1221-1230, 2016.
69. Reidy K, Kang HM, Hostetter T and Susztak K: Molecular mechanisms of diabetic kidney disease. *J Clin Invest* 124: 2333-2340, 2014.
70. Shankland SJ: The podocyte's response to injury: role in proteinuria and glomerulosclerosis. *Kidney Int* 69: 2131-2147, 2006.
71. Ying Q and Wu G: Molecular mechanisms involved in podocyte EMT and concomitant diabetic kidney diseases: An update. *Ren Fail* 39: 474-483, 2017.
72. May CJ, Saleem M and Welsh GI: Podocyte dedifferentiation: a specialized process for a specialized cell. *Front Endocrinol (Lausanne)* 5: 148, 2014.
73. Guo Y, Xiong Z and Guo X: Histone demethylase KDM6B regulates human podocyte differentiation in vitro. *Biochem J* 476: 1741-1751, 2019.
74. Wan J, Hou X, Zhou Z, Geng J, Tian J, Bai X and Nie J: WT1 ameliorates podocyte injury via repression of EZH2/β-catenin pathway in diabetic nephropathy. *Free Radic Biol Med* 108: 280-299, 2017.

75. Nishad R, Meshram P, Singh AK, Reddy GB and Pasupulati AK: Activation of Notch1 signaling in podocytes by glucose-derived AGEs contributes to proteinuria. *BMJ Open Diabetes Res Care* 8: e001203, 2020.
76. Liebisch M and Wolf G: AGE-Induced Suppression of EZH2 mediates injury of podocytes by reducing H3K27me3. *Am J Nephrol* 51: 676-692, 2020.
77. Lin CL, Hsu YC, Huang YT, Shih YH, Wang CJ, Chiang WC and Chang PJ: A KDM6A-KLF10 reinforcing feedback mechanism aggravates diabetic podocyte dysfunction. *EMBO Mol Med* 11: e9828, 2019.
78. Muñoz IM and Rouse J: Control of histone methylation and genome stability by PTIP. *EMBO Rep* 10: 239-245, 2009.
79. Patel SR, Kim D, Levitan I and Dressler GR: The BRCT-domain containing protein PTIP links PAX2 to a histone H3, lysine 4 methyltransferase complex. *Dev Cell* 13: 580-592, 2007.
80. Cao A, Li J, Asadi M, Basgen JM, Zhu B, Yi Z, Jiang S, Doka T, El Shamy O, Patel N, *et al*: DACH1 protects podocytes from experimental diabetic injury and modulates PTIP-H3K4Me3 activity. *J Clin Invest* 131: e141279, 2021.
81. Zhang T, Zhang Y, Xu H, Lan J, Feng Z, Huang R, Geng J, Chi H and Bai X: LINC00355 Mediates CTNNB1 promoter methylation and promotes endoplasmic reticulum stress-induced podocyte injury in diabetic nephropathy. *Antioxid Redox Signal* 39: 225-240, 2023.
82. Qi R and Yang C: Renal tubular epithelial cells: The neglected mediator of tubulointerstitial fibrosis after injury. *Cell Death Dis* 9: 1126, 2018.
83. Legouis D, Ricksten SE, Faivre A, Verissimo T, Gariani K, Verney C, Galichon P, Berchtold L, Feraille E, Fernandez M, *et al*: Altered proximal tubular cell glucose metabolism during acute kidney injury is associated with mortality. *Nat Metab* 2: 732-743, 2020.
84. Edwards A, Palm F and Layton AT: A model of mitochondrial O(2) consumption and ATP generation in rat proximal tubule cells. *Am J Physiol Renal Physiol* 318: F248-F259, 2020.
85. Wang Y, Jin M, Cheng CK and Li Q: Tubular injury in diabetic kidney disease: Molecular mechanisms and potential therapeutic perspectives. *Front Endocrinol (Lausanne)* 14: 1238927, 2023.
