Unveiling lactylation: A novel frontier in the pathogenesis of diabetic nephropathy (Review)

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Abstract. Emerging insights into lactate-mediated protein lactylation illuminate novel regulatory axes in the pathogenesis of diabetic nephropathy (DN). While histone lactylation has established epigenetic associations with metabolic memory, expanding proteomic evidence reveals dynamic lactylation landscapes across extracellular matrix components, inflammatory mediators and redox regulators in renal compartments. The present review systematically catalogues DN-relevant histones and non-histone substrates undergoing functional lactylation, while mechanistically dissecting how hyperglycemia-fueled lactate flux drives DN through lactate-mediated protein modification landscapes. The present review further delineates the progress of research on the potential regulatory mechanisms involved in DN and delve into the possible functions and related mechanisms. This mechanistic reappraisal establishes lactylation topology mapping as a prerequisite for developing precision modulation approaches in DN management.

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Contents

1. Introduction

Diabetic nephropathy (DN), an important complication of diabetes mellitus, is characterized by progressive deterioration of kidney function and structural alterations within the kidney. It is the primary etiologic factor of end-stage renal disease worldwide (1). DN pathogenesis is intricate and involves various cellular and molecular mechanisms, including metabolic disturbances, hemodynamic fluctuations, dysregulated mitophagy and endoplasmic reticulum stress, accompanied by elevated reactive oxygen species (ROS) and advanced glycation end products (AGEs), which alter numerous pathways in cells, inducing an inflammatory response, fibrosis and adverse pathological outcomes. Sustained exposure to elevated glucose levels, in conjunction with hypertension, obesity and dyslipidemia, is involved in the emergence and development of DN (2). Glomerular basement membrane thickening, mesangial expansion, interstitial fibrosis and podocyte damage represent the principal histological characteristics of DN (3,4). However, the mechanisms underlying these pathological changes remain poorly understood.

Recent studies have indicated that posttranslational modifications (PTMs) may profoundly regulate protein function, shape cellular phenotypes to adapt to environmental conditions and modulate the occurrence and progression of DN (5-8). PTMs are chemical modifications in proteins that occur after their synthesis and can notably affect their activity,

stability, localization and interactions with other molecules. Examples of PTMs include phosphorylation, glycosylation, acetylation and ubiquitination. Studies have suggested that targeting specific PTMs or the enzymes that mediate their modification may offer an alternative way to modulate the disease process and potentially decelerate the progression of DN (9,10). Lactate and lactate-mediated lactylation are novel epigenetic modifications. Lactate and lactylation serve as a bridge between metabolic reprogramming and epigenetic modifications, and they have been found to participate in the pathogenesis and progression of various diseases, particularly cancer (such as gastric cancer, colorectal cancer, breast cancer, lung cancer and melanoma), cardiovascular diseases and metabolic disorders (11,12). DN, which is associated with metabolic diseases, has attracted increasing attention due to its roles in lactate and lactylation. However, current research on lactylation in kidney diseases is limited, and the best of our knowledge neither phenotypic analyses nor mechanistic studies have been performed. Therefore, a systematic review and further investigations into the cellular functions of lactylation in DN are warranted.

2. Lactate accumulation within the kidney

Glucose metabolism serves as the principal mechanism of energy metabolism within cells. In a quiescent state, cells convert glucose into pyruvate, and under optimal oxygen conditions, pyruvate is fully oxidized in the mitochondria to yield carbon dioxide and water, producing substantial energy. In hypoxic environments, pyruvate is converted into lactate, a reaction catalyzed by lactate dehydrogenase (LDH). For a long time, lactate has been considered a superfluous and detrimental metabolic byproduct in mammals. However, the understanding of lactate has progressively expanded (13). Investigations have revealed that lactate carries out a substantial role in the pathophysiological processes underlying disorders, fostering a revised understanding of this metabolic product. At the dawn of the 20th century, Warburg *et al* (14) reported that, under conditions of ample oxygen, tumor cells can still preferentially generate lactate via glycolysis after assimilating glucose, and this metabolic trait can facilitate cancer cell proliferation and invasion. The latter phenomenon is known as the classic 'Warburg effect' in lactate metabolism and is intricately associated with multiple autoimmune and inflammatory disorders, tumors and metabolic diseases.

The kidney is a high-energy-consuming organ that performs important functions in maintaining body homeostasis. In a healthy kidney, there is a net uptake of lactate via gluconeogenesis, and the kidney has a higher net lactate clearance rate when compared with skeletal muscle, heart and other tissues, with only the liver clearing more lactate from the circulation (15). Consequently, lactate may play a key role in the initiation and progression of diabetic nephropathy. A previous study suggests that urinary lactate excretion is considerably increased by ~2.7-fold in patients with DN (16). A notable association was observed between urinary lactate levels and eGFR; in addition, elevated lactate levels were shown to induce fibrosis and impair mitochondrial function in DN (16,17). Azushima *et al* (18) suggested that dysregulated kidney metabolism, leading to increased lactate biosynthesis, might be involved in DN pathogenesis. Moreover, elevated urinary lactate concentrations in individuals with DN have also been demonstrated to be potential biomarkers for predicting the progression of kidney diseases. Studies indicate that a higher urine lactate/creatinine ratio reflects increased renal glycolysis and impaired mitochondrial oxidative phosphorylation and is associated with faster eGFR decline in type 2 diabetes and DN cohorts. Urinary lactate is therefore considered a non-invasive metabolic stress marker and may complement albuminuria and tubular injury markers for risk stratification, but it does not specify which downstream pathways or cell types are affected (17,19,20). However, the precise underlying mechanism remains elusive.

Lactylation-related modifications have been implicated as potential diagnostic and prognostic indicators in DN, but they are still in the early biomarker-discovery phase rather than in established routine clinical use. Mechanistic and lactylome studies show that global lactylation and specific lactylated proteins are upregulated in diabetic kidney tissue and associate with podocyte injury, mitochondrial dysfunction, inflammation and renal fibrosis in rodent and human DN models (21-23). Urinary lactate, as a proxy for the lactate-lactylation axis, has been identified as a non-invasive early diagnostic biomarker for DN, with meta- and cohort analyses showing elevated urinary lactate precedes or predicts albuminuria and kidney-function decline (18,24). Machine-learning and lactylation-related gene/protein signatures built from omics data are being tested as prognostic risk scores in other diseases (for example, gastric cancer and lung adenocarcinoma) and analogous approaches are now being explored in DN-related fibrotic and inflammatory pathways, though DN-specific clinical-prognostic models remain largely preclinical (24-27). In DN specifically, lactylation is currently positioned as a pathophysiological biomarker and therapeutic target rather than a fully validated, clinically deployed diagnostic/prognostic test (22-24). Compared with conventional biomarkers of DN (for example, albumin-to-creatinine ratio, serum creatinine/eGFR and tubular proteins such as NGAL or KIM-1), lactylation-linked measures offer several conceptual and mechanistic advantages, even if the majority are still investigational (20,21,28,29). Lactylation integrates metabolic stress (glycolysis upregulation), inflammation and epigenetic reprogramming into a single PTM layer, so alterations in lactylated sites may appear before overt structural damage or sustained proteinuria (21,23,24). This metabolic-epigenetic readout may capture subclinical tubular and immune-cell activation earlier than late-stage glomerular or tubular leakage markers (22,28). Lactylation targets specific residues on key proteins, allowing site-specific biomarkers that directly reflect distinct pathogenic processes (autophagy suppression, mitochondrial dysfunction or inflammasome activation) rather than generic tubular injury (21-23). This specificity may improve stratification of DN phenotypes (predominantly inflammatory vs. fibrotic) and improve targeted therapies. Lactylation is tightly coupled to intracellular lactate concentration and glycolytic flux, so it can rapidly reflect changes in glucose control, hypoxia or drug effects (for example, SGLT2 inhibitors or GLP-1R agonists) that traditional biomarkers change slowly (21,22,24). This dynamic range may be useful for monitoring treatment response or detecting subclinical relapses before conventional tests

