Post-translational modifications in diabetic kidney disease (Review)

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Abstract. Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease, with increasing global prevalence, resulting in a notable increase in the risk of kidney failure and cardiovascular events. Post-translational modifications (PTMs) are biochemical modifications that occur on specific residues on proteins, leading to an increase in the diversity of proteins and modulation of protein functions. PTMs encompass numerous processes, including phosphorylation, acetylation, methylation, ubiquitination, small ubiquitin-like modifier-ylation, glycosylation, palmitoylation, glutathionylation, S-nitrosylation, sulfhydration, as well as lactylation and neddylation. PTMs are associated with the occurrence and progression of DKD. The present review aimed to summarize PTMs and their roles in the pathophysiological mechanisms of DKD, including cell death, oxidative stress, mitochondrial dysfunction, inflammation and fibrosis.

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1. Introduction

Diabetic kidney disease (DKD), a prevalent form of secondary nephropathy affecting 30-40% of the global diabetic population, is clinically characterized by persistent microalbuminuria accompanied by progressive deterioration of glomerular filtration function (1,2). The pathophysiological alterations of DKD primarily manifest as excessive extracellular matrix (ECM) accumulation, sustained activation of the inflammatory microenvironment, redox imbalance-mediated oxidative stress and mitochondrial dysfunction (3) (Fig. 1). Hyperglycemia-induced metabolic derangements trigger aberrant regulation of key signaling cascades, such as the AMP-activated protein kinase (AMPK), PI3K/Akt and MAPK pathways, which collectively orchestrate the molecular mechanisms driving disease onset and progression (4).

Post-translational modifications (PTMs) are key epigenetic mechanisms that govern cellular biological processes, including phosphorylation, acetylation, methylation, ubiquitination, small ubiquitin-like modifier (SUMO)ylation, glycosylation, redox modification. Novel PTMs (such as lactylation and neddylation) have also been identified with the application of mass spectrometry-proteomics (5). PTMs refer to covalent alterations occurring in proteins or peptides. These modifications enhance the functional diversity of the proteome, which is achieved via the covalent attachment or detachment of regulatory subunits, or through the degradation of target proteins in an enzyme-dependent or -independent manner (6). These processes increase the intricacy of protein modulation by affecting protein status, subcellular localization, transportation and communication with other molecules. Consequently, understanding of the PTM-mediated mechanisms in DKD is key for the discovery of innovative targets for therapy development. The present review aimed to summarize the effect of PTMs on cell death, oxidative stress, mitochondrial dysfunction, inflammation and fibrosis in the development and progression of DKD.

2. Types of PTMs

Phosphorylation. Phosphorylation is an enzymatic reaction of protein kinases that mediates the linkage between specific amino acid residues of target proteins and phosphate groups in ATP (7). Protein kinases and phosphatases catalyze the transfer or removal, respectively, of phosphate groups to their substrates, dynamically modulating the function of proteins through allosteric regulation to activate enzyme activity (such as Ser/Thr and Tyr residues) or via the engagement of interaction domains to trigger signal transduction (such as Tyr residues) (6). Protein phosphorylation is implicated in numerous processes, including gene transcription, cell cycle progression, activation of cell signaling and cell apoptosis. Previous studies have shown that disruption of phosphorylation contributes to a range of diseases, including cancer, cardiovascular disease, respiratory illness, immune imbalance, metabolic disorders and nervous system disease (8-10).

Acetylation. Acetylation is a type of histone modification that is linked to the pathogenesis of diabetes. Histone acetylation is a process whereby acetyl groups are transferred to lysine residues, which alters the charge of histone proteins, facilitating the binding of transcription factors to gene promoters and promoting gene expression (11). The dynamic balance of histone acetylation/deacetylation is regulated by the coordinated action of histone acetyltransferase (HAT) and histone deacetylase (HDAC). HATs include GCN5, p300/CBP-associated factor (PCAF) and the MYST family. At present, four classes of HDACs have been identified: i) Class I (HDAC1-3 and 8); ii) class II (HDAC4-7, 9 and 10); iii) class III, sirtuin family (SIRT1-7) and iv) class IV (HDAC11) (12). Moreover, acetylation of non-histone proteins has been reported to serve a key role in multiple cellular processes, including regulation of gene expression, DNA damage repair, cell cycle modulation, protein folding, interactions between proteins, autophagy, signal transduction and cell metabolism (13). Consequently, abnormal acetylation is involved in the pathogenesis of various diseases, including DKD.

Methylation. Protein methylation encompasses two primary categories: i) Histone methylation and ii) non-histone methylation. Histone methylation and demethylation modifications typically occur on the amino terminal lysine or arginine residues of histones, and are written by histone methyltransferases [such as enhancer of zeste homologue (EZH)2, G9a and SET7/9) and erased by histone demethylases [HDMs; such as lysine-specific demethylase (KDM)6A] (14). Histone methylation exerts different regulatory effects on genes due to the different locations of the methylated histone residues. The methylation of H3K4, H3K36 and H3K79 is typically associated with gene transcriptional activation, whereas methylation of H3K9, H3K27 and H4K20 is associated with gene transcriptional suppression (14,15). Apart from methylating histones, methylation also occurs on non-histone proteins, which is associated with the pathogenesis of DKD (16). However, the role of non-histone methylation in DKD requires further exploration.

Ubiquitination. PTMs exert regulatory effects on all aspects of protein function, including alteration of the proteolytic stability of proteins. Ubiquitination, recognized as the primary PTM involved in governing protein stability, is a reversible process (17). It can either activate or inactivate proteins and modulate protein-protein interactions via the ubiquitin-proteasomal system (UPS) (18). Ubiquitination relies on the conjugation of ubiquitin, mediated by ubiquitin-activating E1 enzyme, ubiquitin-conjugating E2 proteins and ubiquitin-protein E3 ligase, whereas deubiquitinases [such as ubiquitin-specific protease (USP)14/22 and OTU domain-containing protein 5 (OTUD5)] remove ubiquitin and counter this process (19,20). As well as proteasomal degradation, ubiquitination also directs substrate proteins to participate in cell signaling pathways, such as NF-κB, TGF-β and Wnt/β-catenin pathways. Ubiquitination is associated with numerous processes, such as cell proliferation, DNA repair, gene transcription, protein degradation, apoptosis and signal transduction (21,22).

SUMOylation. SUMOylation is a highly dynamic enzymatic cascade similar to ubiquitination involved in multiple cellular processes, including nuclear-cytosolic transport, transcriptional modulation, apoptosis, regulation of protein stability, cell stress response and cell cycle regulation (23). It is a reversible modification associated with the covalent attachment of SUMO1-5 to substrate proteins (24). The precursor SUMO is processed by sentrin/SUMO-specific proteases (SENPs) to generate mature SUMOs, which are conjugated to the target proteins through an enzymatic cascade catalyzed by SUMO-activating E1 enzyme, SUMO-conjugating E2 enzyme and SUMO E3 ligase (6,23). SUMOylation is reversed by SENPs, which recognize and remove the SUMO conjugate from the conjugated proteins (6,23,24).

Glycosylation. Hyperglycemia contributes to the pathogenesis of DKD by disrupting the equilibrium of enzyme-driven glycosylation and non-enzymatic glycation (NEG). Glycosylation, in which carbohydrates are attached to specific amino acids, comprises two primary types: i) N-linked and ii) O-linked protein glycosylation, including O-linked N-acetylglucosamine glycosylation (O-GlcNAcylation) (25). N-linked glycosylation predominantly occurs in the endoplasmic reticulum (ER) and Golgi apparatus. Through linkage to asparagine residues of proteins via N-acetylglucosamine, glycans exerts key roles in protein folding, stability and transportation (26). Adequate N-glycosylation is crucial for the correct membrane localization of various key proteins, including nephrin and podocin, enabling the interactions of these proteins with other molecules, and further maintains the normal function of the glomerular filtration barrier (27). O-GlcNAcylation is the reversable addition of the O-GlcNAc moiety of uridine-diphosphate GlcNAc (UDP-GlcNAc) to serine or threonine residues of proteins covalently, which is catalyzed by O-GlcNAc transferase (OGT) and hydrolyzed by O-GlcNAcase (OGA) (28,29). Disruption of this dynamic equilibrium impacts multiple cell and metabolic processes, such as transcriptional regulation, ferroptosis and autophagy (30). NEG is an irreversible conjugation process that reduces sugars onto a free amino group of proteins, resulting in the formation of initial Schiff's base, an Amadori product and advanced glycation end products (AGEs) (31). As the role of NEG in

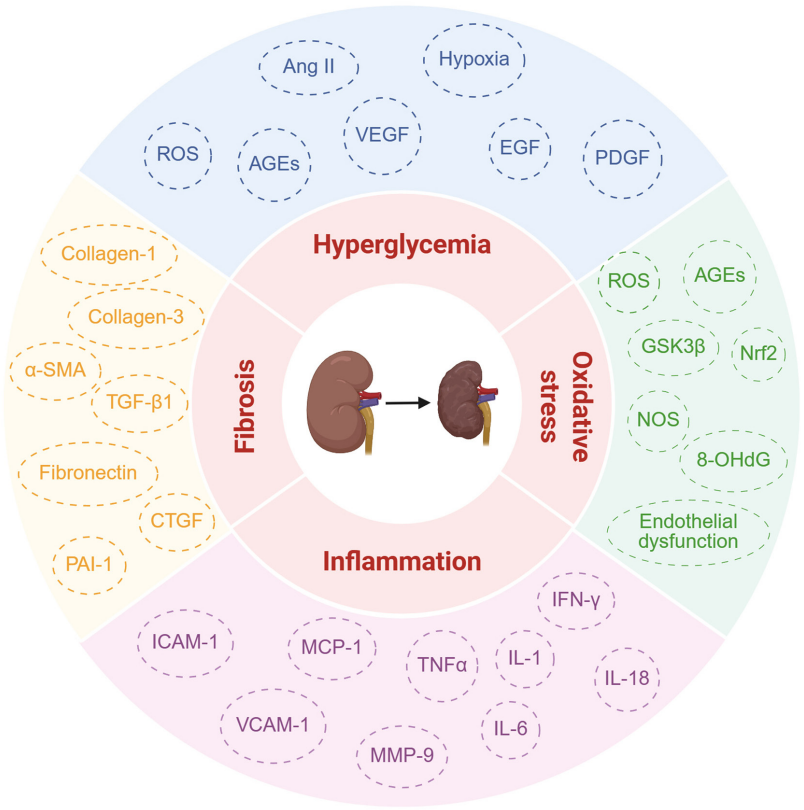

Figure 1. Pathological mechanisms of DKD. The key pathogenic factors in DKD include continual hyperglycemia, oxidative stress, inflammation and fibrosis. These processes promote intrinsic renal cell injury and renal dysfunction, driven by key mediators such as Nrf2, pro-inflammatory and pro-fibrotic factors, growth factors and adhesion molecules. Created with BioRender.com. AGEs, advanced glycation end products; Ang II, angiotensin II; CTGF, connective tissue growth factor; DKD, diabetic kidney disease; EGF, epidermal growth factor; GSK3β, glycogen synthase kinase 3β; MCP-1, monocyte chemoattractant protein-1; NOS, nitric oxide synthase; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; α-SMA, α-smooth muscle actin.