86. Liu Y: Cellular and molecular mechanisms of renal fibrosis. *Nat Rev Nephrol* 7: 684-696, 2011.
87. Sun L, Liu L, Jiang J, Liu K, Zhu J, Wu L, Lu X, Huang Z, Yuan Y, Crowley SD, *et al*: Transcription factor Twist1 drives fibroblast activation to promote kidney fibrosis via signaling proteins Prrx1/TNC. *Kidney Int*: Aug 22, 2024 (Epub ahead of print).
88. Bai M, Xu S, Jiang M, Guo Y, Hu D, He J, Wang T, Zhang Y, Guo Y, Zhang Y, *et al*: Meis1 targets protein tyrosine phosphatase receptor J in fibroblast to retard chronic kidney disease progression. *Adv Sci (Weinh)*: Aug 20, 2024 (Epub ahead of print).
89. Kim DH, Sung M, Park MS, Sun EG, Yoon S, Yoo KH, Radhakrishnan K, Jung SY, Bae WK, Cho SH and Chung JJ: Galectin 3-binding protein (LGALS3BP) depletion attenuates hepatic fibrosis by reducing transforming growth factor- β 1 (TGF- β 1) availability and inhibits hepatocarcinogenesis. *Cancer Commun (Lond)*: Jul 28, 2024 (Epub ahead of print).
90. Fesneau O, Thevin V, Pinet V, Goldsmith C, Vieille B, M'Homa Soudja S, Lattanzio R, Hahne M, Dardalhon V, Hernandez-Vargas H, *et al*: An intestinal T(H)17 cell-derived subset can initiate cancer. *Nat Immunol* 25: 1637-1649, 2024.
91. Gifford CC, Tang J, Costello A, Khakoo NS, Nguyen TQ, Goldschmeding R, Higgins PJ and Samarakoon R: Negative regulators of TGF- β 1 signaling in renal fibrosis; pathological mechanisms and novel therapeutic opportunities. *Clin Sci (Lond)* 135: 275-303, 2021.
92. You JB, Cao Y, You QY, Liu ZY, Wang XC, Ling H, Sha JM and Tao H: The landscape of histone modification in organ fibrosis. *Eur J Pharmacol* 977: 176748, 2024.
93. Zou J, Yu C, Zhang C, Guan Y, Zhang Y, Tolbert E, Zhang W, Zhao T, Bayliss G, Li X, *et al*: Inhibition of MLL1-menin interaction attenuates renal fibrosis in obstructive nephropathy. *FASEB J* 37: e22712, 2023.
94. Hu HH, Chen DQ, Wang YN, Feng YL, Cao G, Vaziri ND and Zhao YY: New insights into TGF- β /Smad signaling in tissue fibrosis. *Chem Biol Interact* 292: 76-83, 2018.
95. Wang J, Pan J, Li H, Long J, Fang F, Chen J, Zhu X, Xiang X and Zhang D: lncRNA ZEB1-AS1 was suppressed by p53 for renal fibrosis in diabetic nephropathy. *Mol Ther Nucleic Acids* 12: 741-750, 2018.
96. Irifuku T, Doi S, Sasaki K, Doi T, Nakashima A, Ueno T, Yamada K, Arihiro K, Kohno N and Masaki T: Inhibition of H3K9 histone methyltransferase G9a attenuates renal fibrosis and retains klotho expression. *Kidney Int* 89: 147-157, 2016.
97. Ike T, Doi S, Nakashima A, Sasaki K, Ishiuchi N, Asano T and Masaki T: The hypoxia-inducible factor- α prolyl hydroxylase inhibitor FG4592 ameliorates renal fibrosis by inducing the H3K9 demethylase JMJD1A. *Am J Physiol Renal Physiol* 323: F539-F552, 2022.
98. Wang S, Zuo A, Jiang W, Xie J, Lin H, Sun W, Zhao M, Xia J, Shao J, Zhao X, *et al*: JMJD1A/NR4A1 signaling regulates the procession of renal tubular epithelial interstitial fibrosis induced by AGEs in HK-2. *Front Med (Lausanne)* 8: 807694, 2022.