deteriorate. Lactylome and lactylation-related gene/protein signatures can be combined with transcriptomic, proteomic and metabolomic data to build composite risk scores that outperform single-variable biomarkers in capturing heterogeneous progression trajectories (25-27,30). Such models can be embedded into decision-support tools for personalized prognostication (for example, distinguishing slow- vs. fast-progressors) in DN. Lactylation involves 'writers' (for example, p300/CBP), 'erasers' [histone deactylases (HDACs) or sirtuins (SIRT)] and 'readers', therefore, abnormal lactylation patterns can pinpoint druggable nodes in DN, blurring the line between biomarker and therapeutic target (21,23,24). This contrasts with traditional biomarkers such as albuminuria, which are readouts of damage rather than actionable molecular targets themselves. Nevertheless, there are limitations to the use of lactylation as a biomarker of DN. Indeed, the majority of lactylation data in DN are still preclinical or small-scale human cohorts, and robust, standardized assays for global or site-specific lactylation are not yet available in routine pathology. In addition, lactylation-based signatures require LC-MS/MS or advanced antibody-based platforms (for example, pan-lactylation western blotting or immunofluorescence), which are more complex and expensive compared with current ELISA- or urine dipstick-based tests. Therefore, lactylation-related modifications are emerging as promising research-class diagnostic and prognostic indicators in DN, with key advantages in mechanistic depth, pathway specificity and therapeutic-target alignment; however, they are not yet substitutes for traditional biomarkers in clinical practice and will require larger validation studies and assay standardization before being adopted in guidelines.

Biogenesis of lactate. The synthesis of lactase is predominantly facilitated by multiple LDH isoenzymes with high renal expression (31). LDH is a tetrameric protein composed of LDHA and LDHB isoforms, which exhibit distinct kinetic characteristics. Specifically, LDHA and LDHB demonstrate greater affinities for pyruvate and lactate, respectively (32). In the kidney, LDHA has been identified as being produced mainly in proximal segments, whereas LDHB is localized in distal segments. Furthermore, a previous study suggested cell-specific production of both LDH isoforms in response to acute and chronic kidney disease (CKD). Hypoxia may increase LDHA production, while LDHB levels remain relatively stable, and CKD downregulates both isoforms (33). These discoveries suggest that lactate cell-cell shuttling, identified in astrocytes, may also carry out a key role in the kidney. The latter notion delineates a function for lactate in the distribution of oxidative or gluconeogenic substrates and in cellular signaling (34).

Lactate reabsorption in the kidney. Lactate is readily filtered through the glomerular capillary. Consequently, the net reabsorption of lactate must transpire along the nephron. Studies show that renal lactate reabsorption in mammals is high (>95%) (35,36). Lactate is conveyed through two main categories of transporters that are part of solute carrier proteins and exhibit selectivity for monocarboxylates: Proton-coupled monocarboxylate transporters (MCTs) and sodium-coupled MCTs (SMCTs) (37,38). The MCT family comprises several members that facilitate the cotransport of monocarboxylate anions and protons, thereby balancing the amounts of substrate traversing the plasma membrane in response to the combined concentration gradients. Therefore, L-lactate and further MCT substrates traverse from the production site to the utilization site. Proximal tubular cells express proton-linked MCTs, including MCT1 and MCT2, and may help transport lactate from the kidney to the bloodstream or promote lactate or pyruvate uptake from the blood to achieve gluconeogenesis (36). SMCTs include SMCT1 and SMCT2. In mammalian kidneys, SMCT2 (a low-affinity Na^+-lactate cotransporter) controls the majority of lactate reabsorption in the early segment of proximal convoluted tubules (S1), whereas high-affinity SMCT1 in distal proximal tubules (S2-S3) minimizes urinary lactate levels. A study using the c/ebpδ null mouse model demonstrated that the transcription factor C/EBPδ regulates the expression of slc5a8 and slc5a12 by acting on their promoters. Consequently, the functional double knock-out of these Na^+/lactate co-transporters in the kidney led to a 29-fold elevation in urine lactate levels, suggesting that SMCTs account for the predominant lactate reabsorption in the kidneys (39). In the DN, Zucker rats with elevated plasma insulin levels showed elevated circulating lactate levels and diminished muscle MCT4 and MCT1 content compared with control animals (40). In streptozotocin (STZ)-induced diabetes, resting plasma lactate levels are increased (41), and MCT1 and MCT4 densities and lactate transport are reduced (42).

In addition, lactate can enter the intracellular space through GPR81 (or hydroxycarboxylic acid receptor 1), whose activation downregulates cAMP and suppresses the protein kinase A (PKA) pathway (43). Furthermore, lactate-related GPR81 activation may signal via a non-canonical, cAMP/PKA-independent pathway that involves the GPR81 adaptor protein β-arrestin under some conditions (44). In fact, GPR81 is expressed mainly in fat tissue and, to a lesser degree, can also be detected in the brain, kidney, liver, skeletal muscle and immune cells, although its role in non-adipose tissues remains controversial (45).

In immune cells such as macrophages, lactate-induced GPR81 activation triggers an anti-inflammatory signaling cascade. Specifically, GPR81 activation recruits the adaptor protein β-arrestin 2, which interacts with and inhibits the NLRP3 inflammasome or Toll-like receptor 4 (TLR4) signaling complexes, thereby suppressing NF-kB activation and the subsequent release of pro-inflammatory cytokines, including IL-1b and TNF-a (44,46). Furthermore, GPR81-mediated signaling has been shown to inhibit the activity of yes-associated protein, leading to the downregulation of pro-inflammatory responses in macrophages following lipopolysaccharide (LPS) stimulation (47). In models of intestinal and hepatic injury, GPR81 activation has been demonstrated to maintain tissue homeostasis and alleviate inflammatory damage by inhibiting adenylyl cyclase to lower intracellular cAMP levels or by modulating downstream kinase activities (48).

The controversy over GPR81 in the kidney stems from its lower expression levels compared with that in adipose tissue, as well as its functional differences. While some studies have shown that GPR81 activation has anti-inflammatory effects *in vitro* in cultured macrophages and *in vivo* in intestinal, synovial, muscle, myocardial and cancer tissues by suppressing innate immunity (47-49), others have shown that GPR81 can

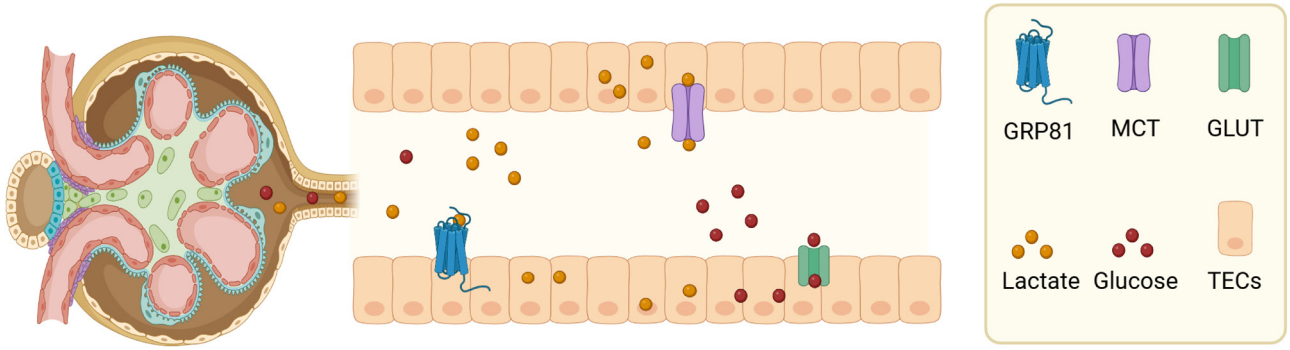

Figure 1. The lactate absorption and accumulation of lactate in the kidney. Filtered lactate is predominantly reabsorbed in the renal tubules via MCTs and SMCTs. Lactate also acts as a signaling molecule by activating the GPR81 receptor, triggering context-dependent downstream effects. MCT, proton-coupled monocarboxylate transporters; SMCTs, sodium-coupled MCTs; GLUT, glucose transporters; GRP81, G protein-coupled receptor 81; TECs, tubular epithelial cells. Figure created in Biorender.com.

promote kidney fibrosis by inhibiting the cAMP/PKA pathway in renal tubular cells (50,51). Lactate binding to GPR81 activates a Gi-coupled signal that inhibits adenylyl cyclase, lowering intracellular cAMP and thereby suppressing PKA/cyclic AMP response element-binding protein (CREB) activity in renal stromal and vascular cells. This loss of cAMP/PKA signaling removes an important antifibrotic inhibitor system: CREB-driven Smad7 expression falls, TGF-β/Smad3 signaling is disinhibited and RhoA/ROCK-dependent cytoskeletal remodeling and α-smooth muscle actin (α-SMA) expression are favored, all of which promote myofibroblast differentiation and extracellular matrix (ECM; collagen, fibronectin) accumulation. At the same time, reduced cAMP/PKA weakens anti-inflammatory tone, allowing increased NF-κB-dependent cytokine production and leukocyte recruitment, further stimulating fibroblast activation within the tubulointerstitium. Because chronic kidney injury increases glycolysis and lactate production, this creates a feed-forward loop that drives progressive renal fibrosis: Hypoxia/glycolysis activates lactate/GPR81 which inhibits cAMP/PKA resulting in amplification of TGF-β signaling and inflammation (52-55). Nevertheless, these mechanisms remain poorly understood, and additional studies are necessary to determine the exact context-specific roles of GPR81 in the kidney (Fig. 1).

