Role of Epigenetic Changes in the Pathophysiology of Diabetic Kidney Disease

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Abstract

Background: Diabetic kidney disease (DKD) is a global health issue. Epigenetic changes play an important role in the pathogenesis of this disease. ***Summary:*** DKD is currently the leading cause of kidney failure worldwide. Although much is known about the pathophysiology of DKD, the research field of epigenetics is relatively new. Several recent studies have demonstrated that diabetes-induced dysregulation of epigenetic mechanisms alters the expression of pathological genes in kidney cells. If these changes persist for a long time, the so-called "metabolic memory" could be established. In this review, we highlight diabetes-induced epigenetic modifications associated with DKD. While there is a substantial amount of literature on epigenetic changes, only a few studies describe the underlying molecular mechanisms. Detailed analyses have shown that epigenetic changes play an important role in known pathological features of DKD, such as podocyte injury, fibrosis, accumulation of extracellular matrix, or oxidative injury, all of which contribute to the pathophysiology of disease. The transforming growth factor-β plays a key role as it is involved in all-mentioned epigenetic types of regulation. ***Key Messages:*** Epigenetic is crucial for the development and progression of DKD, but the detailed molecular mechanisms have to be further analyzed more in detail.

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Introduction

Dynamic gene regulation, such as chemical modifications of mRNA [1], 3D chromatin structure [2], or epigenetics [3], impacts transcript turnover and translation. Epigenetic alterations play an important role in the pathogenesis of diabetic kidney disease (DKD). Epigenetics affect gene expression without changing the DNA sequence itself and regulate numerous physiological and pathophysiological processes. The regulation of epigenetic mechanisms is influenced by the environment [3, 4]. Epigenetic modifications create a kind of "cellular memory" that can be transient, permanent, or heritable through cell divisions or across generations [3, 4].

The major types of epigenetic regulation are DNA methylation, post-translational histone modifications, and non-coding RNAs (ncRNAs) such as long ncRNAs, small interfering RNAs (siRNAs), or micro RNAs (miRNAs) [3, 4]. In recent decades, several epigenetic changes that drive disease have been described. However, the detailed mechanisms are still not fully understood.

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Clinical trials and experimental models showed that patients with diabetes mellitus (DM) exhibit long-term complications despite a relatively short period of poor glucose control many years ago [5, 6]. Al-Dabet et al. [7] used a mouse model of hyperglycemia reversal where they treated mice with STZ (streptozotocin), an animal model for type 1 DM (T1DM). A subgroup of mice received a SGLT2 (sodium dependent glucose cotransporter 2) inhibitor for 6 weeks, while blood glucose levels remain high in another subgroup [7]. Their data showed that the mice in the SGLT2i group had lower albuminuria compared to the diabetic STZ group without the inhibitor, but higher albuminuria compared to the non-diabetic control animals [7]. RNAseq analyses demonstrated that diabetes changed the expression of several hundred genes (291 were upregulated, 746 were downregulated) compared with the control, and the reduction of blood glucose in the SGLT2i group had only marginal effects on the diabetes-induced, altered gene expression (271 upregulated, 274 downregulated) [7]. This phenomenon of persistence of the toxic effects of hyperglycemia is called metabolic memory [5].

For several years, many research groups have studied the molecular mechanisms of metabolic memory, particularly the role of epigenetics, to better understand DKD pathophysiology. Comprehending epigenetic modifications in DKD provides valuable insights into potential therapeutic targets, enabling the translation of these findings into clinical practice. Hyperglycemia, a hallmark of diabetes, can result in epigenetic changes affecting the expression of harmful genes that worsen kidney damage [5, 6].

The importance of epigenetics in modern medicine extends beyond DKD. It offers a framework for understanding how environmental factors influence gene expression and contribute to various diseases. This knowledge guides disease prevention, diagnosis, and treatment strategies. Epigenetic biomarkers could be developed for early detection of diseases, while epigenetic therapies could be explored for their potential to reverse harmful gene expression patterns. Given the potential of epigenetic research to transform our understanding and treatment of diseases like DKD, there is an urgent need for more comprehensive studies in this field.

The aim of this article was to review the literature on epigenetic hallmarks that contribute to the pathophysiology of DKD. We will focus on the impact of histone modifications but will also provide information on the role of DNA methylation and miRNAs.

Overview of DKD Pathophysiology

DKD develops in 25–40% of patients with DM and occurs in patients with T1DM and type 2 DM (T2DM) [8, 9]. In 2021, 11% of the global world population suffered from DM [8, 9]. DKD is the leading cause of kidney failure worldwide with growing prevalence for decades. This disease not only impairs the quality of living of the affected person but is also an enormous economic problem [8, 9]. Unfortunately, DKD can be silent for a long time in patients, making an early diagnosis difficult. The average time of diagnosis of kidney injury is about 7–10 years after onset of DM [8, 9].

DKD is characterized by significant structural changes in kidney morphology. One of the earliest events in DKD are modifications in the thickness and stiffness of the glomerular basement membrane due to glomerular hyperfiltration and direct alteration of collagen metabolism [10, 11]. This is followed by several pathological changes such as mesangial expansion, podocyte injury, and tubulointerstitial fibrosis [11]. Mesangial expansion occurs due to protein leakage, inflammation, and the accumulation of damaged tissue as well as growth stimulation of mesangial cells by high glucose, angiotensin II, and other factors [11–13]. Progressive mesangial destruction leads to glomerulosclerosis [11]. Podocyte injury is a key factor in the development of DKD. Hyperglycemia, oxidative stress, and inflammation impact podocytes, causing foot process effacement, actin rearrangement, increased tight junctions, slit diaphragm abnormalities, and apoptosis [11, 14]. Ultimately, fibrosis and atrophic kidney tissue develop, often through the process of epithelial-to-mesenchymal transition (EMT) [11]. EMT is characterized by the loss of epithelial markers such as E-cadherin, and induction of mesenchymal markers such as α-smooth muscle actin (α-SMA), vimentin, and N-cadherin [15].