DKD has been summarized by Ma *et al* (32) and Parwani and Mandal *et al* (33), the present review focused on the role of classical enzyme-driven glycosylation in DKD.

Redox modification. Redox homeostasis is key for the normal regulation of cellular processes. Excessive generation of reactive oxygen species (ROS) and reactive nitrogen species leads to numerous pathologies, including diabetes complications, cancer, and cardiovascular and neurodegenerative disease (34). Redox modifications can be divided into reversible (S-nitrosylation, S-sulfination, S-glutathione, S-thiothiolate, intermolecular and intramolecular disulfide bonds and S-acylation) and irreversible (S-sulfoxide and S-sulfination) modifications, predominantly targeting the thiol groups of cysteine and methionine residues (6,34,35). Redox modifications occur in numerous processes, including transcriptional regulation, protein folding and stability, cell metabolism, antioxidant homeostasis and signal transduction (36,37).

Lactylation. Zhang *et al* (38) identified histone lactylation was in 2019 and it has since attracted attention (39,40). Serving as a potential modification substrate, lactate modulates epigenetic regulation of histones via the introduction of lactyl functional groups to histones, thereby regulating gene transcription (41). In addition, lactylation targeting non-histone modifications has been documented, which regulates the transcription of genes (42). Lactylation is a highly dynamic modification, which enables rapid adjustment of modification levels in response to metabolic shifts, thereby facilitating adaptive cell responses (43). It is modulated by three functional regulators: i) Writers [such as p300/CBP, KAT5 and acetyl-CoA synthetase 2 (ACSS2)]; ii) readers [such as tripartite motif (TRIM)33] and iii) erasers (such as HDAC1/2/3 and SIRT1/3) (43).

Succinylation. Succinylation refers to the covalent conjugation of a succinyl group to the lysine residue of a substrate protein mediated by a succinyl group donor (11). Lysine succinylation regulates mitochondrial function, gene transcription, DNA repair and tumor formation (44).

Crotonylation. Histone lysine crotonylation (Kcr) was first identified as a PTM in 2011, and is primarily associated with active transcription (45). Kcr is enzymatically regulated by the dynamic balance between crotonyltransferases (such as histone crotonyltransferase, p300/CBP and PCAF) and decrotonylases (such as HDAC1/2/3/8 and SIRT1-3), similar to writers and erasers in histone acetylation (11,46). Abundant evidence has indicated that crotonylation is involved in multiple cell processes including chromatin remodeling, cell cycle progression and cell metabolism (47,48).

Lysine β-hydroxybutyrylation (Kbhb). Kbhb is a type of histone lysine acylation first identified in 2016, which uses β-hydroxybutyrate (BHB) as the substrate and has a broad

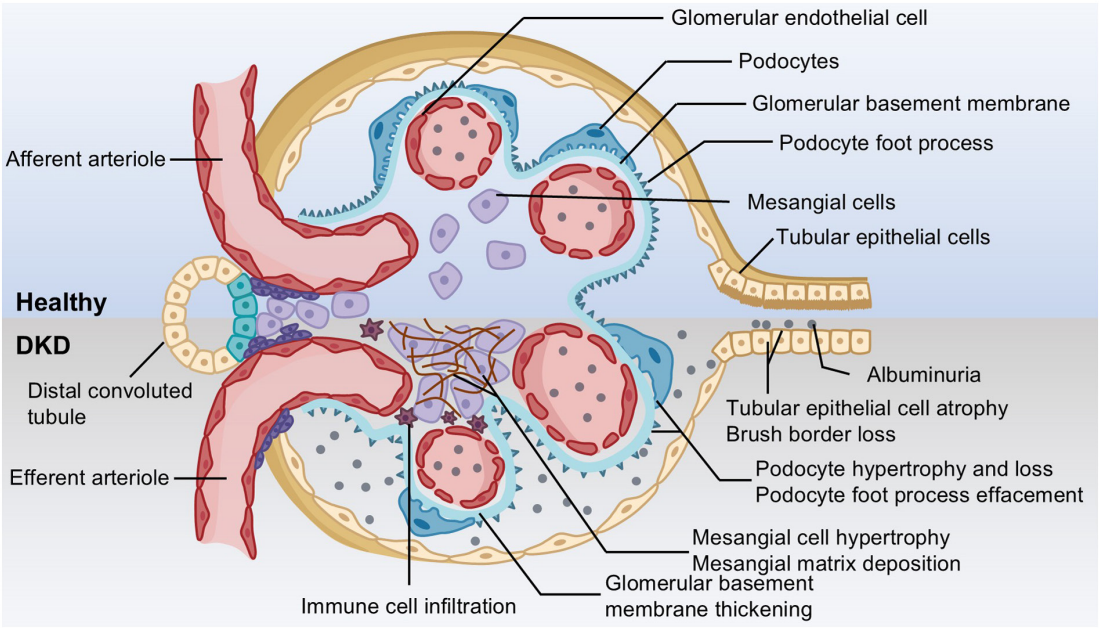

Figure 2. Structural changes in DKD histology. The key pathological features of DKD include glomerular basement membrane thickening, mesangial matrix expansion, podocyte foot process effacement and loss, hypertrophy of mesangial cells and podocytes, tubular epithelial cell atrophy, brush border loss and immune cell infiltration, which contribute to pronounced albuminuria. DKD, diabetic kidney disease.

impact on cell functions, including the modulation of gene expression and cell response to starvation (6). BHB mediates the Kbhb of histone lysine within the promoters of certain starvation-associated genes (such as PPAR and insulin signaling pathways), facilitating rapid adjustment and adaption in response to metabolic fluctuations (49). It is facilitated by p300/CBP, and removed by SIRT13 and HDAC1-3 (11).

3. Pathophysiological mechanisms of DKD

The pathophysiology of DKD is characterized by perturbations in renal hemodynamics, excessive oxidative stress and persistent inflammation (50). A number of cellular processes contribute to the initiation and development of DKD, among which oxidative stress is widely acknowledged as a key driver of cellular injury induced by hyperglycemia (51,52). Oxidative stress triggers renal cell apoptosis and the release of proinflammatory factors, and activates the signaling pathways implicated in renal fibrosis, culminating in renal fibrosis and the deterioration of glomerular filtration function (53). Additionally, studies have indicated that excessive ROS production induces mitochondrial dysfunction and contributes to the activation of proinflammatory factors and the initiation of epithelial-mesenchymal transition (EMT) in DKD (54,55). Collectively, these pathological factors elicit histological changes to glomeruli and renal tubules, thereby promoting the formation of DKD (Fig. 2).

4. Role of PTMs in DKD

Cell death

Phosphorylation. Phosphorylation of proteins is a key PTM for balancing glucose homeostasis, and relies on signaling cascades mediated by protein kinases and phosphatases. Unc-51-like kinase 1 (ULK1), a key serine/threonine protein kinase in autophagy, is modulated by AMPK and mTOR (56). The activated AMPK pathway and activated autophagy protect numerous types of renal cells in response to high glucose by directly activating ULK1 phosphorylation (57-59). Augmented phosphorylation levels of PI3K/Akt/mTOR induce renal apoptosis, glomerular injury and interstitial fibrosis by inhibiting ULK1 phosphorylation (60,61). The MAPK family is associated with the progression of DKD, and consists of p38 MAPK, JNK and ERK, which are involved in apoptosis of renal intrinsic cells in DKD (62-66).

Glycogen synthase kinase 3β (GSK3β) is a highly conserved, redox-sensitive serine/threonine protein kinase. Exposure to the diabetic condition leads to elevated expression of phosphorylated (p)-GSK3β at tyrosine 216 (p-GSK3β^{Y216}), but a decrease in the expression of inhibitory p-GSK3β at serine 9 (67,68). PI3K/Akt signaling inactivates GSK3β by phosphorylating GSK3β at serine 9 (69). Nrf2 is a key regulator in redox balance that can translocate into the nucleus and initiate the transcription of antioxidant genes, such as heme oxygenase-1 (HO-1) (70). Activated GSK3β directly phosphorylates Nrf2 and leads to its nuclear exclusion (71). Additionally, GSK3β phosphorylates Nrf2 at the Tyr568 site and promotes the translocation of Nrf2 out of the nucleus by increasing Fyn phosphorylation and its nuclear retention (71). Overactivated GSK3β phosphorylates Nrf2, thereby facilitating podocyte apoptosis and senescence in DKD (67,72). In addition, enhanced p-GSK3β^{Y216} promotes phosphorylation and degradation of β-catenin, mediating podocyte apoptosis under diabetic conditions (73).

In addition, alteration of phosphorylation states of specific proteins participates in the pathogenesis of DKD. Activation of the JAK/STAT signaling pathway can affect cell senescence, autophagy, apoptosis and ferroptosis in DKD (74-76). The phosphorylation state of STAT3 is also modulated by diverse regulators. In renal tubular epithelial cells (RTECs),

Table I. Effects of phosphorylation on cell death in diabetic kidney disease.