Given the aforementioned findings, the present review created an overview schematic diagram of lactate metabolism in the DN (Fig. 2), from which it can be observed that lactate metabolism in the kidney is key for its pathophysiological effects on the kidney. An in-depth exploration of lactate function in the kidney will help in understanding the development of DN.

3. Lactylation and DN

Discovery of lactylation. When cells undergo metabolic alterations, the metabolic paradigm can shift from oxidative phosphorylation to glycolysis, and the architecture and functionality of proteins within the cells also undergo adaptive transformations. Proteins can employ PTMs to modify their physicochemical properties by adding chemical groups to amino acid residues, thereby altering spatial configuration, increasing structural complexity and governing the diversity and functionality of active proteins. Common forms of PTMs include acetylation, ubiquitination, phosphorylation and glycosylation, which carry out important roles in the development of various diseases (56). Over the past 5 years, lactylation has been considered a new PTM process. Indeed, lactate can serve as a substrate for PTMs, thereby regulating the expression and function of associated genes through lactylation (57).

In 2019, Zhang *et al* (58) first reported the histone lactylation modification, laying the groundwork for subsequent research. Their investigation revealed a mass deviation in lysine residues of protein hydrolysis peptides, consistent with the mass alteration induced by lactate binding to lysine residues. By employing an array of experimental techniques, including western blotting, isotope labeling and mass spectrometry-based quantification, the latter authors validated the presence of histone lactylation. In a different study, same research group also reported that lactate is converted into lactyl-CoA and subsequently transferred to histone lysine residues via lactate acyltransferase, representing the classical process of lactylation modification (59).

Regulation of lactylation. Enzymatic lactylation modifications are predominantly regulated by histone acetyltransferases and HDACs. Currently, several lactyl-CoA transferases, also called writers, have been documented in mammals, including p300/CBP (60), KAT8 (61), general control of amino acid synthesis 5 (GCN5) (62), the GCN5-related N-acetyltransferase (GNAT) family protein YiaC and mitochondrial alanyl-tRNA synthase 1/2 (AARS1/2) (51). Conversely, LDHs, also called 'erasers', include mainly the NAD-dependent protein deacetylases CobB (63), HDAC1-3, SIRT1-3 (64). To the best of our knowledge, studies on non-enzymatic lactylation modifications are relatively rare, and further investigations are warranted (Fig. 3).

Previous studies have revealed that lysine lactylation is regulated by both putative enzymatic (65) and non-enzymatic mechanisms (66), but several key aspects remain controversial. Clarifying these issues is essential for accurate interpretation of lactate-driven epigenetic regulation in DN. Current DN data clearly support increased protein lactylation and both enzymatic and non-enzymatic lactylation routes in kidney disease, but they do not yet directly demonstrate non-enzymatic

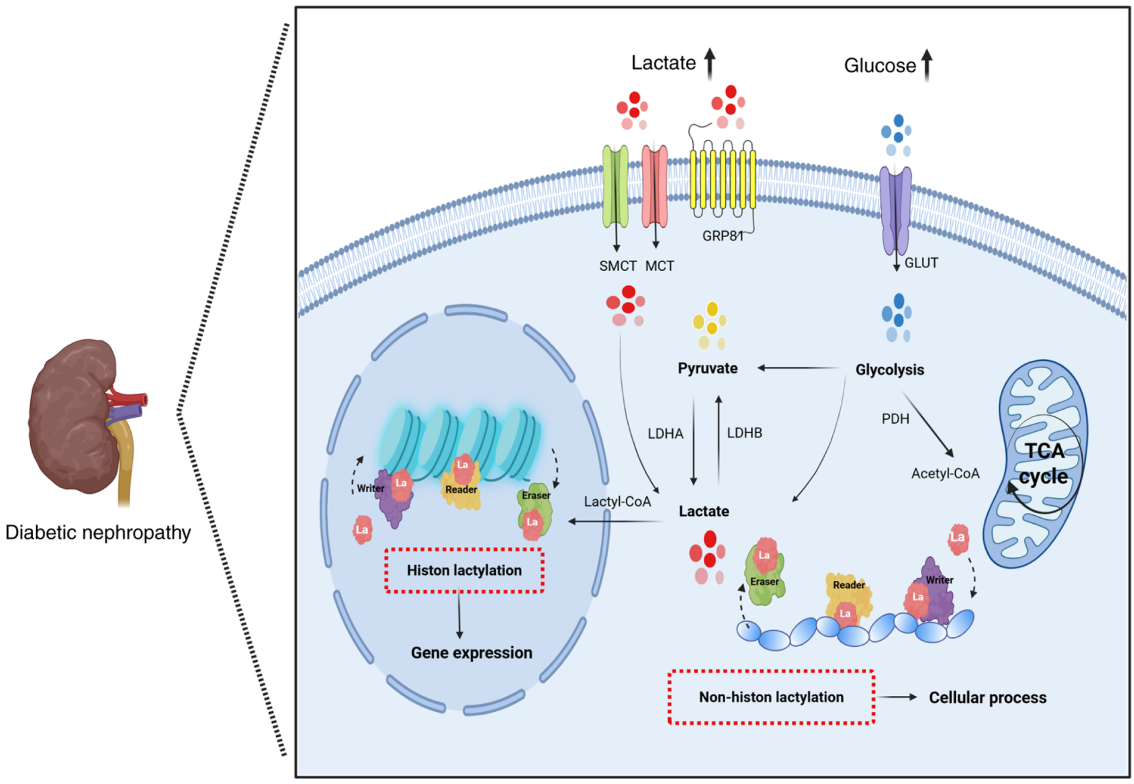

Figure 2. Overview of lactate metabolism and mechanisms of histone or non-histone lactylation in diabetic nephropathy. Intracellular lactate, mainly coming from glucose, directly generates lactate via pyruvate through glycolysis. Intracellular lactate undergoes rapid transport by SMCTs/MCTs. Lactate in the microenvironment partially enters the circulation and undergoes gluconeogenic metabolism in the kidney for regenerating glucose. Lactate in the microenvironment may also be involved in signaling pathways via GPR81 to regulate gene expression. Lactate undergoes conversion into lactyl-CoA, which transfers lactyl groups onto lysine moieties on histones and non-histone proteins for lactylation, a process controlled by epigenetic writers, readers and erasers, impacting gene expression in cells epigenetically. MCTs, proton-coupled monocarboxylate transporters; SMCTs, sodium-coupled monocarboxylate transporters; LDHA, lactate dehydrogenase A; LDHB, lactate dehydrogenase B; PDH, pyruvate dehydrogenase; La, lactylation residue. Figure created in Biorender.com.