Hyperglycemia is the primary cause of pathological events in DKD, alongside hypertension [8, 11]. Hyperglycemia triggers various metabolic pathways and abnormal glucose metabolism, including the polyol pathway, hexosamine pathway, protein kinase C pathway, and the accumulation of advanced glycation end-products (AGEs) [8, 16, 17]. AGEs in turn induce the production of reactive oxygen species (ROS), leading to endothelial dysfunction [8, 16]. AGEs also activate the receptor for AGEs (RAGE) in podocytes and endothelial cells, as well as the NF-κB (nuclear factor-κB) pathway in podocytes [17–20]. RAGE is a multiligand pattern recognition receptor that triggers inflammation [17]. NF-κB signaling promotes inflammation and fibrosis through
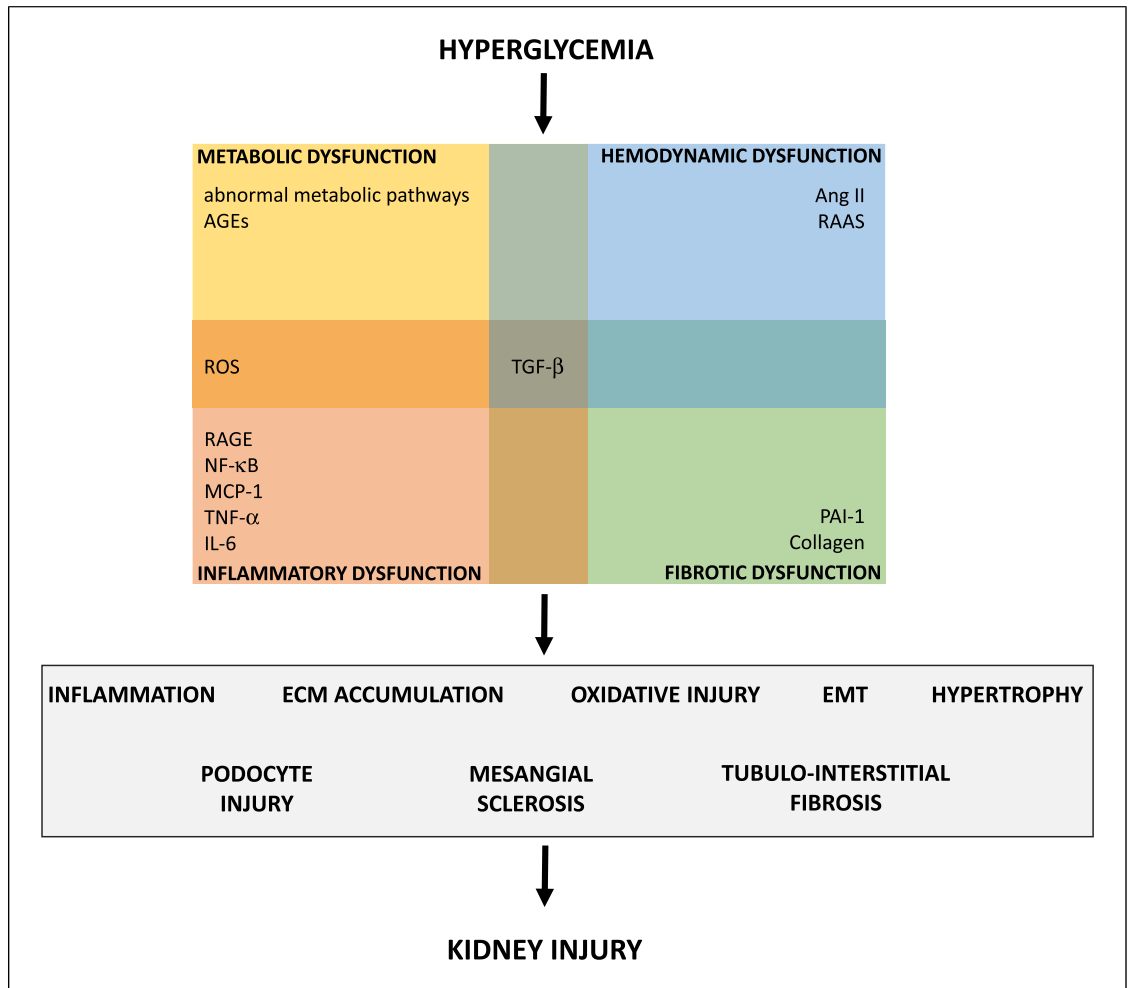
Fig. 1. Overview of hyperglycemia-induced factors contributing to the pathogenesis of DKD. AGEs, advanced glycation end-products; TGF, transforming growth factor; ROS, reactive oxygen species; Ang II, angiotensin II; RAAS, renin-angiotensin-aldosterone system; PAI-1, plasminogen activator inhibitor-1; RAGE, receptor of AGEs; NF-κB, nuclear factor-κB; MCP-1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor-α; IL, interleukin.

adhesion molecules and pro-inflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor (TNF-α), and interleukin (IL-6) [11, 16]. Pro-inflammatory mediators recruit inflammatory cells such as macrophages, that, in turn, produce further cytokines, ROS, and proteases, all contributing to kidney damage [8]. Elevated levels of ROS are also produced through hyperglycemia-mediated mitochondrial dysfunction and activation of NADPH oxidases (NOX) [10, 11, 16]. ROS play an important role in lipid oxidation and thus contribute to tissue damage [11, 16], causing foot process effacement, p53 activation and apoptosis, as well as protein kinase C activation that contributes to mesangial expansion [11]. Another pathological key mechanism in DKD is oxidative stress which can be caused by hyperglycemia, AGEs, and obesity via the upregulation of NF-κB, IL-1β, and IL-6 [11, 16]. In DKD, activation of the renin-angiotensin-aldosterone system (RAAS) induces mitogen-activated protein kinase (MAPK), transforming growth factor (TGF)-β, fibrosis, vascular endothelial growth factor (VEGF), NF-κB, ROS production, and inflammation via MCP-1, epidermal growth factor receptor (EGFR), and plasminogen activator inhibitor-1 (PAI-1), as well as other pro-inflammatory and profibrotic mediators [11, 16, 17]. Several growth factors are involved in DKD pathogenesis, with TGF-β being the best studied [8]. The profibrotic cytokine TGF-β is a multifunctional regulator that affects

Table 1. Histone methylases and their substrates associated with DKD [26–28]