99. Han X and Sun Z: Epigenetic Regulation of KL (Klotho) via H3K27me3 (Histone 3 Lysine [K] 27 Trimethylation) in renal tubule cells. *Hypertension* 75: 1233-1241, 2020.
100. Niculae A, Gherghina ME, Peride I, Tiglis M, Nechita AM and Checherita IA: Pathway from acute kidney injury to chronic kidney disease: Molecules involved in renal fibrosis. *Int J Mol Sci* 24: 14019, 2023.
101. Cohen C, Mhaidly R, Croizer H, Kieffer Y, Leclerc R, Vincent-Salomon A, Robley C, Anglicheau D, Rabant M, Sannier A, *et al*: WNT-dependent interaction between inflammatory fibroblasts and FOLR2+ macrophages promotes fibrosis in chronic kidney disease. *Nat Commun* 15: 743, 2024.
102. Huang R, Fu P and Ma L: Kidney fibrosis: From mechanisms to therapeutic medicines. *Signal Transduct Target Ther* 8: 129, 2023.
103. Liu Y: New insights into epithelial-mesenchymal transition in kidney fibrosis. *J Am Soc Nephrol* 21: 212-222, 2010.
104. Hewitson TD, Holt SG, Tan SJ, Wigg B, Samuel CS and Smith ER: Epigenetic modifications to H3K9 in renal tubulointerstitial cells after unilateral ureteric obstruction and TGF- β 1 Stimulation. *Front Pharmacol* 8: 307, 2017.
105. Zhou X, Zang X, Ponnusamy M, Masucci MV, Tolbert E, Gong R, Zhao TC, Liu N, Bayliss G, Dworkin LD and Zhuang S: Enhancer of Zeste Homolog 2 inhibition attenuates renal fibrosis by maintaining Smad7 and phosphatase and tensin homolog expression. *J Am Soc Nephrol* 27: 2092-2108, 2016.
106. An C, Jiao B, Du H, Tran M, Song B, Wang P, Zhou D and Wang Y: Jumonji domain-containing protein-3 (JMJD3) promotes myeloid fibroblast activation and macrophage polarization in kidney fibrosis. *Br J Pharmacol* 180: 2250-2265, 2023.
107. Steffes MW, Osterby R, Chavers B and Mauer SM: Mesangial expansion as a central mechanism for loss of kidney function in diabetic patients. *Diabetes* 38: 1077-1081, 1989.
108. Thomas HY and Ford Versypt AN: Pathophysiology of mesangial expansion in diabetic nephropathy: Mesangial structure, glomerular biomechanics, and biochemical signaling and regulation. *J Biol Eng* 16: 19, 2022.
109. Kriz W: Maintenance and breakdown of glomerular tuft architecture. *J Am Soc Nephrol* 29: 1075-1077, 2018.
110. Abraham S, Korin B, Chung JJ, Oxburgh L and Shaw AS: The Mesangial cell-the glomerular stromal cell. *Nat Rev Nephrol* 17: 855-864, 2021.
111. Alicic RZ, Rooney MT and Tuttle KR: Diabetic kidney disease: Challenges, progress, and possibilities. *Clin J Am Soc Nephrol* 12: 2032-2045, 2017.
112. Baccora MH, Cortes P, Hassett C, Taube DW and Yee J: Effects of long-term elevated glucose on collagen formation by mesangial cells. *Kidney Int* 72: 1216-1225, 2007.
113. Wu P, Ren Y, Ma Y, Wang Y, Jiang H, Chaudhari S, Davis ME, Zuckerman JE and Ma R: Negative regulation of Smad1 pathway and collagen IV expression by store-operated Ca(2+) entry in glomerular mesangial cells. *Am J Physiol Renal Physiol* 312: F1090-F1100, 2017.
114. Kuo FC, Chao CT and Lin SH: The dynamics and plasticity of epigenetics in diabetic kidney disease: therapeutic applications Vis-à-Vis. *Int J Mol Sci* 23: 843, 2022.