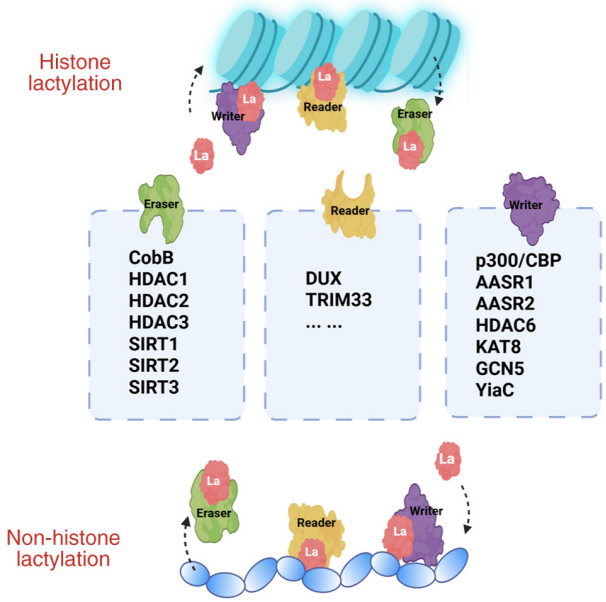

Figure 3. Regulatory mechanisms of enzyme-dependent lactylation. In enzyme-dependent Kla, the 'writer' (modifying enzymes) uses endogenous or exogenous l-lactic acid as a substrate to transfer lactyl groups from lactyl-CoA to lysine residues on histones or non-histones, the 'reader' (modification-binding enzymes) recognizes Kla changes, influencing downstream signaling pathways and triggering biological events. When signal transduction ends, 'erasers' (demodifying enzymes) remove lactyl groups from target proteins, halting the Kla cycle and mitigating the lasting effects of lysine Kla. Figure created in Biorender.com.

(D-lactoylglutathione-driven) lactylation in DN models. Available data in kidney disease and DN show i) global increases in lysine lactylation in db/db mice and other DN models and identify specific lactylated targets such as ACSF2, and histone sites (H3K14la) that drive mitochondrial dysfunction, EMT, inflammasome activation and fibrosis, and ii) conceptual and experimental separation of enzymatic lactylation (L-lactyl-CoA/p300-type) from non-enzymatic D-lactylation via S-D-lactoylglutathione (LGSH), with the latter firmly established biochemically in other systems and explicitly described as the 'non-enzymatic lactylation' route (22,66,67). However, available articles to date primarily infer that both mechanisms may operate under high-lactate/oxidative stress rather than directly mapping LGSH-dependent lactylation sites in DN tissue; thus, the presence of non-enzymatic lactylation in DN should be framed as mechanistically plausible and supported at the conceptual level, but not yet conclusively demonstrated by DN-specific LGSH tracing or stereospecific (L-vs. D-) lactyl-proteomics (23,68).

Enzymatic pathway (lactyl-CoA and p300/AARS1 dependent). Evidence suggests that intracellular L-lactate can be converted to lactyl-CoA, which then serves as an acyl-donor for lysine lactylation catalyzed by acyltransferases such as p300, while AARS1 and other aminoacyl-tRNA synthetases have also been reported to act as lactyltransferases that directly use lactate and ATP (69). However, the very low steady-state concentration of

lactyl-CoA and the modest effect of p300 knockdown on global lactylation levels have raised the issue of whether p300 is the predominant physiological lactyltransferase *in vivo* (67,70-73).

Non-enzymatic pathway (high-lactate-driven). The physiological relevance of non-enzymatic lactylation remains a subject of intense debate. Although Gaffney *et al* (66) provided foundational evidence by demonstrating that lactyl-CoA and S-D-LGSH can act as non-enzymatic acyl donors for lysine residues *in vitro*, translating these findings to the diabetic kidney remains contentious. As argued by Zhao *et al* (74) and Chen *et al* (67), the low intracellular abundance of lactyl-CoA relative to acetyl-CoA challenges the kinetic viability of spontaneous lactylation as a competitor to enzymatic acetylation under pathophysiological conditions. Furthermore, the majority of DN-related studies rely on pan-anti-Kla antibodies (75-77). Which lack the stereospecificity required to distinguish between enzymatic L-lactylation (the product of L-lactate-driven enzymatic pathways) and non-enzymatic D-lactylation (the byproduct of the glyoxalase-linked non-enzymatic route) (71,72). Consequently, the 'lactylome' expansion observed in diabetic models, while associated with high glycolytic flux, may be predominantly driven by the recruitment of p300/CBP or other acting as acyltransferases (78). Thus, while the non-enzymatic pathway is chemically plausible, its actual contribution to the pathogenesis of DN remains inferred from correlative data rather than confirmed by direct, site-specific mapping of D-lactylation *in vivo*.

Potential impact on DN and 'metabolic memory'. DN is characterized by long-term exposure of renal cells, particularly podocytes and tubular epithelial cells, to a high-glucose, high-lactate microenvironment, and has been associated with elevated lactate to increased histone lactylation, epithelial-mesenchymal transition (EMT), inflammation and fibrosis in diabetic kidneys. Under such sustained conditions, non-enzymatic lactylation of histone and non-histone proteins could serve as a relatively slow-turnover 'molecular archive' of prior metabolic states, thereby contributing to the phenomenon of metabolic memory in DN, but this hypothesis has yet to be rigorously tested *in vivo* and should be interpreted with caution (23,24,68,79).

Future studies combining quantitative metabolomics, isotopic tracing and site-specific lactylation profiling in diabetic kidneys are needed to disentangle enzymatic vs. non-enzymatic (for example, acyltransferase-dependent lactoyl-CoA pathways vs. glyoxalase-2-mediated lactoyl-glutathione chemistry) sources of protein lactylation and to map their relative contributions to DN progression. In parallel, integrating flux-resolved lactate tracing with stoichiometric lactyl-proteomics at defined stages of diabetic kidney injury will be essential to associate specific lactylation events to upstream metabolic nodes, clarify how 'writer' and 'eraser' activities are rewired in the diabetic milieu, and identify targetable lactylation sites that drive inflammation, fibrosis and mitochondrial dysfunction (21,22,66).

Classification of lactylation modifications. Lactylation modification primarily encompasses histone and non-histone lactylation. Histone lactylation primarily influences gene expression by altering chromosome architecture, regulating transcription factor binding and altering promoter accessibility. Non-histone lactylation predominantly governs protein functions via steric hindrance, conformational alterations and charge neutralization, thus impacting molecular interactions, enzyme activity, subcellular localization and protein function (80).

Although the enzymatic mechanisms are still being investigated, the phenotypic outcomes driven by those enzymes are already observed and well described in DN. Indeed, experimental and translational work shows that histone and non-histone lactylation are markedly upregulated in diabetic kidneys and associate lactate accumulation to EMT, podocyte injury, endothelial-mesenchymal transition and fibrosis. Lactylome and site-specific studies demonstrate that specific lactylation events are tightly coupled to defined pathogenic programs in DN, such as mitochondrial dysfunction and profibrotic gene expression (21,23,24,68). Compared with conventional DN biomarkers (albuminuria, eGFR, NAG or L-FABP), lactylation-based readouts may offer several theoretical advantages. Pathway specificity: Lactylation directly reports the activity of the lactate-lactylation axis, integrating metabolic stress with epigenetic and signaling changes, whereas albuminuria and creatinine mainly reflect structural damage or filtration loss (20,21,23,24). Cell-type and site resolution: Histone or protein lactylation can be quantified at specific residues and in defined renal compartments (podocytes, tubular cells, endothelial cells), potentially distinguishing the predominant pathogenic mechanisms in individual patients (21,23,24). Dynamic association with treatment: Interventions that lower lactate or inhibit LDH/p300/MCTs reduce histone lactylation and ameliorate DN phenotypes in experimental models, suggesting that lactylation levels might serve as pharmacodynamic markers of pathway-targeted therapies (21,24,67,68).

Histone lactylation in DN. Histones, which are fundamental proteins that associate with DNA and form the chromatin architecture, encompass H2A, H2B, H3 and H4, also referred to as the core histones, which are characterized by highly conserved amino acid sequences (81). Initial evidence for histone lactylation arises from high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) data, in which lactylation of lysine residues was detected with a mass shift identical to that resulting from the addition of a lactate group to the ε-amino group of lysine, suggesting that lactylation modification can transpire to the core histone H3 (58). Currently, numerous studies have pinpointed lactylation sites on histones across various species; the primary sites recognized to undergo lactylation include H3K9 (82), H3K14 (83), H3K18, H3K23 (84), H3K56 (85), H4K5 (86), H4K8 (87), H4K12 (88) and H4K16 (89), with H3K18 emerging as the most thoroughly investigated lactylation site (90). Histone lactylation predominantly enhances gene transcription, modulates cell necrosis and proliferation, programs macrophages and initiates and progresses tumors (60,91,92).