Writers	Alias	Substrate(s)	Methylation
KMT1A, B, E, F	SUV39H1/2, SETDB1/2	H3K9	Di-/trimethylation
KMT2H	ASH1L	H3K4, H3K9, H4K20	Mono-/di-/trimethylation
KMT4	DOT1L	H3K79	Mono-/di-/trimethylation
KMT5A	SETD8	H4K20	Monomethylation
KMT6B, A	EZH1/2	H3K27	Mono-/di-/trimethylation
KMT7	SETD7, SET7/9	H3K4	Dimethylation
KMT8A	PRDM2	H3K9	Mono-/di-/trimethylation
KMT8D	PRDM8	H3K9	Dimethylation
KMT8E, F	PRDM3/16	H3K9	Monomethylation

KMT, lysine methyltransferase.

various cell types, including kidney cells [5, 21]. TGF-β acts via multiple signaling pathways such as Smad or MAPK. In kidney injury, upregulated TGF-β causes ECM (extracellular matrix) production, which leads to glomerulosclerosis as well as tubulointerstitial fibrosis, cellular hypertrophy, apoptosis, and podocyte foot process effacement. TGF-β also takes part in the process of EMT [5, 21]. Figure 1 summarizes the pathological consequences of chronic hyperglycemia contributing to DKD.

Post-Translational Histone Modifications in DKD

The nucleosome consists of the four core histone proteins H2A, H2B, H3, and H4 [22, 23]. These proteins can be post-translational modified such as acetylated, methylated, phosphorylated, ubiquitinylated, or SUMOylated, which occurs primarily on the amino terminal ends of the histones [22, 23]. The modification-induced alterations of charge and structure of the histone tails cause chromatin remodeling and promote or inhibit the recruitment of transcriptional complexes, respectively, effector proteins [22, 23].

Post-Translational Histone Methylation in DKD
The addition of methyl groups mostly occurs on histone H3 or H4 sidechain nitrogen atoms of lysine (K) residues and is catalyzed by histone lysine methyltransferases (KMT) [24, 25]. It is a dynamic and reversible process. The removal of methyl groups is mediated by demethylases [24, 25]. Methylation of lysine exists in three possible states: mono-, di-, or trimethylated and can be activating or repressing, de-

pending on the final position of the methyl group [24, 25]; the di- and trimethylation at H3K4 enhances the expression of the respective genes, and methylation of H3K9, H3K27 as well as H4K20 represses gene expression [26]. Up to now, more than 50 lysine methyltransferases (writers) have been characterized that can be divided into two main groups: Suppressor of variegation, Enhancer of Zeste, Trithorax (SET) domain-containing KMTs and non-SET domain-containing KMTs (DOT1L-like proteins) [25]. Histone lysine demethylases (erasers) can be classified into amino oxidase homolog lysine demethylase 1 (KDM1) and JmjC domain-containing histone demethylases (such as KDM 2/3/4/5/6 etc.) [26]. Tables 1 and 2 give a short overview of histone methylases and demethylases, respectively, that are associated with DKD, and their substrates.

Several studies show the influence of post-translational histone methylation on the pathogenesis of DKD. Wang et al. [29] identified key methylation sites that may contribute to the pathogenesis of DKD, noting that diabetic kidney tissue exhibits 121 hypermethylated and 579 hypomethylated sites [29].

Komers et al. [30] analyzed epigenetic changes in mouse (OVE26) and rat STZ models of T1DM. They observed an increase in the activating H3K4me2 mark and a decrease of H3K27me3 in the tested genes of diabetic animals. Regarding the trimethylation of H3K27, they also investigated the expression of KDM6A and enhancer of zeste homolog 2 (EZH2), finding that KDM6A histone demethylase expression was increased in the kidneys of diabetic mice, while EZH2 expression remained unchanged compared to the controls [30]. In contrast, diabetic rats exhibited altered EZH2 expression

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Table 2. Histone demethylases and their substrates associated with DKD [26–28]

Erasers	Alias	Substrate(s)	Methylation
KDM1A	LSD1	H3K4	Mono-/dimethylation
KDM1B	LSD2	H3K4, H3K9	Mono-/dimethylation
KDM3A-C	JHDM2A/B, JMJD1C	H3K9	Mono-/dimethylation
KDM4A-D	JMJD2A-D	H3K9, H3K36, H1.4K26	Di-/trimethylation
KDM5A-D	JARID1A-D	H3K4	Di-/trimethylation
KDM6A, B	UTX, JMJD3	H3K27	Di-/trimethylation
KDM7A, B	JHDM1D, PHF8	H3K9, H3K27, H4K20	Mono-/dimethylation

KDM, lysine demethylases.

without changes in KDM6A, indicating species-specific mechanisms of H3K27me3 loss in DKD [30]. Chen et al. [31] demonstrated that pharmacological prevention of KDM6A upregulation (that was also detected in patients with DKD) improved diabetes-induced kidney abnormalities and dysfunctions [31]. Additionally, the inhibition of KMT5A associated with reduced H4K20me1 [32], the upregulation of SET7/9 and changes in H3K4 methylation [33–36] as well as Dot1l and H3K79me2 [37] are involved in epigenetic dysregulation in DKD.

Impact of TGF-β1 on Histone Methylation in DKD

The upregulation of TGF-β1 in kidney cells is involved in cellular pathophysiological events in kidney disease. Sun et al. [38] showed that TGF-β1-induced expression of CTGF (connective tissue growth factor), Collagen I (Col I), and PAI-1 is associated with increased levels of the activating methylation marks H3K4me1/2/3 in high glucose-treated rat mesangial cells compared to the control. The changes in methylation marks at the promotors of *CTGF*, *COL I*, and *PAI-1* genes are accompanied by a TGF-β1-mediated increase in the expression of the methyltransferases SET7/9 [38]. Congruently, the levels of the repressive marks H3K9me2/3 were decreased at the promotors of these genes under high glucose, but detailed mechanisms were not mentioned [38]. TGF-β1-mediated activation of SET7/9, associated with decreased H3K9 methylation and increased levels of the activating methylation at H3K4, also regulates p21 gene expression [39], which is involved in glomerular cell hypertrophy and senescence [7, 40–42].

Bai et al. [43] demonstrated the involvement of the histone lysine demethylase KDM6A in TGF-β1-mediated injury. The upregulation of this demethylase was associated with an increased expression of TGF-β, vimentin, and N-cadherin. Further analyses showed an enhanced methylation of the promotor region of E-cadherin, leading to a reduced E-cadherin expression [43].