Model	Cell type	Target	Mechanism	(Refs.)
STZ-induced mice and 30/34.5/40 mM D-glucose-induced podocytes	Podocytes	AMPKα, PI3K/Akt, YAP, MAPK and p66Shc	Podocyte insulin resistance, autophagy and cell apoptosis	(61,63,78,79,337,338)
30 mM D-glucose-induced podocytes	Podocytes	JNK, JAK2/STAT3, GSK3β and FAK	Cell apoptosis and autophagy	(64,72,74,80)
STZ-induced rats and 25 mM D-glucose-induced podocytes	Podocytes	PERK	Cell apoptosis	(81)
db/db mice and 25/40 mM D-glucose-induced podocytes	Podocytes	EGFR/ERK, GSK3β and IRS-1	Cell senescence and apoptosis	(65,67)
KK-Ay mice and 30 mM D-glucose-induced podocytes	Podocytes	PERK	Cell apoptosis	(82)
STZ-induced mice and 25/30/33 mM D-glucose-induced HK2 cells	Tubular epithelial cells	NF-κB, STAT3, Smad3, AMPK and Tgm2	Cell senescence, apoptosis, autophagy and ferroptosis	(59,75-77,83)
STZ-induced rats and 30 mM D-glucose-induced NRK-52E cells	Tubular epithelial cells	LKB1 and AMPK	Autophagy	(58)
STZ/NAM-induced Wistar rats, proximal tubular cells and NRK-52E cells	Tubular epithelial cells	Akt/FoxO1	Cell apoptosis	(84)
db/db mice and 30 mM D-glucose-induced HK2 cells	Tubular epithelial cells	MAPK	Cell apoptosis	(85)
STZ-induced mice after UNx treatment	Renal tissue	PI3K/Akt/mTOR and Akt/FoxO3a	Autophagy	(60,86)
STZ-induced mice	Renal tissue	ERK	Renal injury	(66)
30 mM D-glucose-induced human mesangial cells	Mesangial cells	AMPK	Autophagy	(57)
STZ-induced mice and 30 mM D-glucose-induced human renal glomerular endothelial cells	Glomerular endothelial cells	PI3K/Akt/mTOR	Autophagy and EndMT	(87)

AMPK, AMP-activated protein kinase; EGFR, epidermal growth factor receptor; EndMT, endothelial-mesenchymal transition; FAK, focal adhesion kinase; Fox, forkhead box; GSK3β, glycogen synthase kinase 3β; IRS-1, insulin receptor substrate 1; LKB1, liver kinase B1; NAM, nicotinamide; STZ, streptozotocin; Tgm2, transglutaminase 2; UNx, unilateral nephrectomy; YAP, YAP1, yes-associated protein.

sulfhydrated SIRT1 induces dephosphorylation and deacetylation of STAT3, thereby decreasing high glucose-induced cell apoptosis, oxidative stress, inflammation response and EMT progression (77). Furthermore, increasing numbers of phosphorylated proteins have been shown to participate in the damage of renal cells in DKD (Table I) (78-87). This research contributes to a more comprehensive understanding of the pathogenesis of DKD and provides a theoretical basis for considering PTMs as a therapeutic target for DKD.

Acetylation. HAT p300/CBP is a key co-transcriptional activator that regulates the expression of numerous prooxidant, proinflammatory and profibrotic genes by mediating H3K27 acetylation, and is associated with mediation of diabetes-accelerated renal damage (88). Numerous targets of p300/CBP participate in the regulation of DKD development, including inducible nitric oxide synthase (NOS) and polo-like kinase 1 (PLK1) (89,90). ACSS2 epigenetically activates Raptor expression by histone H3K9 acetylation, promoting activation of the mTOR complex (mTORC)1 pathway and inhibiting podocyte autophagy (91). Upregulated acetylation levels of Beclin1 are associated with exacerbation of podocyte injury in diabetic conditions and a mutation at K414R suppresses hyperactivated autophagy, thus ameliorating podocyte impairment, highlighting the key role of PTMs in the pathological process of DKD (92).

Multiple HDACs regulate the activities of numerous proteins involved in cell death during the progression of DKD. Specifically, inhibition of transcription factor EB

(TFEB) deacetylation induced by HDAC6 promotes TFEB activation and alleviates RTEC damage (93,94). Moreover, HDAC6-mediated deacetylation of α-tubulin suppresses autophagy and enhances motility of podocytes in DKD (95). HDAC4 suppresses podocyte autophagy and promotes podocyte apoptosis by acetylating STAT1 under diabetic conditions (96). SIRT1 activation can deacetylate forkhead box (Fox)O3a or regulate the NF-κB signaling pathway, while subsequently suppressing renal cell apoptosis (97-99). SIRT3 upregulation also antagonizes hyperglycemia-mediated tubular apoptosis by regulating the accumulation of ROS and modulating the ROS-sensitive Akt/FoxO signaling pathway (100). In parallel, SIRT6 inhibits the transcription of Notch1/4 by deacetylating histone H3K9, and protects podocytes against apoptosis and inflammation by enhancing autophagic flux (101). These results indicate that HDACs serve as potential therapeutic targets in DKD.

Methylation. Recruitment of EZH2, a methyltransferase that produces histone H3 lysine 27 tri-methylation (H3K27me3), at the Fox A1 promoter region promotes podocyte damage and apoptosis in the early stage of DKD (102,103). Inhibition of EZH2 by GSK126 attenuates podocyte injury and hyperglycemia-induced ferroptosis (104,105). By contrast, EZH2/H3K27me3 mitigates podocyte pyroptosis in DKD by increasing early growth response protein 1 (EGR1) in type 1 diabetic nephropathy (T1DN) (106). Moreover, AGEs induce downregulation of EZH2 in podocytes and decrease H3K27me3, which in turn leads to the upregulated expression of pathological factors (such as TGF-β1 and SNAI1) that contribute to podocyte injury in late DKD (107). KDM6A, a HDM that removes the di- and tri-methyl groups from histone H3K27, is activated in patients with DKD and mice with T1DN (108). Suppression of KDM6A by administration of GSK-J4 ameliorates the early lesions of db/db mice, including renal dysfunction, mesangial matrix accumulation, inflammation and apoptosis (109). The aforementioned studies indicate that levels of H3K27 are affected by multiple factors, such as cell types and environment, and the stage of DKD, thereby changing the transcription of its target genes.

Ubiquitination. Numerous altered ubiquitination statuses of proteins are associated with podocyte dysfunction. Specifically, TRIM29 promotes podocyte pyroptosis by interacting with inhibitor of NF-κBα (IκBα) to mediate its ubiquitination-dependent degradation, which triggers NF-κB activation (21). In addition, TRIM63 regulates PPARα ubiquitination and degradation, contributing to podocyte injury (110). The E3 ligase c-Cbl binds to podocin and increases the ubiquitination of podocin, leading to podocyte injury in DKD (111). Moreover, the deubiquitination of sperm-associated antigen 5 by USP14 activates Akt/mTOR signaling, exacerbating high glucose-induced autophagy and podocyte injury (112). The ubiquitination state of the receptor-interacting protein kinase (RIPK)1/RIPK3 pathway downregulated by ubiquitin C-terminal hydrolase L1, a crucial member of the deubiquitination family, serves a key role in podocyte necroptosis and apoptosis (113).

Lysine 63 ubiquitination (Lys63-Ub) is increased in the RTECs of DKD, and associated with autophagy deregulation and apoptosis activation (114). The apoptosis of RTECs is prevented by eukaryotic translation initiation factor 2α ubiquitination and degradation mediated by HMG-CoA reductase degradation 1 (115). Additionally, ARAP1 maintains persistent epidermal growth factor receptor (EGFR) activation by decreasing EGFR ubiquitination and subsequently activates TGF-β/Smad3 and hypoxia inducible factor 1α (HIF-1α) signaling, causing injury of RTECs and mesangial cells (MCs) (116,117). The aforementioned studies demonstrate that targets of ubiquitination, such as Lys63-Ub, may be a promising direction for DKD therapy.

SUMOylation. SUMOylation and deSUMOylation serve vital roles in the pathogenesis of numerous nephropathic diseases (118-120). In DKD, Kruppel-like factor (KLF)15 upregulates the expression of SUMO1 and enhances the SUMOylation of P53, subsequently inhibiting the proliferation of MCs (121). However, the role of SUMOylation in other aspects of DKD has not yet been clarified.

Glycosylation. Numerous studies have confirmed an increased number of O-GlcNAc-positive cells in the glomeruli and enhanced staining in the tubules in DKD (122,123). Hyperglycemia-driven elevation of O-GlcNAc modification contributes to DKD progression via the inhibition of Akt phosphorylation, thus abnormally activating endothelial NOS (eNOS) (124). A mutually reinforcing cycle is formed between activation of O-GlcNAcylation and the intrarenal renin-angiotensin-aldosterone system (RAAS), exacerbating glucose toxicity, while this effect is inhibited by RAAS blockers via increasing OGA levels (124). Akimoto *et al* (125) found that aberrant O-GlcNAcylation of α-actinin 4 and actin impairs cytoskeletal structure and adhesive function, leading to morphological changes in podocyte foot processes. This may trigger the early damage to the glomerular filtration barrier in DKD. Pharmacological inhibition of O-GlcNAcylation by OSMI1, an inhibitor targeting OGT, decreases podocyte apoptosis under diabetic conditions (126). Notably, O-GlcNAc modification exhibits a bidirectional paradox in tubular epithelial cells. During prolonged fasting conditions in RTECs, it is essential for renal lipolysis and exerts a protective effect against lipotoxicity (127). However, O-GlcNAcylation disrupts the homeostasis of retinol signals in HK2 cells (an immortalized proximal tubule epithelial cell line from normal adult human kidney) by extensively modifying the key molecules in the retinol signaling pathway, such as signaling receptor and transporter of retinol 6 and retinaldehyde dehydrogenases 1 (128). Moreover, diabetic conditions promote OGT-mediated O-GlcNAcylation of acyl-CoA synthetase long chain family member 4 (ACSL4), thereby stabilizing ACSL4 and facilitating tubular ferroptosis in DKD (129). This functional discrepancy may be attributed to modification targets, cell type and microenvironmental metabolic status. Additionally, as a subtype of glycosylation, inhibition of core fucosylation mitigates renal pathological changes, renal fibrosis and podocyte injury by downregulating the phosphorylation of Smad2/3 and ERK (130). Targeting protein O-GlcNAcylation may be a promising therapeutic approach for rescuing DKD progression.

Redox modification. Glutathione (GSH) is a primary endogenous antioxidant (131). Protein glutathionylation is a key PTM involved in the pathogenesis of complex diseases, including cardiovascular disease, acute lung injury and renal disease (132-134). Evidence regarding functional changes

induced by redox modifications as well as the increasing number of glutathionylated proteins indicate a role for glutathionylation in DKD (135,136). Notably, in patients with type 2 diabetes and microangiopathy, the levels of glutathionylated hemoglobin are markedly elevated whereas GSH levels are decreased (136). In normal podocytes, myosin 9A (Myo9A), Ras homolog family member A (RhoA) and actin are S-nitrosylated while the diabetic microenvironment induces the de-nitrosylation of Myo9A, actin and RhoA, causing increased RhoA activity and impaired podocyte migration (137). Moreover, oxidative modifications of serum albumin in patients with DKD not only trigger the activation of neutrophils but also result in inaccurate measurement of serum albumin (138). The aforementioned studies demonstrate that redox modification not only participates in the pathogenesis of DKD, but also affects the measurements of biochemical indexes.