Studies assessing the implications of histone lactylation in the onset and development of DN are rare. Nevertheless, Zhang *et al* (77) reported that H3K14 lactylation may be involved in DN through the regulation of EMT. The researchers discovered that AGE-dependent induction of

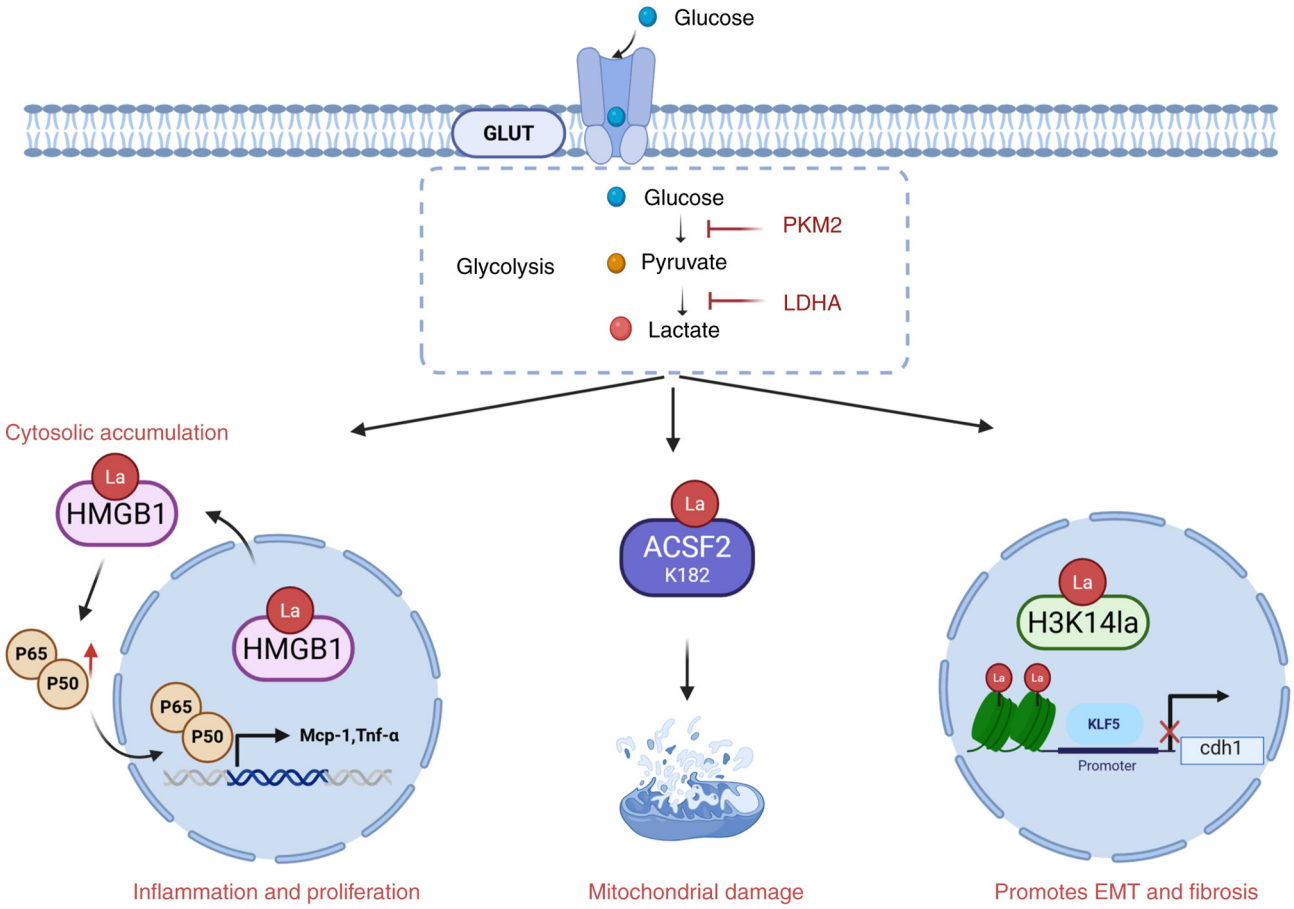

Figure 4. Lactylation facilitates disease development and progression in diabetic nephropathy. Current research on lactylation regulation in diabetic nephropathy has shown that ACSF2, H3K14 and HMGB1 undergo lactylation in diabetic nephropathy, which enhanced epithelial-mesenchymal transition, mitochondrial damage and inflammation, thus exacerbating DN progression. PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase A; GLUT, glucose transporters; La, lactylation residue; ACSF2, acyl CoA synthetase family member 2; HMGB1, High Mobility Group Box-1; KLF5, Krüppel-like Factor 5; EMT, epithelial-mesenchymal transition. Figure created in Biorender.com.

renal tubular epithelial cells (RTECs) increased kidney lactate levels, and that reducing lactate levels could notably hinder EMT progression and ameliorate renal tubular fibrosis in DN. Mechanistically, lactate can upregulate histone 3 lysine 14 lactylation (H3K14la) in DN. Further ChIP-sequencing (seq) and RNA-seq data indicated that histone lactylation is involved in EMT by upregulating Krüppel-like factor 5 (KLF5).

Furthermore, KLF5 binds the cdh1 promoter and suppresses its transcription, thereby accelerating EMT in DN. In a separate study on RTECs, it was found that H3 lysine 18 lactylation (H3K18la) levels were notably elevated in the kidneys of DN mice. Furthermore, the study revealed that a Kruppel-like zinc finger protein transcription factor family member, Glis1 could bind to the lactyltransferase KAT5 and markedly reduce the binding affinity between histones and KAT5, thereby further decreasing H3K18 lactylation levels of H3K18 (93) (Fig. 4).

Non-histone lactylation in DN. Non-histone lactylation represents another pronounced regulatory site for lactylation; however, lysine moieties on non-histone proteins more rarely accept lactoyl substitutions than histones (60). A previous study revealed that proteins with lactylation in the fungus Botrytis cinerea are predominantly localized in the nucleus, mitochondria and cytoplasm and participate in various cellular processes (94). In protozoan parasites, a diverse array of non-histone lactylated proteins is also present, actively engaging in processes such as splicing, cap binding, RNA export, translation and degradation, the majority of which of which are involved in glycolysis and can undergo lactylation (95). To date, research on non-histone proteins regulated by lactylation in DN is scarce. The present review focuses primarily on non-histone proteins confirmed to be regulated by lactylation and summarizes the identified targets implicated in DN progression (Table I). Although lactylation of the majority of non-histone proteins, such as p53, was first characterized in cancer and other systems, their downstream signaling roles are highly relevant to DN. For example, in podocytes exposed to a diabetic milieu, p53 activation is a well-established driver of apoptosis via transcriptional upregulation of pro-apoptotic genes (for example, Bax, PUMA and Noxa) and caspase activation (21,58,80,96-99).

ACSF2. Acyl-CoA synthetase family member 2 (ACSF2) is a non-histone protein that has been demonstrated to be subject to lactylation and to exert functional effects during the development of DN. ACSF2 catalyzes the first reaction of fatty acid metabolism via the formation of a thioester with CoA (100). ACSF2 and other genes controlling fatty acid oxidation can be

Table I. An overview of associated non-histone lactylation under investigation.