115. Boi R, Ebeffors K and Nyström J: The role of the mesangium in glomerular function. *Acta Physiol (Oxf)* 239: e14045, 2023.
116. Zhong W, Hong C, Dong Y, Li Y, Xiao C and Liu X: ASH2L aggravates fibrosis and inflammation through HIPK2 in high glucose-induced glomerular mesangial cells. *Genes (Basel)* 13: 2244, 2022.
117. Zhong W, Hong C, Zhang Y, Li Y, Xiao C and Liu X: ASH2L-mediated H3K4me3 drives diabetic nephropathy through HIPK2 and Notch1 pathway. *Transl Res* 264: 85-96, 2024.
118. Chen YX, Zhu SY, Huang C, Xu CY, Fang XD and Tu WP: lncRNA Dlx6os1 accelerates diabetic nephropathy progression by epigenetically repressing SOX6 via Recruiting EZH2. *Kidney Blood Press Res* 47: 177-184, 2022.
119. Hung PH, Hsu YC, Chen TH, Ho C and Lin CL: The histone demethylase inhibitor GSK-J4 Is a therapeutic target for the kidney fibrosis of diabetic kidney disease via DKK1 Modulation. *Int J Mol Sci* 23: 9407, 2022.

120. Chen H, Huang Y, Zhu X, Liu C, Yuan Y, Su H, Zhang C, Liu C, Xiong M, Qu Y, *et al*: Histone demethylase UTX is a therapeutic target for diabetic kidney disease. *J Physiol* 597: 1643-1660, 2019.
121. Jia Y, Reddy MA, Das S, Oh HJ, Abdollahi M, Yuan H, Zhang E, Lanting L, Wang M and Natarajan R: Dysregulation of histone H3 lysine 27 trimethylation in transforming growth factor- β 1-induced gene expression in mesangial cells and diabetic kidney. *J Biol Chem* 294: 12695-12707, 2019.
122. Satchell SC and Braet F: Glomerular endothelial cell fenestrations: An integral component of the glomerular filtration barrier. *Am J Physiol Renal Physiol* 296: F947-F956, 2009.
123. Savage CO: The biology of the glomerulus: endothelial cells. *Kidney Int* 45: 314-319, 1994.
124. Lassén E and Daehn IS: Molecular mechanisms in early diabetic kidney disease: Glomerular endothelial cell dysfunction. *Int J Mol Sci* 21: 9456, 2020.
125. Thakar S, Katakia YT, Ramakrishnan SK, Pandya Thakkar N and Majumder S: Intermittent high glucose elevates nuclear localization of EZH2 to Cause H3K27me3-dependent repression of KLF2 leading to endothelial inflammation. *Cells* 10: 2548, 2021.
126. Takizawa F, Mizutani S, Ogawa Y and Sawada N: Glucose-independent persistence of PAI-1 gene expression and H3K4 tri-methylation in type 1 diabetic mouse endothelium: implication in metabolic memory. *Biochem Biophys Res Commun* 433: 66-72, 2013.
127. Huang T, Li X, Wang F, Lu L, Hou W, Zhu M and Miao C: The CREB/KMT5A complex regulates PTP1B to modulate high glucose-induced endothelial inflammatory factor levels in diabetic nephropathy. *Cell Death Dis* 12: 333, 2021.
128. Alvandi Z and Bischoff J: Endothelial-Mesenchymal transition in cardiovascular disease. *Arterioscler Thromb Vasc Biol* 41: 2357-2369, 2021.
129. Glaser SF, Heumüller AW, Tombor L, Hofmann P, Muhly-Reinholz M, Fischer A, Günther S, Kokot KE, Hassel D, Kumar S, *et al*: The histone demethylase JMJD2B regulates endothelial-to-mesenchymal transition. *Proc Natl Acad Sci USA* 117: 4180-4187, 2020.
130. Pandya Thakkar N, Pereira BMV, Katakia YT, Ramakrishnan SK, Thakar S, Sakhuja A, Rajeev G, Soorya S, Thieme K and Majumder S: Elevated H3K4me3 Through MLL2-WDR82 upon hyperglycemia causes jagged ligand dependent notch activation to interplay with differentiation state of endothelial cells. *Front Cell Dev Biol* 10: 839109, 2022.