Succinylation. Lysine succinylation is a naturally occurring PTM that alters the stability and function of substrate proteins. This modification is modulated by enzymes such as SIRT5 and serves a pivotal role in the pathogenesis of DKD. For example, upregulation of SIRT5 inhibits the succinylation of NIMA-related kinase 7 (NEK7), disrupts the interaction between NEK7 and NOD-like receptor protein 3 (NLRP3), and suppresses podocyte pyroptosis and oxidative stress-induced injury under hyperglycemia (139). However, whether protein succinylation is involved in the cell cycle of other renal cells remains unclear.

Oxidative stress

Phosphorylation. The PI3K/Akt pathway modulates FoxO3a activity by phosphorylating its three residues (Thr32, Ser253 and Ser315) and excludes FoxO3a from the nucleus (140). Klotho prevents podocyte injury against palmitate-induced oxidative stress by decreasing the phosphorylation of FoxO3a, promoting its nuclear translocation and upregulating the expression of antioxidants, including manganese superoxide dismutase (MnSOD) (140). However, in streptozotocin (STZ)-induced rats, activation of the PI3K/Akt/FoxO3 pathway alleviates inflammation and oxidative stress in MCs (141). Furthermore, activation of the AMPK/SIRT1/PPARγ coactivator 1α (PGC1α) pathway mitigates oxidative stress in db/db mice (142). Additionally, GSK3β knockdown enhances the antioxidant response driven by Nrf2 and suppresses oxidative stress, leading to the alleviation of oxidative stress and podocyte injury (67). Specifically, the elevated phosphorylation of GSK3β at serine 9 reduces the protein stability of GSK3β and diminishes its inhibitory effect on Nrf2, protecting podocytes and RTECs from oxidative stress (67,143). The insulin receptor (IR) is key for insulin action. Protein tyrosine-phosphatase 1B (PTP1B) attenuates insulin signaling by dephosphorylating IR and IR substrate 1, and knockdown of PTP1B protects podocytes from ER stress by improving insulin sensitivity (144). Targeting protein kinases and phosphatases may provide more options for DKD treatment.

Acetylation. Members of the SIRT family serve a pivotal role in DKD pathogenesis. Activation of the SIRT1/PGC1α/Nrf1 and SIRT1/NF-κB pathways effectively attenuates DKD, induces autophagic flux, mitigates oxidative stress and alleviates mitochondrial dysfunction in podocytes (77,145,146). Moreover, SIRT1 can interact with ACSS2. ACSS2 promotes mitochondrial oxidative stress and triggers renal tubular inflammation in DKD by modulating the SIRT1/carbohydrate responsive element binding protein (ChREBP) pathway (147). Polysulfides can attenuate diabetic renal pathological lesions via inactivation of p65 NF-κB and STAT3 phosphorylation/acetylation by sulfhydrating SIRT1, thereby reducing high glucose-induced oxidative stress, cell apoptosis, inflammation and EMT (77). Furthermore, the enhancement of mitochondrial oxidative stress in DKD is mediated by the reduction of SIRT3 activity and a subsequent increase in acetylated isocitrate dehydrogenase 2/SOD2 (148). General control of amino acid synthesis 5-like 1-mediated acetylation of MnSOD also exacerbates oxidative stress-induced renal injury in DKD (149). The aforementioned studies demonstrate the key role of the SIRT family in response to oxidative stress in DKD.

Methylation. Numerous alterations in the levels of proteins involved in oxidative stress are regulated by the alteration of histone methylation status. Expression of monocyte chemoattractant protein-1 (MCP-1) is elevated due to the recruitment of SET7/9 and H3K4me1 to its promoters in db/db mice (150). Decreased levels of HIF-1α suppress oxidative stress and inflammation via HDM KDM3A in human umbilical vein endothelial cells exposed to hypoxia and diabetic conditions (151). Siddiqi *et al* (152) demonstrated that inhibition of EZH2 with DZNep can increase podocyte injury, oxidative stress and proteinuria in diabetic rats. Moreover, S-adenosylhomocysteine hydrolase inhibition induces podocyte injury and oxidative stress via the EZH2/EGR1/thioredoxin-interacting protein/NLRP3 signaling cascade in STZ-induced T1DN mice (153). At present, the fundamental mechanism by which EZH2 serves different roles in various DKD models and cells remains unclear. Due to the involvement of multiple cell types in the pathogenesis of DKD and the cell context-specific gene regulation mediated by EZH2, EZH2 may serve a dual role in different renal cells in DKD (154).

Ubiquitination. Hyperglycemia prompts Von Hippel-Lindau tumor suppressor E3 ubiquitin ligase to ubiquitinate glucose-6-phosphate dehydrogenase, leading to ROS production and podocyte injury (155). Moreover, under diabetic conditions, sustained activation of PH domain and leucine-rich repeat protein phosphatase 1 promotes the nuclear retention of FoxO1 via prevention of its ubiquitination, inducing aberrations in renal gluconeogenesis and the activation of the apoptotic cascade, and exacerbating oxidative stress in diabetic rats (156). Oxidative stress and apoptosis are decreased in RTECs by promoting SIRT1 expression via suppressing its ubiquitination (157). Moreover, the phosphorylation of c-Cbl at Tyr731 facilitates the combination of c-Cbl and SIRT1, which triggers polyubiquitination of SIRT1 by c-Cbl and promotes SIRT1 degradation, decreasing the antioxidant effects of FoxO3a in DKD (158). Connexin32 (Cx32) upregulates SIRT1 expression by inhibiting the ubiquitination of Lys335 of SIRT1 by suppressing Smad specific E3 ubiquitin protein ligase 1 (Smurf1), thus alleviating oxidative stress in DKD (157). In addition, Cx32 decreases renal oxidative stress levels and ameliorates the pathological progression of diabetic renal fibrosis by promoting NADPH oxidase 4 polyubiquitination and degradation (159). Nrf2 is an important antioxidant in response to oxidative stress. Suppression of the ubiquitination of Nrf2 ameliorates experimental DKD through antioxidation

and regulation of the Keap1/Nrf2 signaling pathway (160,161). Additionally, ubiquitination participates in ferroptosis induced by oxidative stress. Ginkgolide B alleviates oxidative stress and ferroptosis by inhibiting glutathione peroxidase (GPX)4 ubiquitination to improve changes in renal structure in mice with DKD (162). Stimulator of interferon genes protein inhibition alleviates ferroptosis and oxidative stress in DKD via stabilization of ferroportin 1 (FPN1) protein levels by decreasing FPN1 ubiquitination for proteasomal degradation (163). In addition, 2-deoxy-d-ribose induces ferroptosis in RTECs by degrading the cystine/glutamate antiporter SLC7A11 protein via the UPS, resulting in decreased intracellular cystine uptake (164). These findings underscore the key role of ubiquitination and deubiquitination in DKD development, and highlight the potential therapeutic targets.

Glycosylation. In early stage DKD, ectonucleoside triphosphate diphosphohydrolase 5 (ENTPD5), a nucleotide hydrolase located in the ER, modulates the N-glycosylation of proteins and facilitates renal cell proliferation (165). Separately, in late stage DKD, sustained hyperglycemia activates the hexosamine biosynthesis pathway to increase the levels of UDP-GlcNAc, which triggers a feedback mechanism that suppresses transcription factor SP1 activity and downregulates ENTPD5 expression, aggravating ER stress (165). Additionally, O-GlcNAcylation of the mineralocorticoid receptor directly enhances both the protein abundance levels and transcriptional activity of the receptor under diabetic conditions (166). These findings provide novel directions for the diagnosis and targets of DKD.

Redox modification. Hypoglutathionemia and elevated oxidative stress levels contribute to the early biochemical abnormalities in diabetes (167). Additionally, reactive carbonyl derivate levels increase in patients with diabetes, and this elevation is more pronounced in diabetic patients undergoing hemodialysis, suggesting that both diabetic state and hemodialysis contribute to the enhancement of protein oxidation (168).

Succinylation. A previous study showed that K99 succinylation of hydroxysteroid 17β dehydrogenase 10 (HSD17B10) maintains mitochondrial RNA ribonuclease P (RNase P) stability (169). Astragaloside IV alleviates hyperglycemia-induced oxidative stress and mitochondrial dysfunction in HK2 cells by upregulating carnitine palmitoyltransferase 1A-mediated K99 succinylation of HSD17B10 to maintain RNase P activity (169).

Mitochondrial dysfunction

Phosphorylation. Extensive alterations of cell signaling pathways serve a broad role in maintaining mitochondrial homeostasis and optimizing oxidative phosphorylation. Inactivated AMPK and PI3K/Akt signaling and abnormal activation of the JNK pathway participate in mitochondrial dysfunction under diabetic conditions, modifying mitochondrial dynamic homeostasis and energy metabolism disorder in DKD (170-174). Finerenone treatment can reduce mitochondrial fragmentation and restore mitophagy via PI3K/Akt/eNOS signaling in HK2 cells exposed to diabetic conditions and tubular cells of mice with DKD (172). In addition, elevated SIRT1 phosphorylation at Ser47 is associated with mitochondrial dysfunction in podocytes (175). Inhibiting SIRT1 phosphorylation-mediated ubiquitin-proteasome degradation restores the capacity of SIRT1 to promote PGC1α deacetylation and nuclear translocation, and thereby upregulates genes associated with mitochondrial biosynthesis and antioxidant defense in DKD (176).