Authors, year	Protein	Site	Disease	Molecule or pathway	(Refs.)
Chen *et al*, 2024	ACSF2	K182	Diabetic nephropathy	Aggravated renal tubule injury with excessive ROS accumulation, resulting in mitochondrial damage.	(75)
Wang *et al*, 2022	PKM2	K62	Wound healing	Suppresses its tetramer-to-dimer transition, inducing its pyruvate kinase activity and decreasing nuclear amounts to suppress inflammatory metabolic adaptation.	(122)
Du *et al*, 2023	HMGB1	Pan	Liver ischemia-reperfusion injury	Suppressed macrophage chemotaxis and inflammatory activation.	(139)
Huang *et al*, 2024	YY1	K183	Autoimmune uveitis	Promoted microglial dysfunction by increasing inflammatory cytokine secretion and enhancing cell migration and proliferation.	(151)
			Retinopathy of prematurity	Increases the transcriptional ability of YY1, directly upregulates FGF2 and promotes angiogenesis.	(152)
Fan *et al*, 2022	Snail	Pan	Myocardial infarction	Disrupts endothelial cell function and triggers mesenchymal-like function after hypoxia via TGF-β/Smad2 pathway activation.	(162)
Wu *et al*, 2025		K9	Idiopathic pulmonary fibrosis	Increases ROS production and mtDNA release by promoting peroxisome proliferator-activated receptor γ coactivator 1α and PTEN-induced kinase 1/ PARKIN pathways	(304)
An *et al*, 2023	Fis1	K20	Sepsis-induced acute kidney injury	Promotes excessive mitochondrial fission and then induces ATP depletion, mitochondrial reactive oxygen species accumulation and mitochondrial apoptosis.	(172)
Qiao *et al*, 2024	Ezrin	K263	Sepsis-associated acute kidney injury	Interaction with MYD88 and IRAK1, activating the NF-KB pathway, promotes inflammatory responses.	(178)
Luo *et al*, 2022	HIF-1α	Pan	Prostate cancer	Promotes angiogenesis and vasculogenic mimicry.	(187)
Li *et al*, 2025		K12	Tumorigenesis	Increased transcriptional activity by increased promoter occupancy and upregulation of hypoxia-responsive related genes.	(302)
Cheng *et al*, 2024	PFKP	K688	Colorectal cancer	Attenuated enzyme activity formed a negative feedback loop in glycolysis and lactic acid production.	(193)
Yan *et al*, 2024	SOX9	Pan	Non-small cell lung cancer	Promote cell stemness, migration and invasion via promoting glycolysis.	(200)
Wang *et al*, 2023	Mecp2	K271	Cardiovascular disease	Alters MAPK signaling by regulating EGFR phosphorylation, thereby regulating Vcam-1, Icam-1, Mcp-1, IL-1β, IL-6 and Enos in ECs, which in turn inhibits atherosclerosis.	(206)
Li *et al*, 2024	NEDD4	K33	APAP-induced liver injury	Suppresses protein interaction with Caspase-11. Restraining lactylation decreases non-canonical pyroptosis in macrophages and alleviates liver injury.	(215)
Huang *et al*, 2024	TFEB	K91	Cancer	Prevents the interaction with E3 ubiquitin ligase WWP2, suppressing TFEB ubiquitination and proteasome degradation, which enhances TFEB activity and autophagy.	(229)

Table I. Continued.

Authors, year	Protein	Site	Disease	Molecule or pathway	(Refs.)
Zong *et al*, 2024	P53	K120/139	Cancer	Lactylation of p53 reduces its liquid-liquid phase separation, DNA binding and transcriptional activation, contributing to tumorigenesis.	(240)
Zhang *et al*, 2024	AMPKα	Pan	Intervertebral disc degeneration	Downregulates AMPKα phosphorylation, enhances NP cell senescence and decreases autophagy and ECM production through glycolysis.	(248)

ACSF2, acyl-CoA synthetase family member 2; ROS, reactive oxygen species; YY1, yin yang 1; FGF2, fibroblast growth factor 2; Fis, fission 1; MYD88, myeloid differentiation factor-88; IRAK1, interleukin-1 receptor associated kinase 1; HIF-1α, hypoxia-inducible factor-1α; PFKP, platelet isoform of phosphofructokinase 1; Mecp2, methylated CpG-binding protein 2; ECs, endothelial cells; APAP, acetaminophen; TFEB, transcription factor EB; WWP2, WW domain-containing protein 2; AMPKα, adenosine monophosphate-activated protein kinase α; NP cell, neural progenitor cell; ECM, extracellular matrix.

induced by hepatocyte nuclear factor 4 (HNF4), which affects adipocyte differentiation by regulating fatty acid oxidation (101). A previous study reported that ACSF2 was highly expressed in RTECs and localized mainly to mitochondria. Proximal renal tubular cells have increased basal metabolism and are enriched in mitochondria. Cells with elevated metabolic rates prefer fatty acid oxidation for energy production, as it yields more ATP than glucose oxidation (68). ACSF2 knockdown in HK2 cells enhances hypoxia-reoxygenation (HR)-related mitophagy, mitochondrial function restoration and reduction in mitochondrial superoxide levels. The aforementioned evidence suggests that ACSF2 may have an important function in kidney disorders.

Further studies revealed that ASCF2 can be regulated by lactylation in DN. Chen *et al* (75) reported markedly enhanced lysine lactylation in the kidneys of both diabetic individuals and db/db mice. Through lactylome analysis of kidney samples from db/db mice, the authors detected 165 (356 lysine lactylation sites) upregulated and 17 (22 lysine lactylation sites) downregulated proteins. Subcellular localization analysis revealed that the majority of proteins were lactylated in mitochondria (115 proteins, 269 sites). Among these mitochondrion-localized proteins, ACSF2 and the corresponding K182la lactylated modification impair mitochondrial function in HK-2 cells exposed to high glucose, indicating that targeting mitochondrial ACSF2 and lactylation might represent a potential approach for DN (75) (Fig. 4).

PKM2. Pyruvate kinase (PK) serves as a pivotal regulator of glycolysis. PK can increase the rate of aerobic glycolysis by catalyzing the conversion of phosphoenolpyruvate to pyruvate and activating the pentose phosphate pathway. Competitive PK represents one of the four distinct forms of this protein (M1, M2, L and R) encoded by two genes (PKM and PKLR), with PKM2 comprising four domains (A, B, C and N). PKM2 expression is apparent from the onset of embryo development and continues over a lifetime in virtually all tissues. Increased PKM2 activity reduces lactate production. Previous research has demonstrated that oxaloacetate is present at high levels and stimulates the Warburg effect via PKM2-mediated pyruvate activation (102). With reduced PKM2 activity, monomeric and dimeric PKM2 subtypes undergo nuclear translocation, followed by interaction with hypoxia inducible factor (HIF)-1α and regulation of various proglycolytic enzymes (103). In the nucleus, dimeric PKM2 functions as a histone kinase to increase c-Myc expression, upregulating the expression of proglycolytic enzymes for the induction of the Warburg effect (104).

Given the role of PKM2 in energy metabolism and the substantial energy demand of the kidney, PKM2 plays a key role in kidney disorders, particularly in DN. DN is characterized by a chronic inflammatory response driven by macrophages, leading to gradual deterioration of glomerular filtration barriers, accompanied by glomerular hypertrophy, ECM buildup and induction of the TGF-β pathway in RTECs, whose transformation is promoted (95). In addition, transcription factors such as NF-κB, STAT3 and HIF-1α are essential for DN initiation and advancement (105). PKM2 regulates various adhesion molecules, chemokines and inflammatory cytokines through the aforementioned pathways. In the context

of DN, PKM2 is phosphorylated in glomerular endothelial cells, leading to its isomerization and nuclear translocation to regulate inflammation (106). These modulatory functions increase STAT3 and NF-κB phosphorylation and upregulate the expression of the adhesion molecule intercellular adhesion molecule-1 (ICAM-1), facilitating the infiltration of inflammatory cells and participating in DN progression (107). Qi *et al* (108) reported that PKM2 activation is associated with reduced levels of toxic glucose metabolites and preserved kidney function, while suppressing PKM2 phosphorylation might diminish kidney inflammation, offering protection against DN (108). Tetrameric PKM2 suppresses PKM2 phosphorylation, inhibits aberrant glycolytic activity and downregulates ICAM-1, type I collagen a3 and TGF-β1 in DN, in addition to preventing renal fibrosis due to elevated albuminuria in diabetic patients (109,110). Tetrameric PKM2 also suppresses macrophage adhesion and NF-κB and STAT3 pathway activation, further alleviating kidney fibrosis (111,112). A decrease in tetrameric PKM2 levels in DN leads to diminished glucose metabolic flux and enhances the accumulation of toxic glucose metabolites in podocytes, confirming the potential of PKM2 in preventing or alleviating severe diabetic microangiopathy (113,114). Since PKM2 is capable of mitigating renal failure in diabetes, pharmacological strategies that increase PKM2 expression may improve the prevention of DN progression (115).