Other analyses showed that TGF-β1 influences the methylation of H3K27 caused by dysregulation of EZH2, KDM6A, and KDM6B [44–47], leading to elevated expression of TGF-β1 target genes [45, 47] and genes of the TGF-β signaling pathway [46]. Additionally, alterations in H3K27 methylation were associated with an enhanced expression of Wnt1, which takes part in insulin sensitivity [44]. Jia et al. [45] showed that upregulation of KDM6A is involved in the TGF-β1 mediated hypertrophy of mesangial cells.

Histone Methylation and Podocyte Injury in DKD

Majumder et al. [48] showed that EZH2 and demethylases KDM6A- and KDM6B-mediated H3K27me3 regulation are involved in podocyte injury in diabetes. Deletion of EZH2 from the podocytes of mice, associated with reduced H3K27 trimethylation, increased the risk for glomerular disease. In contrast, inhibition of histone demethylases KDM6A and KDM6B by GSK-J4 in diabetic db/db mice (a mouse model for human T2DM) ameliorated albuminuria, accumulation of glomerular matrix, podocyte foot process effacement and glomerular increase of α-SMA. They also analyzed kidneys from patients with glomerular sclerosis and showed a decrease of H3K27me3 in glomerular cells and tubuli. In podocytes, the progressive loss of H3K27me3 correlates with the degree of glomerular injury [48]. EZH2 and, accordingly, H3K27me3 are also involved in diabetic podocyte injury caused by oxidative stress [49]. Inhibition of EZH2 expression in rats by DZNep (3-deazaneplanocin A, a histone methylation inhibitor) treatment caused reduced H3K27me3, higher glomerular thioredoxin-interacting protein (TxnIP; involved in cellular stress response as inhibitor of the antioxidant protein

Table 3. Dysregulated miRNAs in DKD

Analyzed material from patients	Detected miRNAs		
Pooled urine samples from patients with DKD	miR-126, miR-155, miR-29b	↑	[104]
Urinary exosomes from patients with T2DM	miR-15b, miR-34a, miR-636, miR-133b, miR-342, miR-30a, miR-514a-5p, miR-451a, miR-126-3p, miR-214, miR-503, miR-21-5p, let-7e-5p, miR-23b-3p, miR-155-5p, miR-28-3p, miR-425-5p, miR-4491, miR-2117, miR-4507, miR-5088-5P, miR-1587, miR-219a-3p, miR-5091, miR-498, miR-4687-3p, miR-516b-5p, miR-4534, miR-1275, miR-5007-3p, miR-4516, miR-4270, miR-4756, miR-615-3p	↑	[105–112]
Urine samples from pediatric patients with T1DM	miR-377	↑	[113]
Serum from patients with T2DM with DKD	miR-145-5p, miR-874-3p, miR-101-3p, miR-99b, miR-122	↑	[114, 115]
Serum from patients with T1DM with DKD	miR-518-3p, miR-34a-5p, miR-126-5p, miR-425-5p, miR-618, miR-139-5p	↑	[116]
Plasma from patients with T1DM with DKD	miRNA-21, miR-21-3p and miR-378-3p	↑	[117, 118]
Urinary samples from patients with DKD	miR-27b-3p, miR-1228-3p	↓	[119]
Urine samples from pediatric patients with T1DM	miR-216a	↓	[113]
Urinary exosomes from patients with T2DM with DKD	miR-21-3p, miR-4792, miR-375, miR-1268a, miR-501-5p, miR-582, miR-30b-5p, miR-125b-5p, miR-663a, miR-3137, miR-3147	↓	[106–108, 110, 112]
Urinary exosomes from patients with T1DM with DKD	miR-30e-5p	↓	[120]
Serum samples from patients with DKD	miR-23a-3p, miR-26a-5p, miR-27a-3p	↓	[121]
Serum from patients with T2DM with DKD	miR-20a, miR-486	↓	[115]
Plasma from patients with T1DM with DKD	miR-16-5p, miR-29a-3p	↓	[118]

↑, upregulation; ↓, downregulation; DKD, diabetic kidney disease; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

thioredoxin) expression and enhanced oxidative stress [49]. Moreover, the data show that depletion of EZH2 in diabetic rats goes along with changes in podocyte structure like vacuolization and foot process effacement [49]. In vitro cell culture studies demonstrated that EZH2 regulates H3K27me3 at the gene promotor of *TxnIP* via the *trans*-acting transcription factor paired box 6 (Pax6) [49].

We also analyzed EZH2 and H3K27me3 in diabetic podocyte injury. Our data showed that diabetic conditions decreased the expression of EZH2 and accordingly the trimethylation of H3K27 in mouse podocytes in vitro and in vivo in db/db mice [50]. Suppression of EZH2 in cultured podocytes was associated with increased levels of TGF-β1 and SNAI1 (a transcription factor that regulates the expression of E-cadherin [15]) as well as the cyclin-dependent kinase inhibitor p27^{Kip1} [50]. We assume that the induction of p27^{Kip1} in murine cultured podocytes results in cell cycle arrest and cellular hypertrophy [51]. Additionally, downregulation of EZH2 activated RAGE, the transcription factor NF-κB and subsequently TNF-α expression [50, 51]. Moreover, our data [52] demonstrated that EZH2 and the trimethylation of H3K27 are also involved in hypoxia responses, which is a key pathophysiological event in diabetic disorders. Both, incubation of murine differentiated podocytes at 10% O$_2$ and housing mice at 10% O$_2$ significantly reduced