Phosphorylation of multiple proteins causes disruption of mitochondrial dynamics and leads to loss of mitochondrial voltage potential under high-glucose conditions. Dynamin-related protein 1 (Drp1) is a key regulator of mitochondrial fission. Cyclin-dependent kinase 5 phosphorylates Drp1 at Ser616 and thus produces excessive ROS, leading to EMT progression in HK2 cells (177). Enhanced phosphorylation of Drp1 at Ser637 (p-Drp1^{Ser637}) by Rho-associated coiled coil-containing protein kinase 1 promotes the transposition of Drp1 to the mitochondrial surface and accounts for excessive mitochondrial fission in mouse podocytes (178-180). By contrast, resveratrol decreases Drp1 levels while increasing p-Drp1^{Ser637} levels, blocking mitochondrial fission in MCs by inhibition of phosphodiesterase-4D/protein kinase A signaling (181). The functional consequences of serine phosphorylation of Drp1 may be dependent on cell type and stimulation. Mitophagy is a specialized form of autophagy that mediates the selective elimination of damaged or dysfunctional mitochondria (182). The phosphorylated form of FUN14 domain-containing 1 (FUNDC1) inhibits the induction of mitophagy by blocking the interaction between the FUNDC1 LC3-interacting region and LC3 (183,184). In addition, activated Src kinase serves as a negative modulator of mitophagy in DKD by inducing the phosphorylation of FUNDC1 at Tyr18, which impairs the ability of podocytes to clear damaged mitochondria (185). Studies have demonstrated the key role of aberrant protein phosphorylation in the progression of DKD (Table II) (81,186-190). However, further validation at different stages of human DKD are needed to fully understand the impact of PTMs.

Acetylation. Protein acetylation is a key component of diverse metabolic reactions. SIRT1 sustains mitochondrial homeostasis by mediating mitochondrial biogenesis and mitophagy in DKD (191,192). It has been hypothesized that the SIRT3/SOD2/GPX4 signaling pathway participates in the regulation of ferroptosis in DKD via maintenance of mitochondrial redox homeostasis (193). SIRT6 upregulation alleviates mitochondrial dysfunction and podocyte apoptosis via AMPK activation mediated by its deacetylation of H3K9 and H3K56 (194). In addition, activation of SIRT1 exerts a renoprotective role in restoring mitochondrial homeostasis, providing a preclinical research basis for small molecule drugs targeting the SIRT family.

Ubiquitination. TRIM22, a E3 ubiquitin ligase, is highly expressed in patients with DKD, interacts with optic atrophy 1 and induces its ubiquitination, thus altering mitochondrial fusion-associated proteins involved in respiration/ATP synthesis, influencing ROS production and mitochondrial function in DKD (195). Long non-coding RNA PVT1 is involved in mitochondrial dysfunction by interacting with TRIM56 at the post-transcriptional level to induce AMPK ubiquitination, leading to aberrant mitochondrial biology and increasing mitochondrial DNA leakage in podocytes in DKD (196). Additionally, interference with Smurf2 inhibits both RUNX family transcription factor 3 ubiquitination and the TLR4/NF-κB signaling pathway, which alleviates mitochondrial dysfunction

Table II. Effects of phosphorylation on mitochondrial dysfunction in diabetic kidney disease.

Model	Cell type	Target	Mechanism	(Refs.)
STZ-induced mice and 30 mM D-glucose-induced podocytes	Podocytes	PI3K/Akt/TSC2/mTOR	Mitophagy	(173)
STZ-induced rats and 25/35 mM D-glucose-induced podocytes	Podocytes	AMPK, PERK and Larp1	Mitochondrial dysfunction, MAMs and mtDNA replication	(81,170,186)
STZ-induced rats/mice and 30 mM D-glucose-induced podocytes	Podocytes	Drp1	Mitochondrial dynamic homeostasis and MAMs	(177,179,186,187)
db/db mice and 30 mM D-glucose-induced human podocytes	Podocytes	FUNDC1	Mitophagy	(185)
Akita mice and 25 mM D-glucose-induced podocytes	Podocytes	JNK and IRS-1	Podocyte dysfunction and insulin resistance	(174)
STZ-induced mice and 30/40 mM D-glucose-induced HK2 cells	Tubular epithelial cells	AMPK and PI3K/Akt	Mitochondrial quality control and fragmentation, and mitophagy	(171,172)
40 mM D-glucose-induced HK2 cells	Tubular epithelial cells	p66Shc and PPAR	Mitochondrial fragmentation	(188,339)
db/db mice and 30 mM D-glucose-induced proximal tubular cells	Tubular epithelial cells	AMPK	Mitochondrial dysfunction	(4,189)
STZ-induced mice and 30 mM D-glucose-induced primary glomerular endothelial cells	Glomerular endothelial cells	SIRT1	Mitochondrial dysfunction	(176)
db/db mice	Renal tissue	AMPK, MAPK and c-Jun	Mitochondrial dysfunction, oxidative stress and renal fibrosis	(190)

AMPK, AMP-activated protein kinase; Drp1, dynamin-related protein 1; FUNDC1, FUN14 domain-containing 1; IRS-1, insulin receptor substrate 1; MAM, mitochondria-associated endoplasmic reticulum membrane; mtDNA, mitochondrial DNA; SIRT1, sirtuin 1; STZ, streptozotocin.

and tubular injury (197). Another E3 ubiquitin ligase, Cullin3, directly interacts with mitochondrial ribosomal protein L12 to induce its ubiquitination, resulting in mitochondrial biosynthesis dysfunction in RTECs (198). However, the effect of ubiquitination on the mitochondrial homeostasis of MCs and endothelial cells needs further investigation.

SUMOylation. DeSUMOylation of RNA binding motif protein X-linked serves a key role in determining the microRNA (miRNA/miR) composition of renal cell exosomes, which prevents the protective miRNAs from inhibiting mitochondrial damage in DKD (199).

Redox modification. In chronic diabetes, mitochondrial proteins are susceptible to PTMs triggered by glycation and oxidation. Oxidative and nitrosative stresses promote mitochondrial oxidative dysfunction in STZ-induced diabetic rats (200). Carbonyl-mediated modifications selectively target key protein components of major mitochondrial cycles, including oxidative phosphorylation and fatty acid β-oxidation (201). Methylglyoxal, a dicarbonyl compound that accumulates to high levels in the hyperglycemic environment, exerts an inhibitory impact on both the tricarboxylic acid cycle and the electron respiratory chain (202). Notably, such modifications are specific to certain mitochondrial proteins and trigger disturbances in mitochondria involved in renal cellular toxicity and the progression of DKD (202).

Lactylation. The expression of lysine lactylation is notably elevated in renal tissues from patients with diabetes as well as db/db mice (43,203,204). Lactylation of acyl-CoA synthetase family member 2 at lysine 182 contributes to tubular mitochondrial dysfunction, which accelerates the progression of DKD (203). However, research on the roles of lactylation in other renal cell types is lacking.

Inflammation

Phosphorylation. NF-κB, interacting with IκB and IκB kinase (IKK), is a key intracellular molecule regulating

inflammation and is abnormally activated in DKD (205,206). FoxM1 transcriptionally activates SIRT4, and suppresses phosphorylation of NF-κB (Ser536) and the levels of NLRP3 inflammasome to ameliorate renal damage and podocyte pyroptosis in DKD (207). Inflammation in DKD is decreased by activation of the Nrf2-mediated antioxidant pathway and inhibition of the MAPK-mediated inflammatory pathway, such as ERK1/2, JNK and MAPK (205,208,209). Treatment with salidroside triggers the phosphorylation of Akt and GSK3β; suppressed expression of p-Akt (Ser473) and p-GSK3β (Ser9) inhibits oxidative stress and inflammation in DKD rats (210). Upregulated phosphorylation of SH2 domain-containing protein-tyrosine phosphatase-2 (SHP2) is detected in macrophages in both diabetic patients and mouse models (211,212). Macrophage SHP2 deficiency alleviates DKD via the suppression of MAPK/NF-κB-dependent inflammation, subsequently attenuating renal dysfunction, collagen deposition, fibrosis and inflammatory response in STZ-treated mice (211). Dephosphorylation of STAT3 (Tyr705) ameliorates tubulointerstitial inflammation and glomerulosclerosis in DKD (213,214). Monitoring the dynamic changes of the phosphorylated status of proteins during DKD progression may improve understanding of the pathogenesis of DKD.

Acetylation. High-glucose stimulation increases H3K9/14Ac at the receptor for AGEs, plasminogen activator inhibitor-1 and MCP-1 promoters, performing key roles in rat MCs in DKD, whereas losartan reverses the H3K9/14Ac marks at targeted genes (215). PCAF serves an essential role in regulating inflammatory molecules through H3K18ac, providing a potential therapeutic target for inflammation-associated renal diseases (216-218). HDACs also participate in the inflammatory response in DKD. Apelin-13 inhibits diabetes-induced elevation of inflammatory factors and histone hyperacetylation by upregulation of HDAC1 (219). Gene silencing of HDAC4 decreases the inflammatory response and apoptosis induced by hyperglycemia in podocytes (96). Upregulation of SIRT1 inhibits inflammation through decreasing the induction of inflammatory cytokines and reducing acetylated-NF-κB (220-223). SIRT6 protects podocytes from inflammation by inhibiting the Notch pathway (101). Moreover, upregulation of SIRT7 decreases inflammation and improves renal function in glomerular endothelial cells by regulating the H3K18ac level of death-associated protein kinase-3 (224). These findings support the impact of acetylation on DKD and the potential mechanisms of existing therapeutic drugs, such as losartan.

Methylation. Different histone modifications are involved in the inflammatory response in DKD. SET7/9 and H3K4me1 expression are markedly increased, whereas H3K9me2 and H3K9me3 are decreased by inflammation induced by hyperglycemia (225,226). Moreover, the diabetic environment attenuates SET domain-containing protein 8 (SETD8) levels, as well as their downstream target H4K20me1. Upregulation of H4K20me1 inhibits endothelial inflammation in DKD by occupying the promoter regions of diverse target genes, including IL-1 receptor-associated kinase 1, Wnt family member 5A and PTP1B (227-229). Additionally, yes-associated protein 1 promotes hyperglycemia-induced inflammation and ECM deposition by triggering the activation of NF-κB/jumonji domain-containing protein-3 signaling in MCs (230). In addition, KDM6A regulates the transcription of inflammatory genes in a manner dependent on its demethylase activity (109). These results support that epigenetic alternations are associated with sustained pro-inflammatory pathways and partly explain the phenomenon of 'hyperglycemic memory' in DKD. This refers to the persistent susceptibility of diabetic patients to develop complications stemming from early hyperglycemic exposure, even following effective implementation of blood glucose control (231).