Indeed, research demonstrates that PTMs can modify the structural and functional features of PKM2, playing a pivotal role in endogenous allosteric regulation (116,117). For example, citrullination of PKM2 R106 results in a reprogrammed interaction of PKM2 ligands for increased activity (118), whereas SUMOylation of PKM2 K270 induces a conformational shift of PKM2 from the tetramer to the dimer, diminishing PK activity (119). Furthermore, PKM2 acetylation at K433 increases its activity (120), whereas O-GlcNAcylation or K311 sacculation impedes PKM2 activity and results in an enhanced Warburg effect (121). In addition, PKM2 can undergo lactylation. For the first time, Wang *et al* (122) identified PKM2 as a lactylation substrate in proinflammatory macrophages. They demonstrated that PKM2 lactylation enhances its PK activity and diminishes its tetramer-to-dimer transition and nuclear localization. Lactate reduces glycolysis by activating PKM2 to a greater extent, thereby promoting macrophage phenotypic changes along the inflammatory-reparative continuum. Increased PKM2 lactylation at K62 may directly convert PKM2 into a tetramer with increased PK activity.

HMGB1. HMGB1, a cytoplasmic protein with an HMG-box domain, serves as a quintessential representative of damage-associated molecular patterns. It can translocate into the nuclear compartment, where it binds to nucleosomes to regulate gene transcription. HMGB1 resides within the nuclear compartment and functions as a DNA-scaffolding protein (123,124). In addition, nuclear HMGB1 may be secreted into the extracellular space, where it acts as a key inducer of the inflammatory response by recruiting and activating macrophages and other immune cells (125,126). Under typical conditions, HMGB1 primarily facilitates gene transcription, DNA repair and various other biological processes (127). Upon release from immune or damaged cells, it functions as an inflammatory modulator that binds to membrane receptors, activating downstream intracellular pathways, including the NF-kB-mediated proinflammatory response, in the pathogenesis of kidney disease (128).

Multiple studies have elucidated function of HMGB1 in DN (129-136). Circulating and urinary HMGB1 levels are both high in patients with DN. Serum from mice with DN induces HMGB1 expression, suggesting a potential association between increased HMGB1 levels and DN (129). The increase in HMGB1 secretion contributes to DN progression by modulating the TLR2/TLR4-NF-κB pathway. In addition to HMGB1 upregulation in the presence of DN serum, elevated apoptosis and reduced autophagy were observed in MPC5, a mouse podocyte line. HMGB1 downregulation mitigated DN serum-dependent podocyte apoptosis, indicating that HMGB1 may act as an important risk factor for podocyte damage (130). In DN biopsy samples, both TLR4 and HMGB1 are overexpressed in tubular regions, suggesting that HMGB1 is involved in the TLR4-mediated tubular inflammatory response in DN (131). The HMGB1 suppressor glycyrrhizic acid was shown to improve inflammatory responses in STZ-induced DN rats by modulating receptor for AGE (RAGE)/TLR4-associated ERK and p38 MAPK/NF-kB induction (132). Notably, HMGB1 was found to increase autophagy under conditions of oxidative stress and other stimuli, particularly in cancer cells (133). The autophagy inducer rapamycin (Rap) promotes histological and renal functions in an ischemia/reperfusion rat model via the inhibition of HMGB1 release (134). Previous data suggest that renal tubular cells and podocytes are the primary sources of secreted HMGB1 within the kidney (135). In addition, evidence indicates that RAGE is the principal receptor for HMGB1, and suppression of bone marrow-derived RAGE has been shown to enhance kidney function in mice with experimental DN (136).

HMGB1 can also undergo PTM through lactylation. HMGB1 secretion involves two phases: Nuclear-to-cytoplasmic transport and exosomal release into the extracellular milieu. HMGB1 translocation from the nuclear compartment to the cytosol is facilitated by various PTMs (137). Yang *et al* (138) first showed that HMGB1 may be secreted into exosomes (exos) by macrophages during sepsis following lactylation. In hepatocytes, reducing HMGB1 lactylation and secretion, either by inhibiting lactate production or by using a p300 suppressor, could blunt HMGB1 cytoplasmic accumulation and subsequent exosomal secretion. It could inhibit macrophage chemotaxis and improve the subsequent inflammatory response, eventually protecting against liver ischemia-reperfusion (LI/R) injury (139). Wu *et al* (140) revealed that HMGB1 is markedly upregulated in the kidneys of DN mice and in mesangial cells treated with high glucose, with cytosolic HMGB1 increasing the inflammatory response and proliferation in mesangial cells. Mechanistically, they reported that cytoplasmic HMGB1 accumulation is modulated by the nucleocytoplasmic translocation of lactate-dependent HMGB1 acetylation and lactylation and further induces NF-κB signaling via direct binding to IκBα, which helps explain the regulation of HMGB1 lactylation (Fig. 4). In patients with acute kidney injury (AKI) with acute decompensated heart failure, Zhu *et al* (141) indicate that lactate serves as an independent predictor. Combined application of lactate and low-dose LPS to mice considerably provokes HMGB1 lactylation levels. Additionally, lactate-mediated

HMGB1 lactylation is positively associated with circulating neutrophil extracellular traps levels.

YY1. YY1, also referred to as δ, NF-E1, UCRBP and CF1, is an important constituent of the GL1-Kruppel group of ubiquitously expressed and evolutionarily conserved zinc-finger transcription factors. The YY1 gene is located on human chromosome 14q32.2. The YY1 protein comprises 414 amino acid residues and has a relative molecular weight of 65 kDa. Adjacent to the N2 terminus of YY1, there is an acidic domain, followed by a sequence linking 12 guanosine nucleotides and a region abundant in Gly and Ala. The four zinc fingers at its C-terminus engage with target promoters, which typically harbor YY1 binding elements: CCAT and ACAT. YY1 is a multifunctional protein with regulatory roles in normal physiological processes, for example, developmental processes and cell differentiation and division, and performs dual functions of both repressing and activating transcription, resulting in its designation as Yin-Yang 1 (142). Shi *et al* (143) first reported that YY1 is a transcription factor that interacts with the adenoviral P5 promoter and that its transcriptional repression activity can be converted to transcriptional activation by adenoviral E1A. Reflective of this dual functionality, YY1 can both inhibit and activate transcription, contingent on the cotranscription factors it recruits.

Mounting evidence suggests that YY1 is involved in the pathogenesis of DN. Indeed, YY1 is important for the initiation of renal fibrosis associated with DN. In addition, YY1 serves as a notable modulator of α-SMA and epithelial-EMT-related proteins in high glucose (HG)-induced DN. In both cultured HK-2 cells and diabetic mouse models, HG markedly increased YY1 levels and nuclear translocation through mTORC1/P70S6K signaling. Moreover, YY1 downregulation via short hairpin RNA substantially diminished HG-dependent α-SMA expression and activity and inhibited HG-triggered EMT, thereby alleviating kidney fibrosis in db/db mice with DN. YY1 overexpression elevated creatinine, blood urea nitrogen and urinary albumin levels; enhanced Masson and Sirius red staining signals; and upregulated laminin and type IV collagen, thereby promoting kidney fibrosis in a DN mouse model (144). Another investigation revealed that YY1 is upregulated by diabetic hyperglycemia in DN mice. Notably, YY1 is exclusively upregulated in mesangial cells, which are important for ECM production and the subsequent development of glomerulosclerosis in DN (145).

Additionally, the divergent functions of YY1 in various diseases might be attributed to the recruitment of distinct cofactors upon its stimulation, which subsequently modulates YY1 function to either suppress or activate transcription (146). Numerous studies have reported that YY1 binds to a diverse array of transcription factors. YY1 forms a complex with nuclear factor erythroid 2-related factor 2, binding to the TGFβ1 promoter and acting as a cofactor for YY1. YY1 directly binds to the TGFβ1 promoter and suppresses TGFβ1 expression transcriptionally in human kidney mesangial cells. In mice, although YY1 levels are high in mesangial cells at the early stages of DN lesions, they are reduced at later disease stages. YY1 silencing in the kidney exacerbates glomerulosclerosis, which is mitigated by YY1 overexpression (147).