Table 4. TGF-β-related dysregulation of miRNAs in DKD

miRNA	In vivo detection	Supposed mechanisms	
let-7d		TGF-β1 decreases let-7d in NRK-52E cells -> Col I ↑, E-cadherin ↓	[130]
let-7d	↓ in glomeruli of STZ-treated mice	TGF-β1 decreases let-7d in mouse mesangial cells -> TGF-R1 ↑	[131]
miR-34a-5p	↑ in db/db mice	Upregulation of miR-34a-5p -> SIRT1 ↓ -> TGF-β1 ↑, fibronectin ↑ -> kidney fibrosis	[132]
miR-130b	↓ in glomeruli of STZ-treated mice	TGF-β1 decreases miR-130b in mouse mesangial cells -> TGF-R1 ↑, Col4A1 ↑, Col12A1 ↑, CTGF ↑, PAI-1 ↑	[131]
miR-143/145	↑ in glomeruli of db/db mice	TGF-β1 -> SMAD signaling or mTOR -> miR-143/145 ↑ in human podocytes -> WT-1 ↓, Zonula-1 ↓, Col I ↑, α-SMA ↑	[133]
miR-154-5p	↑ in glomeruli of STZ and high-fat diet rats	miR-154-5p ↑ in rat mesangial cells -> TGF-β1/SMAD3 ↑ -> cell proliferation ↑	[134]
miR-192, miR-200b/c	↑ in glomeruli of STZ-treated and db/db mice	miR-192 in mouse mesangial cells ↑-> miR-200b/c ↑ -> TGF-β1 ↑ -> Col IA2 ↑, Col IVA1 ↑	[135, 136]
miR-199b-3p	↓ STZ mice	Downregulation of miR-199b-3p in HK-2 cells -> KDM6A ↑ -> E-cadherin ↓, TGF-β1 ↑, vimentin ↑, N-cadherin ↑	[43]
miR-204	↓ in patients with DKD	miR-204 knockdown in mice -> TGF-β1 ↑, Col IA1 ↑, MCP-1 ↑	[137]
miR-205	↓ in db/db mice	TGF-β1 downregulates miR-205 via HDAC2 -> fibronectin ↑, Col I ↑, SNAI1 ↑, CTGF ↑	[66]
miR-342-3p	↓ in db/db mice	miR-342-3p downregulation in mouse mesangial cells -> TGF-β1 ↑, fibronectin ↑, Col IV ↑, PTEN ↓ via SOX6 ↑	[138]
miR-378	↓ in db/db mice	TGF-β1 reduces miR-378 in NRK-52E cells -> Col I, Col IV, α-SMA	[139]
miR-378	↓ in db/db mice	TGF-β1 decreases miR-378 in primary human mesangial cells -> mesangial cell expansion and proliferation	[139]
miR-1207-5p		miR-1207-5p upregulation in mesangial cells -> TGF-β1 ↑, PAI-1 ↑, fibronectin ↑	[140]

↑, upregulation; ↓, downregulation; Col, collagen; STZ, streptozotocin; TGF-R1, transforming growth factor-β receptor 1; CTGF, connective tissue growth factor; PAI, plasminogen activator inhibitor; WT-1, Wilms' tumor 1; mTOR, mechanistic Target of Rapamycin; α-SMA, smooth muscle actin; DKD, diabetic kidney disease; HDAC, histone deacetylase; PTEN, Phosphatase and Tensin homolog; SIRT1, sirtuin 1; KDM6A, lysine demethylase 6A; MCP-1, monocyte chemoattractant protein-1; SOX, SRY-Box Transcription Factor.

EZH2 expression associated with a decrease of H3K27me3 in podocytes [52]. Additionally, pharmacological inhibition of HIFs (hypoxia inducible factor) diminished EZH2 and H3K27me3 in podocytes in vitro and in mice [52].

Lin et al. [53] found that dysregulated KDM6A contributed to podocyte injury in DKD. Cell culture experiments with murine podocytes showed that high glucose treatment of podocytes increased the KDM6A level and decreased the expression of nephrin (combined with an enhanced DNA methylation at the nephrin [*NPHS1*] promotor) [53]. Overexpression of KDM6A in podocytes reduced the expression of nephrin, WT1, and the trimethylation of H3K27 [53].

Moreover, GSK-J4 treatment ameliorated diabetic-induced albuminuria and normalized podocyte morphology. The knockout of KDM6A in diabetic STZ mice corrected features of DKD like GBM thickness and glomerular sclerosis [53].

Histone Methylation and Oxidative Stress in DKD

As mentioned above, epigenetic dysregulation induced TxnIP expression in podocytes, leading to oxidative stress. Similar data were published by De Marinis et al. [54] for mesangial cells. They found an increased expression of TxnIP in diabetic Sur1-E1506KD/D mice (a mouse model that develops diabetes and early signs of DKD) and in the glomeruli of db/db mice associated
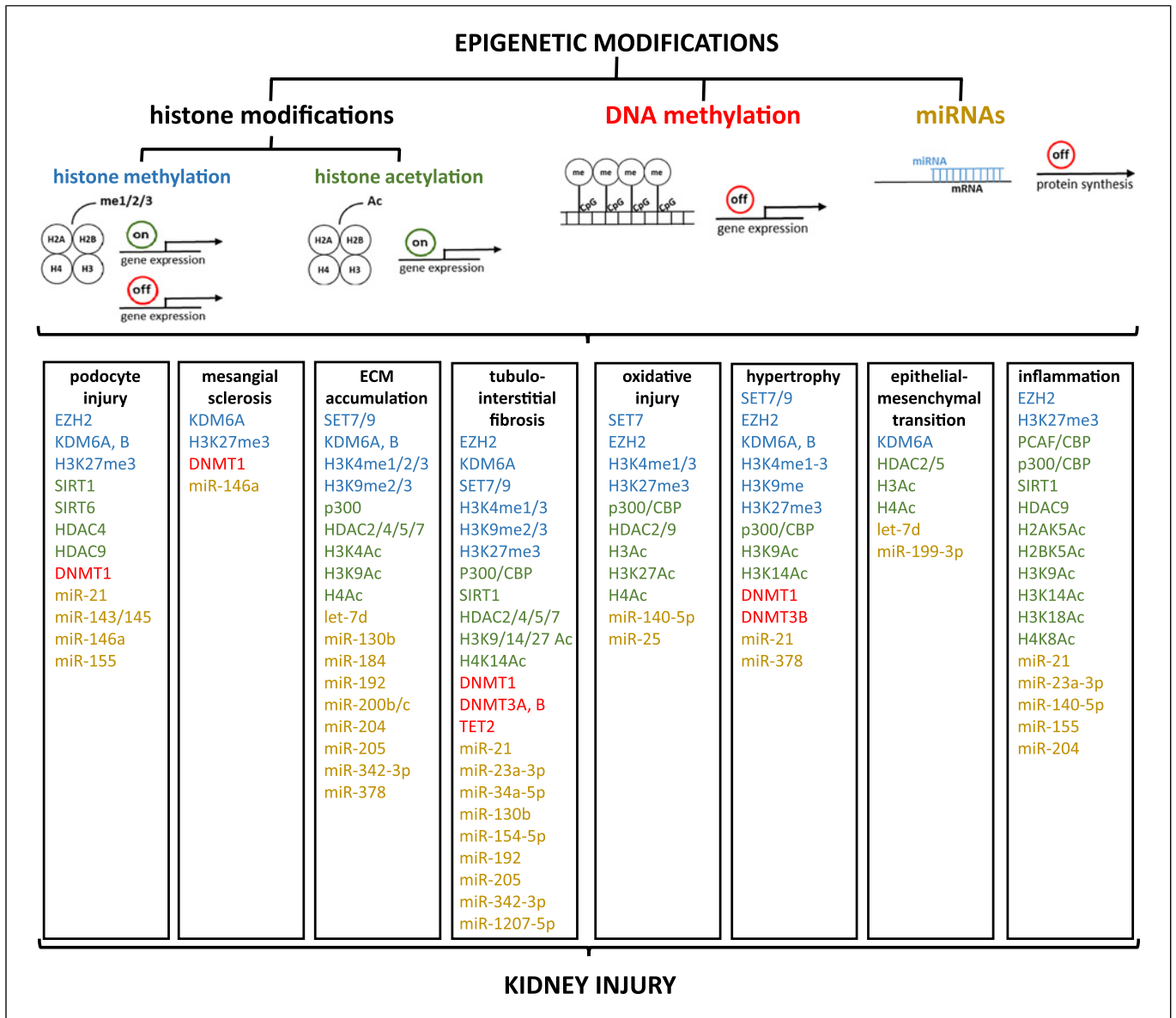
Fig. 2. Schematic illustration of epigenetic changes found during the literature review, assigned to the respective pathological pathways associated with kidney injury. me, methylation; Ac, acetylation; miR, mi RNA; ECM, extracellular matrix; EZH2, enhancer of zeste homolog 2; KDM, lysine demethylases; SIRT, silent information regulator sirtuin; HDAC, histone lysine de-acetylases; DNMT, DNA methyltransferases; SET, Suppressor of variegation, Enhancer of Zeste, Trithorax; TET, ten-eleven translocation; CBP, CREB-binding protein; PCAF, p300/CBP-associated factor.