Ubiquitination. Ubiquitin-modifying enzymes and deubiquitinases act in conjunction to regulate the transmission of intracellular ubiquitin signaling to maintain normal cell activities. OTUD5, a deubiquitinating enzyme, deubiquitinates K63-linked TGF-β-activated kinase 1 (TAK1) at the K158 site through its active site C224, which prevents TAK1 phosphorylation and decreases downstream inflammatory responses in podocytes during DKD (232). E3 ubiquitin ligase speckle-type BTB-POZ protein promotes NLRP3 degradation by elevating K48-linked polyubiquitination of NLRP3 (233). TGF-β1 is profibrogenic in renal fibrosis (234). Latent TGF-β1, unlike the active form of TGF-β1, protects against inflammation and fibrosis by blocking the E3-ligase Arkadia-mediated Smad7 ubiquitin proteasomal degradation pathway in STZ-induced T1DN (234). Obstruction of ubiquitin degradation of IKK induced by decreased ubiquitin ligase NEDD4L and inhibition of TNF receptor-associated factor 6 K63 polyubiquitination mediated by USP25 can decrease the activation of NF-κB and relieve inflammation (19,235). Parkin inhibits pathological progression of DKD by promoting the ubiquitination of GATA-binding protein 4 (GATA4) and downregulating GATA4/growth arrest-specific protein 1 signaling to inhibit premature senescence, renal inflammation and fibrosis (236). The aforementioned studies demonstrate that protein ubiquitination performs an important role in inflammation in DKD.

SUMOylation. In diabetic mice, the expression of SENP6 is decreased in glomerular tissue; this downregulation exacerbates injury to the glomerular filtration barrier. Mechanistically, SENP6 enhances the ubiquitination of the Notch1 intracellular domain (N1ICD) by deSUMOylating Notch1, subsequently reducing N1ICD and inhibiting Notch1 signaling activation in podocytes (237). Moreover, SENP6 deSUMOylates KDM6A and decreases the binding affinity of KDM6A to endothelin-1 (Edn1) via upregulation of H3K27me2/3 at its promoter (237). Numerous studies have indicated that hyperglycemia-induced activation of NF-κB inflammatory signaling is mediated by the SUMO E3 ligase protein inhibitor of activated STAT y and IκBα SUMOylation (238,239). These findings indicate that the combined effect of various PTMs regulate the pathogenesis of DKD.

Glycosylation. Protein glycosylation serves an important role in protein stability, binding, folding and activity, and is a key PTM of proteins. In mouse kidney endothelial cells, hyperglycemia causes increased methylglyoxal modification of the corepressor mSin3A, which results in increased recruitment of OGT and enhanced O-GlcNAcylation of Sp3 (240). This modification of Sp3 causes an increase in angiopoietin 2 expression, sensitizing microvascular endothelial cells to the proinflammatory effects of TNFα (240).

Crotonylation. Histone Kcr, a PTM, was first identified in 2011 (45). Sodium crotonate (NaCr) may mitigate DKD through an antidiabetic effect, as well as by inducing ACSS2 and P300-induced histone Kcr (241).

Fibrosis

Phosphorylation. TGF-β1 induces profibrotic and inflammatory genes, which serve key roles in glomerular dysfunction and the mesangial matrix expansion associated with DKD (242,243). Multiple protein kinases and phosphatases have an essential role in renal fibrosis. TGF-β1 stimulation results in the phosphorylation/activation of PKCβII, a direct substrate of mTORC2, thus modulating renal fibrosis in DKD (244). Activation of AMPK and Akt signaling alleviates renal injury and fibrosis in DKD (245-247). Activation of MAPK signaling aggravates fibrosis under diabetic conditions (248-250). Activation of the GSK3β and Nrf2/HO-1 pathways also causes inhibitory regulation of EMT and exerts anti-renal fibrosis activity, delaying the progression of DKD (251,252). The suppression of phosphorylation of EGFR and NF-κB are involved in amelioration of renal tubulointerstitial fibrosis (253-255). Targeting shared profibrotic pathways via modulation of protein phosphorylation may serve as a novel therapeutic strategy for DKD (Table III) (130,190,256-260).

Acetylation. Different acetylated states of proteins perform different functions. For example, p300-dependent H3K27 acetylation on the PLK1 gene promoter ameliorates renal fibrosis of DKD (90). Moreover, sterol regulatory element-binding transcription factor 1a K333 acetylation mediated by the acetyltransferase CBP is key for Smad3 association and they cooperatively mediate TGF-β transcriptional responses (261). In addition, numerous deacetylases contribute to renal fibrosis in DKD. HDAC2 serves a key role in the development of ECM accumulation, EMT and renal interstitial fibrosis in diabetic kidneys by regulating the acetylation of substrates, including Edn1 and miR-205 (262-264). SIRT1 activation markedly suppresses endothelial-mesenchymal transition (EndMT) progression, and attenuates albuminuria and glomerulopathy via regulation of the acetylation of NF-κB, FoxO1 and FoxO3a (265-267). SIRT3 deficiency in endothelial cells stimulates TGF-β/Smad3-dependent mesenchymal transformation in RTECs (268). SIRT6 has been demonstrated to directly interact with Smad3, a key downstream mediator of TGF-β, and inhibits its nuclear accumulation and transcriptional activity by deacetylating it in HK2 cells (269). Furthermore, FoxO3a exerts a renoprotective effect against diabetic kidney injury via the SIRT6/Smad3 pathway (Table III) (269,270). These studies reveal the vital role of imbalanced acetylation in renal fibrosis in DKD.

Methylation. EZH2/H3K27me3 recruitment at the promoters of profibrotic genes is downregulated in rat MCs in T1DN and reciprocally upregulates expression of these profibrotic genes, such as connective tissue growth factor and Serpine1 (271). Moreover, EZH2 alleviates the progression of renal interstitial fibrosis in T1DN by regulating its downstream genes, such as MMP9 (272). In type 2 diabetic nephropathy, OGT stabilizes EZH2 by promoting its glycosylation and then inhibiting MC hyperproliferation and fibrosis by enhancing the enrichment of EZH2/H3K27me3 in the hairy and enhancer of split 1 promoter (273). However, the role of EZH2 in DKD remains controversial. In early DKD, enhanced expression of EZH2 is associated with decreased DEPTOR levels and increased mTOR activity, inducing MC hypertrophy and matrix expansion (274). Under diabetic conditions, recruitment of EZH2 inhibits SOX6, induces cell proliferation, fibrosis and inflammatory cytokine release in MCs (275). The method used to establish DKD models and context-dependent factors affects the function of EZH2 in renal fibrosis. To explain the role of EZH2 in renal fibrosis, the association between EZH2 expression and histological characteristics of patients with DKD should be assessed.

The enhanced recruitment of SET7/9 and elevated H3K4me at the p21 promoter, concurrent with the decreased H3K9me level are observed in the glomeruli of diabetic rats, resulting in increased mesangial hypertrophy (276). Histone H2AK119 mono-ubiquitination (H2AK119-Ub) downregulates SET7/9 (277). Genetic suppression of SET7/9 decreases profibrotic gene expression and prevents EndMT by regulating insulin-like growth factor-binding protein 5 (278,279). Additionally, SETD8/H4K20me1 regulates EndMT in DKD by modulating methylation of its downstream targets, such as profilin 2 and enolase 1 (280-282). However, additional studies are required to examine the effects of SET7/9 and SETD8 in other cell types in the progression of DKD.

Beyond methyltransferases that act on the lysine sites of proteins, elevated protein arginine methyltransferase 1 expression activates activating transcription factor 6 by recruiting H4R3me2as to the promoter, promoting ER stress and EMT activation in HK2 cells (283).

In addition, demethylases are associated with renal fibrosis. Expression of fibrotic proteins and dickkopf-1 is negatively regulated by the KDM6A inhibitor GSK-J4, attenuating glomerulosclerosis and renal fibrosis in mice with DKD (284,285). The HDM KDM3A is recruited to the CTGF promoter to activate transcription, augmenting hyperglycemia-induced CTGF induction in RTECs (286). Additionally, histone lysine-specific demethylase 1 aggravates renal fibrosis by decreasing SIRT3 expression and activating the TGF-β1/Smad3 pathway (Table III) (287).

Numerous inhibitors (such as tazemetostat, GSK126 and GSK-J4) of methyltransferases and demethylases are undergoing clinical trials for cancer treatment (288,289). Such preclinical research utilizing pharmacological drugs that target methylation may advance DKD treatment.

Ubiquitination. During the progression of renal fibrosis, numerous proteins undergo ubiquitination and deubiquitination (290). E3 ubiquitin ligase of the TRIM subfamily of RING-containing proteins is notably associated with renal fibrosis in DKD (195,291). TRIM18 promotes EMT, inflammation and fibrosis in HK2 cells via ubiquitination of PTP1B and activates STAT3 signaling (292). Upregulation of TRIM13 suppresses mesangial collagen synthesis in DKD by promoting ubiquitination of C/EBP homologous protein, providing insight into the application of histone ubiquitination in the management of DKD (293). Smurf1/2, HECT-type E3 ubiquitin ligases, participate in renal fibrosis by ubiquitinating TGR5 and ChREBP (294-296). Additionally, serum creatinine enhances the interaction between c-Cbl and CKIP-1 by promoting the phosphorylation of c-Cbl, thereby increasing

Table III. Post-translational modification in renal fibrosis in diabetic kidney disease.