131. Vastenhouw NL and Schier AF: Bivalent histone modifications in early embryogenesis. *Curr Opin Cell Biol* 24: 374-386, 2012.
132. Conway E, Healy E and Bracken AP: PRC2 mediated H3K27 methylations in cellular identity and cancer. *Curr Opin Cell Biol* 37: 42-48, 2015.
133. Miller SA, Damle M, Kim J and Kingston RE: Full methylation of H3K27 by PRC2 is dispensable for initial embryoid body formation but required to maintain differentiated cell identity. *Development* 148: dev196329, 2021.
134. Lavarone E, Barbieri CM and Pasini D: Dissecting the role of H3K27 acetylation and methylation in PRC2 mediated control of cellular identity. *Nat Commun* 10: 1679, 2019.
135. Soofi A, Kutschat AP, Azam M, Laszczyk AM and Dressler GR: Regeneration after acute kidney injury requires PTIP-mediated epigenetic modifications. *JCI insight* 5: e130204, 2020.
136. El-Dahr SS and Saifudeen Z: Epigenetic regulation of renal development. *Semin Cell Dev Biol* 91: 111-118, 2019.
137. Jin J, Liu XM, Shao W and Meng XM: Nucleic acid and protein methylation modification in renal diseases. *Acta Pharmacol Sin* 45: 661-673, 2024.
138. Yu C and Zhuang S: Histone methyltransferases as therapeutic targets for kidney diseases. *Front Pharmacol* 10: 1393, 2019.
139. Ho TCS, Chan AHY and Ganesan A: Thirty Years of HDAC Inhibitors: 2020 insight and hindsight. *J Med Chem* 63: 12460-12484, 2020.
140. Bhat KP, Ümit Kaniskan H, Jin J and Gozani O: Epigenetics and beyond: Targeting writers of protein lysine methylation to treat disease. *Nat Rev Drug Discov* 20: 265-286, 2021.
141. Kourtidou C and Tziomalos K: The role of histone modifications in the pathogenesis of diabetic kidney disease. *Int J Mol Sci* 24: 6007, 2023.
142. Jones PA, Issa JP and Baylin S: Targeting the cancer epigenome for therapy. *Nat Rev Genet* 17: 630-641, 2016.
143. Zhang Q, Chen X, Cao J, Yang W, Wan G, Feng Q, Zhou S, Yang H, Wang N, Liu Z, *et al*: Discovery of a Novel Covalent EZH2 inhibitor based on tazemetostat scaffold for the treatment of ovarian cancer. *J Med Chem* 66: 1725-1741, 2023.
144. Vejmelkova K, Pokorna P, Noskova K, Faustmannova A, Drabova K, Pavelka Z, Bajciová V, Broz M, Tinka P, Jezova M, *et al*: Tazemetostat in the therapy of pediatric INI1-negative malignant rhabdoid tumors. *Sci Rep* 13: 21623, 2023.
145. Ni J, Hou X, Wang X, Shi Y, Xu L, Zheng X, Liu N, Qiu A and Zhuang S: 3-deazaneplanocin A protects against cisplatin-induced renal tubular cell apoptosis and acute kidney injury by restoration of E-cadherin expression. *Cell Death Dis* 10: 355, 2019.
146. Tellez CS, Picchi MA, Juri D, Do K, Desai DH, Amin SG, Hutt JA, Filipczak PT and Belinsky SA: Chromatin remodeling by the histone methyltransferase EZH2 drives lung pre-malignancy and is a target for cancer prevention. *Clin Epigenetics* 13: 44, 2021.
147. De La Rosa J, Urdiciain A, Zazpe I, Zelaya MV, Meléndez B, Rey JA, Idoate MA and Castresana JS: The synergistic effect of DZ-NEP, panobinostat and temozolomide reduces clonogenicity and induces apoptosis in glioblastoma cells. *Int J Oncol* 56: 283-300, 2020.