with higher methylation of H3K4 and reduced H3K27me3 [54].

Epigenetic histone modifications are involved in lipid metabolism [55]. High levels of 12/15 lipoxygenase (12/15-LO) in diabetes increased oxidized lipid products that cause oxidative stress and subsequently glomerular dysfunction and fibrosis [55]. These oxidized lipid products induced the translocation of SET7 to the promotors of profibrotic genes and consequently raised the methylation of H3K4me1/3 in rat mesangial cells [55].

Several studies provide evidence that post-translational histone methylation influences the pathogenesis of DKD. Key findings include alterations in histone methylation marks, such as H3K4me2 and H3K27me3, and species-specific changes in histone-modifying enzymes like EZH2,

KDM6A, and SET7/9. These modifications affect gene expression linked to kidney dysfunction, hypertrophy, podocyte injury, and oxidative stress, highlighting their role in the epigenetic regulation of DKD.

Post-Translational Histone Acetylation in DKD

The acetylation/deacetylation of histone proteins is catalyzed by histone lysine acetyltransferases (HATs), respectively, histone lysine deacetylases (HDACs) [56]. In humans, HATs are particularly members of Gcn5 (Gcn5-related N-acetyltransferases)/PCAF (p300/CBP-associated factor) family, MYST family (with Tat-interactive protein 60 kD [Tip60], monocyticleukaemia zinc finger protein [MOZ], monocytic leukemic zinc finger-related factor [MORF], or human acetylase binding to ORC1 [HBO1]) or p300/CBP family [56, 57]. HDACs are divided into 4 classes: class I Rpd3-like proteins with HDAC1/2/3/8, class II Hda1-like proteins with HDAC4/5/6/7/9/10, class III Sir2-like proteins (silent information regulator sirtuin [SIRT] 1–7) and class 4 with HDAC11 [56, 58]. HATs and HDACs are mostly found in a complex with other proteins [56, 58].

Kidney biopsies from patients with DKD showed an upregulation of HDAC6 in tubular cells and infiltrated macrophages that are round to the diluted tubules [59]. Another study of podocytes from diabetic mice and in kidney biopsies from patient with podocytopathies demonstrated the involvement of SIRT6 in podocyte injury [60]. Studies on diabetic mice indicated that the deletion of SIRT6 in podocytes worsens podocyte injury and proteinuria [60].

Reddy et al. [61] analyzed epigenetic modifications in kidney glomeruli of diabetic mice. They revealed that changes in histone methylation and histone acetylation often occurred simultaneously [61]. The db/db diabetic mice showed a decrease in repressive histone marks H3K9me2/3 and H3K27me3, while the activating methylation marks H3K36me3 and H3K4me1, as well as the acetylation of H3K9, were increased [61]. Analyses of histone modification enzymes indicated the upregulation of the HATs Tip60, MOZ, and MORF, as well as of HDAC7 and HDAC9, and of the H3K4 histone methylases Setd7 and Setd4 [61]. Studies on mesangial cells cultured under diabetic conditions showed that the changes in histone methylation/acetylation were accompanied by the upregulation of RAGE, PAI-1, and MCP-1 [61].

Role of TGF-β1 in Dysregulated Histone Acetylation in DKD

Several studies have demonstrated a diabetes-induced dysregulation of HDACs associated with TGF-β-mediated kidney damage, including podocyte injury [62], ECM accumulation [63–67], fibrosis [63, 66–68], or EMT [64, 65, 69]. Members of the PCAF family are also involved in TGF-β1-associated epigenetic dysregulation. Malek et al. [70] displayed increased levels of PCAF/CBP in diabetic STZ rats, which were associated with the activation of NF-κB and TGF-β signaling and an increase of H2AK5Ac, H2BK5Ac, H3K18Ac, and H4K8Ac [70]. Yuan et al. [71] showed a role of p300/CBP in the activation of TGF-β target genes like PAI-2 and p21 in mesangial cells and in glomeruli from diabetic mice, associated with an increased acetylation of H3K9/14 [71]. Active p300 associated with the acetylation of H3K4 induced the synthesis of Col I during kidney fibrosis under diabetic conditions [72].