A, Phosphorylation

Model	Cell type	Target	Mechanism	(Refs.)
STZ-induced mice and 33 mM D-glucose-induced podocytes	Podocytes	Smad2/3, ERK and AMPK	EMT and renal fibrosis	(130,246)
STZ-induced mice and 25/30/35 mM D-glucose-induced HK2 cells	Tubular epithelial cells	Smad3 and NF-κB	Autophagy-lysosome system, EMT and fibrosis	(242,243,255)
STZ-induced rats and 30/40 mM D-glucose-induced NRK-52E cells	Tubular epithelial cells	MAPK, NF-κB and IκBα	Tubulointerstitial fibrosis	(250,254)
STZ-induced rats and 15-50 mM D-glucose-induced HK2 cells	Tubular epithelial cells	MAPK	Fibrosis	(256)
STZ-induced mice, db/db mice and 30 mM D-glucose-induced HK2 cells	Tubular epithelial cells	AMPK	Renal fibrosis	(245,247)
STZ-induced mice and 30 mM D-glucose-induced RTECs	Tubular epithelial cells	Akt	Renal fibrosis	(248)
db/db mice and 30 mM D-glucose-induced NRK-52E cells	Tubular epithelial cells	EGFR	EMT and ECM accumulation	(253)
db/db mice and 18.8/30 mM D-glucose-induced mesangial cells	Mesangial cells	PTEN, Akt, Smad3	Hypertrophy, ECM accumulation and renal fibrosis	(257,258)
STZ-induced rats and 30 mM D-glucose-induced human renal mesangial cells	Mesangial cells	GSK3β	Renal fibrosis	(251)
db/db mice	Renal tissue	AMPK and Jun	Renal fibrosis	(190)
STZ-induced mice	Renal tissue	β-catenin	Renal fibrosis	(259,260)

B, Acetylation

Model	Cell type	Target	Mechanism	(Refs.)
STZ-induced mice and 30 mM D-glucose-induced podocytes	Podocytes	SIRT1/p53, NF-κB	Podocyte loss and podocyte EMT	(146,265)
STZ-induced mice and 30 mM D-glucose-induced HK2 cells	Tubular epithelial cells	MnSOD, p53	EMT and fibrosis	(149,340)
db/db mice and 30/60 mM D-glucose-induced HK2 cells	Tubular epithelial cells	H3K27ac/PLK1, SIRT1/YY1 and FoxO3a/SIRT6/Smad3	EMT and renal fibrosis	(90,269,341)
STZ-induced rats and TGF-β1-induced NRK-52E cells	Tubular epithelial cells	HDAC2	ECM accumulation and EMT	(262)
db/db mice and TGF-β1-induced HK2 cells	Tubular epithelial cells	HDAC2/H3K9ac/SP1/mic roRNA-205	ECM accumulation and interstitial fibrosis	(264)
STZ-induced mice and 25 mM D-glucose-induced mesangial cells	Mesangial cells	SIRT1/FoxO	Fibrosis	(267)
STZ-induced mice and HUVECs	Endothelial cells	SIRT3	EndMT	(268)

Table III. Continued.

B, Acetylation

Model	Cell type	Target	Mechanism	(Refs.)
30 mM D-glucose-induced mesangial cells	Mesangial cells	Akt/SIRT1 and FoxO3a	Renal fibrosis	(270)
STZ-induced mice, normal aging mice, and mice after UUO	Connecting tubule/collecting duct	Dot1la/H3K79ac2/Edn1	Renal fibrosis	(263)

C, Methylation

Model	Cell type	Target	Mechanism	(Refs.)
STZ-induced mice and 30 mM D-glucose-induced HK2 cells	Tubular epithelial cells	KDM6A/E-cadherin and PRMT1/ H4R2me2as/ATF6	EMT and renal fibrosis	(283,284)
STZ-induced mice and 35 mM D-glucose-induced NRK-52E cells	Tubular epithelial cells	MRTF-A/H3K4/WDR5	Renal fibrosis	(342)
STZ-induced mice and 35 mM D-glucose-induced RTECs	Tubular epithelial cells	KDM3A/CTGF	Renal fibrosis	(286)
25 mM D-glucose-induced rat mesangial cells	Mesangial cells	SET7/12(S)-HETE and EZH2/H3K27me3/ DEPTO R/mTOR	Mesangial cell hypertrophy, matrix expansion and renal fibrosis	(274,278)
STZ-induced mice and 35 mM D-glucose-induced rat mesangial cells	Mesangial cells	GSK-J4/DKK1	Glomerulosclerosis and fibrosis	(285)
STZ-induced rats and mice, and 25/30 mM D-glucose-induced mesangial cells	Mesangial cells	EZH2/H3K27me3 and SET7/9/p21	Renal fibrosis	(271,276)
db/db mice and 25 mM D-glucose-induced mesangial cells	Mesangial cells	EZH2/H3K27me3/ HES1	Renal fibrosis	(273)
STZ-induced mice and 25 mM D-glucose-induced SV40 MES13 cells	Mesangial cells	EZH2/SOX6	Cell proliferation, fibrosis and inflammation	(275)
STZ-induced mice and 25 mM D-glucose-induced immortalized HGECs	Endothelial cells	SET7/IGFBP5	EndMT	(279)
STZ-induced rats and 25 mM D-glucose-induced HGECs	Endothelial cells	SETD8/H4K20me1/ elk1/BACH1	EndMT	(280)
STZ-induced rats and 25 mM D-glucose-induced HUVECs	Endothelial cells	SETD8/PFN2 and KTM5A/ENO1	EndMT	(281,282)
STZ-induced rats and TGF-β1-induced NRK-49F cells	Renal fibroblast cell	LSD1/SIRT3/TGF-β1/ Smad3	Renal fibrosis	(287)
STZ-induced rats	Glomeruli and renal tissue	H2AK119-Ub/SET7 and EZH2/H3K27me3/ MMP9	Renal fibrosis	(272,277)

D, Ubiquitination

Model	Cell type	Target	Mechanism	(Refs.)
db/db mice and 30 mM D-glucose-induced HK2 cells	Tubular epithelial cells	TRIM18/STAT3	EMT, inflammation and renal fibrosis	(292)

Table III. Continued.

D, Ubiquitination

Model	Cell type	Target	Mechanism	(Refs.)
STZ-induced mice and 24.5/25/25.5/30 mM D-glucose-induced HK2 cells	Tubular epithelial cells	USP36/DOCK4, MEX3C/PTEN, Hrd1/Nrf2 and lysine 63	EMT and renal fibrosis	(22,300,343,344)
db/db mice and 30 mM D-glucose-induced NRK-52E cells	Tubular epithelial cells	USP9X/Cx43 and USP22/Snail1	EMT and ECM accumulation	(298,301)
STZ-induced rats and 25 mM D-glucose-induced NRK-52E cells	Tubular epithelial cells	SnoN	EMT and ECM deposition	(303,304)
STZ-induced mice and 30 mM D-glucose-induced rat mesangial cells	Mesangial cells	Smurf1/Nox4	Renal fibrosis	(294)
STZ-induced mice and 30 mM D-glucose/TGF-β1-induced human mesangial cells	Mesangial cells	TRIM13/CHOP	Renal fibrosis	(293)
db/db mice and 30 mM D-glucose-induced mesangial cells	Mesangial cells	Smurf1/TGR5	Renal fibrosis	(295)
STZ-induced mice and 30 mM D-glucose-induced mesangial cells	Mesangial cells	CKIP-1	ECM, inflammation and renal fibrosis	(297)
STZ-induced rats and 25 mM D-glucose-induced SV40-MES13 cells	Mesangial cells	KDM3A	Inflammation and fibrosis	(302)
db/db mice and LPA-induced SV40 MES13 cells	Mesangial cells	Smurf2/ChREBP	Mesangial cell fibrosis	(296)
AGEs-induced mesangial cells	Mesangial cells	USP9X/Nrf2/AR2	Accumulation of ECM and fibrosis	(299)
STZ-induced rats	Glomeruli	SET7/9 and SUV39H1	Renal fibrosis	(318)

AGEs, advanced glycation end products; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; EndMT, endothelial-mesenchymal transition; HGEC, human glomerular endothelial cell; HUVEC, human umbilical vein endothelial cell; LPA, lysophosphatidic acid; RTEC, renal tubular epithelial cell; STZ, streptozotocin; UUO, unilateral ureteral obstruction.

c-Cbl-mediated ubiquitination of CKIP-1 to downregulate its expression, which exacerbates renal inflammatory fibrosis in diabetic mice (297). USP modulates EMT and the production of ECM components by deubiquitinating and stabilizing their respective substrates (22,298). For example, USP9X decreases Nrf2 ubiquitination and deubiquitinates Cx43 to regulate the EMT process (299-301). Ubiquitination and degradation of KDM3A increases TGF-β-induced factor 1 transcriptional activity, inactivating TGF-β1/Smad2/3 signaling and suppressing the progression of DKD (302). TAK1 mediates the phosphorylation of Ski-related novel protein N (SnoN), leading to SnoN ubiquitination and degradation, which enhances EMT and ECM deposition to promote renal fibrosis during DKD (Table III) (303,304). Modulation of ubiquitination may play a promising role in the treatment of DKD.

SUMOylation. High glucose enhances the SUMOylation of STAT1, which prevents STAT1 from exerting an effective protective function in inhibiting EMT (305). Furthermore, diabetic conditions activate TGF-β/Smad signaling via SUMO2/3 mediated SUMOylation of Smad4 in MCs (306,307).

Glycosylation. O-GlcNAc augments the protein stability, transcriptional activity and nuclear translocation of ChREBP. Diabetic conditions increase the levels of O-GlcNAcylated ChREBP, which further lead to lipid accumulation and upregulation of fibrotic proteins in MCs (308). In addition, O-GlcNAc is, in part, coupled to the profibrotic MAPK signaling pathway via inhibition of Akt phosphorylation and potentially through ROS (309).

Redox modification. The hyperglycemia-induced increases in phosphorylation and oxidation of mitochondrial proteins

contributes to tubular dysfunction during DKD (310). S-nitrosylation serves a role in the precise regulation of glomerular homeostasis by modulating multiple important signaling pathways in DKD models. Specifically, S-nitrosylation of laminin prevents the development of glomerular nodules, while denitrosylation of S-nitrosoglutathione reductase and increased S-nitrosylation of β3-integrin collectively result in diffuse glomerulosclerosis in podocytes (311,312).

Lactylation. An elevation in histone lactylation is observed in mice with DKD. H3K14la promotes the transcription of KLF5 in RTECs of DKD (313,314). Notably, disruption of the lactate/H3K14la/KLF5 pathway mitigates renal dysfunction and DKD pathology (313). In addition, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), a key glycolytic enzyme, is associated with renal fibrosis and dysfunction. Lactate generated from PFKFB3-mediated tubular glycolytic reprogramming significantly enhances histone lactylation, particularly H4K12la, which is enriched at the promoters of NF-κB signaling genes (such as Ikbkb, Rela and Relb), activating their transcription, and facilitating the inflammatory response and renal fibrosis (39).

Crotonylation. NaCr exerts an antidiabetic effect, decreases blood glucose and serum lipid levels, and alleviates renal function and DKD-associated inflammatory and fibrotic damage. NaCr induces histone Kcr and H3K18 crotonylation. However, NaCr and Cr-CoA-induced histone Kcr and renoprotective effects are abrogated by inhibiting the activity of ACSS2 or histone acyltransferase p300 *in vitro* (241). Moreover, ACSS2 notably increases H3K9cr levels in renal tissues and tubular epithelial cells (48,91). Genetic and pharmacological suppression of ACSS2 inhibits H3K9cr-mediated IL-1β expression, which alleviates IL-1β-dependent macrophage activation and tubular senescence to delay renal fibrosis (48). Targeting ACSS2 may serve as a potential therapeutic intervention for the management of DKD, but warrants further preclinical and clinical investigations.