148. Li Y, Ren Y, Wang Y, Tan Y, Wang Q, Cai J, Zhou J, Yang C, Zhao K, Yi K, *et al*: A Compound AC1Q3QWB Selectively Disrupts HOTAIR-Mediated Recruitment of PRC2 and Enhances Cancer Therapy of DZNep. *Theranostics* 9: 4608-4623, 2019.
149. Miranda TB, Cortez CC, Yoo CB, Liang G, Abe M, Kelly TK, Marquez VE and Jones PA: DZNep is a global histone methylation inhibitor that reactivates developmental genes not silenced by DNA methylation. *Mol Cancer Ther* 8: 1579-1588, 2009.
150. Gounder M, Schöffski P, Jones RL, Agulnik M, Cote GM, Villalobos VM, Attia S, Chugh R, Chen TW, Jahan T, *et al*: Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: An international, open-label, phase 2 basket study. *Lancet Oncol* 21: 1423-1432, 2020.
151. Dalpatraj N, Naik A and Thakur N: GSK-J4: An H3K27 histone demethylase inhibitor, as a potential anti-cancer agent. *Int J Cancer* 153: 1130-1138, 2023.
152. Chang Y, Zhang X, Horton JR, Upadhyay AK, Spannhoff A, Liu J, Snyder JP, Bedford MT and Cheng X: Structural basis for G9a-like protein lysine methyltransferase inhibition by BIX-01294. *Nat Struct Mol Biol* 16: 312-317, 2009.
153. Chae YC, Kim JY, Park JW, Kim KB, Oh H, Lee KH and Seo SB: FOXO1 degradation via G9a-mediated methylation promotes cell proliferation in colon cancer. *Nucleic Acids Res* 47: 1692-1705, 2019.
154. Kim Y, Kim YS, Kim DE, Lee JS, Song JH, Kim HG, Cho DH, Jeong SY, Jin DH, Jang SJ, *et al*: BIX-01294 induces autophagy-associated cell death via EHMT2/G9a dysfunction and intracellular reactive oxygen species production. *Autophagy* 9: 2126-2139, 2013.
155. Yokoyama A and Cleary ML: Menin critically links MLL proteins with LEDGF on cancer-associated target genes. *Cancer Cell* 14: 36-46, 2008.
156. Caslini C, Yang Z, El-Osta M, Milne TA, Slany RK and Hess JL: Interaction of MLL amino terminal sequences with menin is required for transformation. *Cancer Res* 67: 7275-7283, 2007.
157. Newman DJ and Cragg GM: Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *J Nat Prod* 83: 770-803, 2020.
158. Sasaki K, Doi S, Nakashima A, Irifuku T, Yamada K, Kokoroishi K, Ueno T, Doi T, Hida E, Arihiro K, *et al*: Inhibition of SET domain-containing lysine methyltransferase 7/9 ameliorates renal fibrosis. *J Am Soc Nephrol* 27: 203-215, 2016.
159. Yu X, Zhao Q, Zhang H, Fan C, Zhang X, Xie Q, Xu C, Liu Y, Wu X, Han Q and Zhang H: Gambogenic acid inhibits LPS-simulated inflammatory response by suppressing NF- κ B and MAPK in macrophages. *Acta Biochim Biophys Sin (Shanghai)* 48: 454-461, 2016.
160. Chen X, Zhang X, Cai H, Yang W, Lei H, Xu H, Wang W, Zhu Q, Kang J, Yin T, *et al*: Targeting USP9x/SOX2 axis contributes to the anti-osteosarcoma effect of neogambogic acid. *Cancer Lett* 469: 277-286, 2020.
161. Xu L, Meng X, Xu N, Fu W, Tan H, Zhang L, Zhou Q, Qian J, Tu S, Li X, *et al*: Gambogenic acid inhibits fibroblast growth factor receptor signaling pathway in erlotinib-resistant non-small-cell lung cancer and suppresses patient-derived xenograft growth. *Cell Death Dis* 9: 262, 2018.