Histone Acetylation and Oxidative Stress in DKD

Changes in histone acetylation also contribute to oxidative stress in DKD. Lazar et al. [73] showed that p300/CBP is involved in the increase of Nox and the production of ROS in diabetic STZ mice via increased activation of H3K27Ac [73]. Liu et al. [74] found that diabetes-mediated upregulation of HDAC9 is involved in ROS generation and inflammation in podocytes. Moreover, altered histone acetylation affected the expression of nephrin and podocin in these cells contributing to the injury of podocytes [74].

The review of the literature shows that diabetic conditions lead to increased activating of acetylation marks, alongside with dysregulation of HDACs and HATs. These changes are associated with inflammation, oxidative stress, and TGF-β1-mediated kidney damage.

DNA Methylation in DKD

In mammalians, there are five DNA methyltransferases (DNMTs): DNMT1, DNMT2, DNMT3a, DNMT3B, DNMT3L. DNA methylation is often associated with transcriptional repression. It happens mainly at CpG sites, where a cytosine nucleotide is followed by a guanine nucleotide (5′ to 3′ direction) [75, 76]. CpG sites are mostly located in the promotor regions of genes but also in the gene body [76]. DNA demethylation is conducted by demethylases, mainly members of the ten-eleven translocation (TET) family (TET1, TET2, and TET3) [77].

Role of CpG Sites in the Progression of DKD

Numerous studies indicate that changes in DNA methylation, particularly in genes that are already known to be associated with kidney disease, contribute to the

progression and clinical manifestation of DKD [78–92]. Interestingly, several of these analyses have identified CpG sites in the *TXNIP* gene [10, 82, 88, 90–93]. For example, Smyth et al. [82] conducted a study involving individuals with T1DM to assess differences in blood-derived DNA methylation between individuals with DKD and those without kidney disease. In meta-analyses of DKD in T1DM, they identified 32 differentially methylated CpGs in blood associated with DKD, mostly hypomethylated [82]. Seven of the CpGs overlapped with predicted transcription factor binding sites. Furthermore, methylation of 21 of the 32 CpGs was predictive of kidney failure development [82]. Li et al. [88] investigated the association between DNA methylation at CpG sites in peripheral blood and kidney function decline in patients with T2DM, identifying 48 CpGs associated with the rate of estimated glomerular filtration rate decline [88]. Notably, both studies [82, 88] observed higher DNA methylation levels at cg17944885, which correlated with the expression of a zinc finger protein and the progression of DKD [82, 88]. In another study, Gluck et al. [93], using micro-dissected human kidney tubule samples, identified 65 CpGs correlated with the degree of kidney fibrosis [93]. Both, Gluck et al. [93] and Li et al. [88] proposed the potential of DNA methylation biomarkers in predicting kidney function decline in diabetes, emphasizing the utility of incorporating DNA methylation data for early identification of high-risk patients [88, 93].

Changes in DNA Methylase Activity in DKD

Literature review reveals studies addressing the role of DNA methylases in kidney disease. Al-Dabet et al. [7], in a study using a mouse model of reversible hyperglycemia, observed persistent high expression of p21 in tubular cells despite lowering blood glucose levels, due to reduced methylation of the *p21* promotor via suppression of DNMT1 and DNMT3B [7]. Gondaliya et al. [94] demonstrated an interaction between miRNA and DNA methylation in regulating gene expression in kidney tubular epithelial cells. Under conditions mimicking DKD (AGEs, high glucose, and angiotensin II), miR-29b downregulation led to an upregulation of DNMT3A, DNMT3B, and DNMT1. This was associated with an increased expression of fibronectin and KIM-1 in these cells [94].

TGF-β1 and DNA Methylation in DKD

Similar to histone modifications, DNA methylation is associated with TGF-β1-mediated injury in DKD. Oba et al. [95] showed that TGF-β1 is demethylated in primary mesangial cells from diabetic db/db mice, associated with a decreased activity of DNMT1 [95]. Yang et al. [96] demonstrated upregulation of TGF-β1 in diabetic rats due to TET2-mediated demethylation of the TGF-β1 promoter contributing to fibrotic changes and exacerbating DKD pathology.

DNA Methylation and Podocyte Injury in DKD

Literature indicates that alterations in DNA methylation contribute to podocyte dysfunction in DKD [53, 97–99]. Treatment of human immortalized podocytes with high glucose in vitro alters DNA methylation and gene expression patterns. Methylation profiling identified 337 hypomethylated genes that were upregulated, while only two genes were hypermethylated and downregulated [98].

Several publications found in the course of this review showed a connection between DNA methylation and the expression of nephrin [53, 97, 99]. Hayashi et al. [97] showed that the expression of the transcription factor Kruppel-like factor 4 (KLF4) is reduced in mouse and human podocytes, which was associated with diminished nephrin expression and proteinuria [97]. Lin et al. [53] explored the KDM6A – KLF10 interrelationship in podocyte injury, revealing that the KDM6A-induced suppression of nephrin and WT1 expression in podocytes was associated with upregulation of its downstream effector KLF10 and recruitment of DNMT1 [53]. Zhang et al. [99] highlighted the role of DNMT1 in podocytes, showing increased DNMT1 levels under diabetic conditions correlating with reduced expression of slit diaphragm proteins like nephrin [99].

The previous findings highlight that changes in DNA methylation, particularly at specific CpG sites, play a crucial role in the progression of DKD and the decline in kidney function in individuals with diabetes. Alterations in DNA methyltransferase activity (e.g., DNMT1, DNMT3A, and DNMT3B) are associated with the regulation of genes involved in podocyte injury (affecting key proteins such as nephrin, with evidence suggesting the involvement of transcription factors), as well as kidney fibrosis and dysfunction, including TGF-β1-mediated dysregulation.