Kbhb. Beyond its role in energy supply, BHB serves as a bioactive molecule that exerts numerous protective effects, including in DKD. BHB antagonizes glomerulosclerosis in diabetic rats via upregulation of MMP2 production through elevation of H3K9bhb at the MMP2 promoter (315). Moreover, BHB ameliorates hyperglycemia-induced podocyte injury *in vitro* (316).

5. Crosstalk of PTMs in DKD

The interaction between PTMs of a protein to modulate protein function through positive/negative regulatory effects is termed PTM crosstalk. Positive crosstalk refers to multiple PTMs that occur in the same local protein sequence area (typically within a span of five amino acids) but do not happen in the same residues, occurring concurrently or with a causal or chronological connection (6). Negative crosstalk is characterized by the direct competition of two PTMs for the same residue in a causal or temporal manner. Crosstalk between multiple PTMs is more frequently observed in key protein domains such as histones and protein kinases in DKD. For example, dysregulation of O-GlcNAcylation of β-actin Ser199 and phosphorylation of β-actin Ser199 contributes to morphological changes in DKD (317). Elevated H2AK119-Ub and H2BK120 mono-ubiquitination (H2BK120-Ub) are observed in diabetic rats (318). Histone H2AK119-Ub and H2BK120-Ub promote diabetic renal fibrosis by upregulating the expression of methyltransferases SET7/9 and SUV39H1, thereby enhancing active H3K4Me2 and suppressive H3K9Me2 marks, respectively (318). Zhang *et al* (263) reported that Dot1l and HDAC2 mutually inhibit their binding to the Edn1 promoter to regulate the production of Edn1, which is involved in renal fibrosis in DKD. A novel ubiquitin-like modification, neddylation, stabilizes RhoA by reducing its ubiquitination, thereby activating the ERK1/2 pathway and driving interstitial fibrosis (319). Moreover, OTUD5 deubiquitinates K63-linked TAK1 at the K158 site, which prevents the phosphorylation of TAK1 and decreases downstream inflammatory responses in podocytes (230). Furthermore, different PTMs jointly regulate DKD progression through combined or antagonistic pathways, yet their cross-interaction networks need systematic elucidation (Fig. 3).

6. Clinical translational potential of PTMs

PTMs modulate gene expression, and protein stability and activity, serving a pivotal role in DKD progression as a key event in the pathological timeline. Despite increasing attention, the majority of PTMs in DKD are still in the preliminary research stage, and their regulatory networks and cell type-specific roles need further clarification (320,321). Notably, studies have identified PTMs as potential biomarkers for DKD occurrence and development (322-324). For example, plasma 2,6-sialylation of triantennary glycan A3E is associated with DKD risk (322). Moreover, patients with DKD exhibit abnormal lactate metabolism, and there is an association between urinary lactate levels and renal tubular injury (323,324). Overall, these findings highlight the translational importance of PTMs in early diagnosis and progression assessment of DKD. Accumulating evidence further demonstrates the therapeutic prospects of targeting PTMs for DKD treatment (320,325). Numerous drugs exert biological effects partly by targeting PTM regulators. For example, metformin, melatonin and resveratrol target SIRT1 to regulate autophagy, oxidative stress, lipid deposition and renal fibrosis in DKD (326-328). Additionally, sodium-glucose cotransporter 2 and RAAS inhibitors exert renoprotective effects on DKD by impacting O-GlcNAcylation (329).

At present, there are numerous small-molecule inhibitors targeting PTMs used in the therapeutic research of DKD models. Small-molecule inhibitors of HDACs (such as trichostatin A, vorinostat and valproic acid targeting class I and II HDACs), methyltransferases (such as GSK-J4 targeting KDM6A) and phosphorylation-related enzymes (such as rapamycin targeting mTOR) have exhibited favorable efficacy in preclinical models, as evidenced by the mitigation of renal fibrosis and inflammation, and improvement of renal function (320,330-332). Despite the encouraging results of PTM activators or inhibitors in experimental models, their clinical therapeutic efficacy is subject to limitations. The wide presence of PTMs *in vivo* and the crosstalk among distinct PTMs poses challenges to selective targeting, as targeting a single modification may

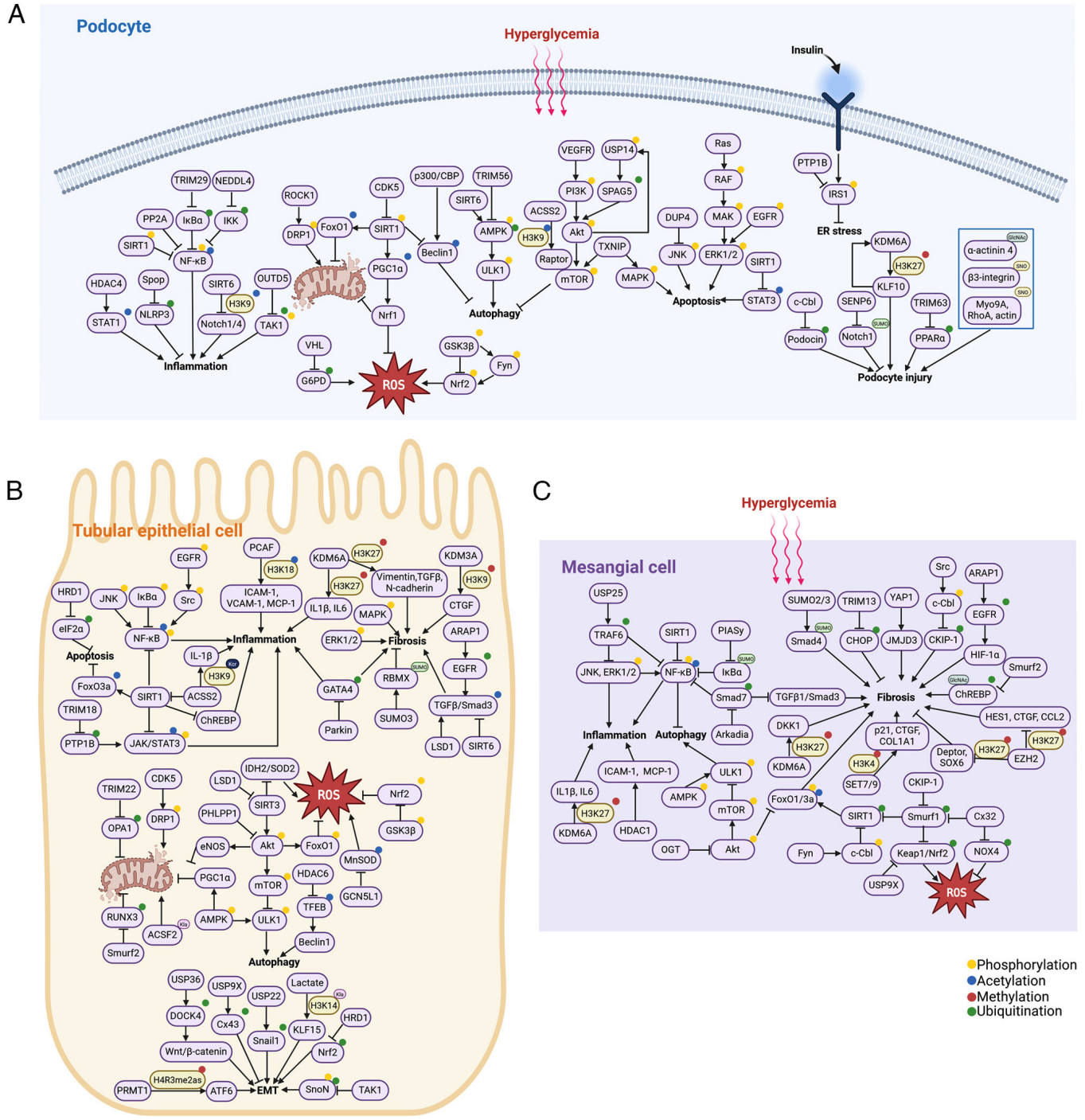

Figure 3. Overview of the crosstalk between post-translational modifications in diabetic kidney disease. Role of crosstalk among PTMs in regulating cell death, oxidative stress, mitochondrial dysfunction, inflammation and fibrosis in (A) podocytes, (B) tubular epithelial and (C) mesangial cells in DKD. Created with BioRender.com.

interfere with interrelated pathways and lead to unexpected consequences. Moreover, individual enzymes typically act on multiple substrates and signaling pathways, causing global changes instead of gene- or organ-specific effects. At present, clinical trials of inhibitors of methyltransferases and HDACs, such as tazemetostat, chidamide and entinostat, are concentrated on therapy for cancer, including various types of relapsed/refractory lymphoma, prostate cancer and renal cell carcinoma (333-336). No specific PTM modulators have been granted approval for clinical trials in DKD to date. The safety and efficacy of PTM interventions in humans await rigorous validation.

7. Conclusion

In summary, PTMs are key regulators that precisely modulate protein function, stability, interactions and subcellular localization. Their pervasive involvement in biological processes provides insights into the pathogenesis of DKD. The evolving research on PTM-regulatory agents, including novel compounds

and ongoing clinical trials, underscores their therapeutic promise. However, current evidence for specific PTMs in DKD relies on cross-sectional studies from preclinical models, with a notable absence of systematic longitudinal research tracing the dynamic PTM alterations throughout the course of DKD onset and progression. Moreover, the intricate crosstalk among different PTM pathways remains poorly elucidated.

To bridge these gaps and advance clinical applications, future research should prioritize several key directions. First, implementing single-cell and spatial multi-omics technologies is essential to delineate PTM landscapes at cellular and compartment-specific resolution in the kidney. Second, the development of highly selective modulators, leveraging advanced structural biology and proteolysis-targeting chimera technology, will help to minimize off-target effects. Third, given the interconnected signaling networks in DKD, investigating rational combination strategies targeting multiple PTMs or integrating PTM modulation with conventional therapy may enhance efficacy and overcome resistance. Finally, translational efforts should prioritize validating specific PTM signatures as non-invasive biomarkers for early diagnosis and precise staging of DKD, ultimately facilitating personalized therapeutic strategies.

Overall, a deeper understanding of PTM-driven mechanisms, combined with innovative technology and translational validation, is pivotal in transforming the landscape of DKD diagnosis and treatment.

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Availability of data and materials

Not applicable.

Authors' contributions

YW and LY conceived the study. MH, ZM, YZ and RY performed the literature review and constructed the figures and tables. MH, ZW, LZ, LW and YW revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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