Dysregulation of miRNAs in DKD

Non-coding RNAs are regulatory molecules that act through various mechanisms and can interact with each other to build complex and dynamic networks. They are divided into small ncRNAs with a length of up to 200 nucleotides (such as miRNAs or siRNAs), long ncRNAs (lncRNAs) with more than 200 nucleotides,

and circular RNAs (circRNAs) [100]. Here, we will focus on the dysregulation of miRNAs in DKD. MiRNAs are negative regulators of the expression of most genes encoded by the human genome that controls gene expression at the post-transcriptional level through incomplete base pairing with the $3'$-untranslated region (UTR) of target messenger RNAs [101, 102]. MiRNAs not only act in cells but also have paracrine effects and affects cellular interactions [103]. That means that miRNAs are also present and highly stable in body fluids like serum, plasma, or urine and thus easily detectable serving as a diagnostic tool [101, 102]. Several studies address the dysregulation of miRNA expression in DKD using urine, serum or plasma samples from patients with diabetic disorders. A short overview of detected miRNAs and their dysregulation in DKD are listed in Table 3.

Currently, numerous miRNAs involved in the pathogenesis of DKD have been described, but targets or functions of only a fraction of these are known [103]. Some studies have analyzed the molecular mechanisms of miRNAs more in detail. Zanchi et al. [122] detected an upregulation of miR-184 in Zucker diabetic fatty (ZDF) rats, showing that tubular miR-184 expression is induced by albumin and is associated with collagen accumulation [122]. Interestingly, the upregulation of miR-184 is epigenetically regulated by DNA demethylation and histone lysine acetylation [122]. Lee et al. [123] analyzed the role of miR-146a in DKD, demonstrating that the downregulation of miR-146a negatively correlates with albuminuria and glomerular damage in patients with T2DM. Animal studies demonstrated that the reduction of miR-146a causes mesangial sclerosis and foot process effacement [123]. Chen et al. [124] have shown that miR-296 regulates the expression of SGLT2 [124]. Wang et al. [125] found that miR-92b-3p, a direct target of Smad7, is one of many miRNAs regulated by AGEs [125].

miRNAs in Oxidative Stress and Inflammation

Several publications describe a role for miRNAs in oxidative stress and inflammation. Sheng et al. [126] demonstrated that miR-23a-3p is involved in inflammatory and fibrotic processes that cause tubular injury in DKD. Targeting miR-23a-3p in HK-2 cells in vitro influenced the expression of IL-6, TNF-α, and fibronectin [126]. Another study showed that miR-140-5p plays a role in ROS generation and inflammation with miR-140-5p being reduced in kidney biopsies from patients with DKD [127]. The authors demonstrated that miR-140-5p targets Toll-like receptor (TLR 4) and

accordingly regulates NF-κB signaling [127]. miR-25 is involved in the regulation of oxidative stress as direct interaction partner of NOX4 [128]. Wang et al. [129] showed that the upregulation of miR-155 in podocytes drives the expression of inflammatory molecules as MCP-1, TNF-α, IL-1β, IL-6 via SIRT1 downregulation. They tested the role of miR-155 in vivo, finding that inhibition of miR-155 in an animal model reduces the albumin-creatinine ratio and inflammatory processes, reversing kidney pathological changes as foot process effacement [129].

TGF-β1 and miRNAs in DKD

Numerous publications underline the importance of miRNAs in TGF-β1-mediated injury in the pathogenesis of DKD, as summarized in Table 4.

Translational Relevance of miRNAs

The translational relevance of miRNAs in kidney disease has been explored in recent studies. Baker et al. [141] performed a tissue-specific approach to analyze miRNA expression profiles across four different types of kidney disease. Their data showed that distinct miRNAs are differentially expressed in glomeruli or proximal tubuli in each type of kidney disease providing an excellent basis for the development of biomarkers [141]. Other studies have already tested miRNAs as therapeutic targets in animal models of DKD [142, 143]. Kölling et al. [142] analyzed miRNA profile in diabetic kidneys and found miR-21 as the most highly upregulated, causing mesangial cell hypertrophy and changes in podocyte phenotype. To investigate the therapeutic potential of silencing miR-21 in ameliorating DKD, they antagonized miR-21 in STZ mice [142]. Silencing miR-21 improved kidney function and reduced pathological changes such as albuminuria, mesangial expansion, podocyte loss, fibrosis, and inflammation [142]. Putta et al. [143] identified miR-192 as a critical regulator of kidney fibrosis in DKD. To test the translational relevance of this miRNA, they treated STZ mice with an inhibitor of miR-192, resulting in a reduction of kidney fibrosis by normalization of the expression of profibrotic genes and upregulation of ant-fibrotic genes [143].

Experimental evidence has shown that numerous miRNAs are involved in the pathogenesis of DKD through mechanisms such as inflammation, fibrosis, oxidative stress, ECM accumulation, and TGF-β1-mediated injury. Some studies have also demonstrated the therapeutic potential of targeting these miRNAs to improve kidney function and slow disease progression.

Conclusion

The literature review showed that epigenetic dysregulation contributes to the pathophysiology of DKD, as illustrated in Figure 2. Mostly, different epigenetic mechanisms, and often a combination of epigenetic modifications, drive kidney injury. But it seems that epigenetic dysregulation can be species and pathway specific. Since epigenetic modifications are dynamic, it is challenging to determine whether they are a cause or a consequence of diseases. On one hand, epigenetic modifications can predispose individuals to certain diseases by affecting the regulation of genes involved in critical biological processes. On the other hand, diseases themselves can induce epigenetic changes. Chronic conditions like hyperglycemia can lead to alterations in the epigenome, which may exacerbate the disease or contribute to its progression.

Only a few studies emphasize the role of epigenetic changes in the pathogenesis of DKD. However, understanding the detailed molecular mechanisms is crucial. Additionally, the literature review identified only one publication that addresses the role of the sex in epigenetic signature. Recent research has clearly illuminated that molecular differences between male and female individuals exist. Loeffler et al. [144] showed that the sex causes differences in the development and the progression of DKD, as well as kidney failure [144]. Therefore, it is important to focus more on sex-related epigenetic changes in the pathogenesis of DKD. Epigenetics has a transformative impact on modern medicine, particularly in understanding the pathophysiology of disease. It enables more personalized and effective therapeutic approaches. Moreover, epigenetic markers can serve as biomarkers for early diagnosis, prognosis, and monitoring of diseases. Additionally, because epigenetic modifications are reversible, they are attractive targets for new therapies. Thus, epigenetics in medicine holds promise for preventing or halting the development of DKD.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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