Furthermore, patients with higher YY1 expression developed DN more slowly compared with those with lower YY1 expression. Additionally, the small-molecule compound eudesmin can suppress TGFβ1 and other profibrotic proteins by upregulating YY1 in human kidney mesangial cells and by alleviating DN lesions in DN mice through YY1 upregulation (148). The findings of Yang *et al* (144) indicated that mitochondrial dysfunction and YY1 upregulation in RTECs occurred earlier than the onset of tubulointerstitial fibrosis (TIF) in DN. Their data also demonstrated the generation of an mTOR-YY1 heterodimer triggered by HG-upregulated YY1, with nuclear translocation impairing mitochondrial function in RTECs by inactivating PGC-1α, leading to TIF in the early stages of DN via EMT. These findings highlight YY1 as a new modulator of mitochondrial function in RTECs, and a reduction in YY1 at the early stages may serve as a promising preventive approach for DN-related TIF.

Previous studies on epigenetic alterations in YY1 include phosphorylation at S118, which plays a role in atherosclerosis (149), and deacetylation, which is associated with renal fibrosis (150). Using a specific YY1-K183la antibody (YY1-K183La), both animal and cell culture data indicated that YY1 could also be subject to lactylation, with microglial activation coexisting in autoimmune uveitis (AU). By modulating YY1 lactylation through interventions targeting lactate levels, YY1 mutations and p300 regulation, microglial activation was markedly mitigated. Furthermore, CUT and Tag analysis demonstrated that YY1 lactylation enhances several inflammatory genes associated with alterations in microglial functions, including migration, proliferation and activation. In summary, these findings suggest that YY1 lactylation is pivotal for microglial activation in AU. For the first time, YY1 lactylation was shown to be a potential pathogenic factor in AU (151). Another investigation of retinal angiogenesis also demonstrated that lactylation at K183 in YY1, a non-histone protein, enhances YY1 transcriptional capacity, directly upregulating FGF2 expression and promoting angiogenesis; the overexpression of p300, a lactylation writer, resulted in increased YY1 lactylation, whereas its inhibition via A485 led to reduced YY1 lactylation in both animal and cell culture assays, suggesting that p300 may modulate YY1 lactylation, thereby influencing the progression of retinal angiogenesis (152).

Snail1. The Snail family is classified within the superfamily of zinc finger proteins. In mammals, the Snail gene family comprises three members: Snail1, Snail2 and Snail3 (153). Members of the Snail family encode products with analogous structures, featuring conserved carboxyl (DNA-binding) and variable amino (regulatory) terminal domains, with the carboxyl terminal end incorporating 4-6 cysteine (Cys)-histidine (His) zinc-finger motifs that establish coordination bonds with Zn^{2+} ions, facilitating binding to oligonucleotide sequences in the E-boxes of target gene promoters and modulating their transcription (154). Snail1, which is located on human chromosome 20q13.2, encompasses 264 amino acids (155). It is pivotal in EMT and considerably influences several pathophysiological events associated with EMT, for example, embryonic development, tumor invasion and metastasis, wound healing and organ fibrosis. Previous investigations have revealed that EMT is essential in renal fibrosis and that Snail1 downregulates E-cadherin by interacting with the CAGGTG

sequence in the E-box of the E-cadherin promoter, thereby initiating a key step in the EMT process (156).

In DN, renal fibrosis is always the endpoint event that influences disease progression and prognosis, highlighting a notable role for Snail1 in this mechanism. Snail1 substantially affects EMT by suppressing E-cadherin expression while promoting the upregulation of vimentin and fibronectin (FN) (157). The activation of Snail1 facilitates EMT in tubular epithelial cells and contributes to TIF (158). Conversely, knockdown of Snail1 reverses EMT in tubular epithelial cells and mitigates the progression of diabetes-related TIF (159). Snail1 induces TIF and alters E-cadherin and FN levels in tubular cells. Notably, K85- and K146-linked ubiquitination of Snail1 destabilizes it and facilitates its degradation via the ubiquitin-proteasome system (UPS) (160). A mechanistic study revealed that USP22, through its deubiquitinase activity, deubiquitinates and stabilizes Snail1. In *in vivo* experiments, disrupting USP22 could ameliorate kidney pathology and enhance kidney function in a db/db mouse diabetes model by downregulating Snail1, thereby inhibiting EMT and diminishing ECM generation (161).

A study in the heart revealed that lactate could accelerate the lactylation of Snail1, facilitating its nuclear translocation and binding to the TGF-β promoter, thereby upregulating TGF-β. Snail1 suppression could diminish lactate-induced EMT following myocardial infarction (MI)/hypoxia and improve cardiac function. These findings indicate that lactate may not only serve as a key prognostic biomarker for heart attack and heart failure but also affect the pathophysiological processes of heart fibrosis via the promotion of EMT after MI. Lactate administration increased Snail1 nuclear translocation in response to hypoxia, with nuclear Snail1 interacting with the TGFβ1 gene for TGF-β1 upregulation. Furthermore, Snail1 suppression inhibited EMT and TGF-β/Smad2 activation associated with lactate upon hypoxia, demonstrating a role for Snail1 in lactate-triggered TGF-β/Smad2-dependent EMT. In animal studies, Snail1 knockdown ameliorated heart function impairment and endothelial-mesenchymal transition induced by lactate post-MI. The study also revealed that lactate stimulates both Snail1 acetylation and lactylation in response to hypoxia/MI. Treatment with the MCT suppressor, α-cyano-4-hydroxycinnamate markedly alleviated Snail1 lactylation induced by lactate, suggesting that lactate-associated Snail1 lactylation and nuclear translocation represent a notable mechanism behind lactate-induced EMT via TGF-β/Smad2 signaling induction after MI (162).

Mitochondrial fission 1 protein (Fis1). Mitochondria are highly dynamic organelles that maintain homeostasis through continuous fusion and fission. Disruption of fission-fusion equilibrium in mitochondria, for example, exaggerated mitochondrial fission, modifies several cellular events, including oxidative stress, apoptosis and inflammatory responses, and contributes to the progression of various diseases such as diabetic nephropathy, renal fibrosis, cardiovascular diseases and neurodegenerative disorders, constituting a hallmark of numerous pathologies (163,164). Fis1, which serves as a mitochondrial outer membrane adaptor, can bind to the fission executor dynamin-related protein 1 to facilitate mitochondrial fission (165). Multiple studies have validated increased Fis1 expression in tubular cells from cases of DN (166). Moreover, strong associations of Fis with Mfn1 and mitochondrial breakdown in tubular cells were observed, indicating a pivotal regulatory role for Fis in mitochondrial dynamics in kidney tubules. Research on Chinese medicines has revealed that formononetin can alleviate albuminuria and kidney histopathology by reducing RTEC apoptosis and mitochondrial breakdown and, more importantly, restoring the expression of Fis1 and apoptosis-associated proteins, for example, Bax, Bcl-2 and cleaved-caspase-3, in HK-2 cells exposed to high glucose (167). Additional results indicated that another herbal compound, astragaloside II, could also ameliorate albuminuria, kidney histopathology, podocyte foot process effacement and podocyte apoptosis in a rat diabetes model, which was partly related to restoring kidney levels of Fis1 and autophagy-associated proteins (168).

Numerous reports have investigated the PTMs of Fis1. A previous investigation revealed that phosphorylated Fis1 could mediate mitochondrial breakdown (169). Additionally, Fis1 can be ubiquitinated by the E3 ubiquitin ligase Parkin, which targets Fis1 for proteasome-dependent degradation and dysregulation of this process is associated with mitochondrial dysfunction and aging (170). High levels of acetyl-CoA induce the acetylation of Fis1, promoting its ubiquitin-proteasomal degradation and thereby attenuating mitochondrial fission (171). Furthermore, An *et al* (172) reported that lactate could induce an increase in Fis1 lactylation at K20 (Fis1 K20la) and further promote aggravated mitochondrial fission and subsequent functional impairment. The activation of PDHA1, a subunit of pyruvate dehydrogenase (which catalyzes the conversion of pyruvate to acetyl-CoA), can reduce Fis1 K20 lactylation, thereby alleviating sepsis-associated AKI (SAKI). These findings emphasized lactylation as a novel PTM of the non-histone Fis1.

Ezrin. Ezrin, a member of the ezrin-radixin-moesin family, also known as p81, can be phosphorylated by the EGFR tyrosine kinase (173). Ezrin is a globular structural protein (molecular weight of 78 kDa) that connects the cell membrane and actin filaments. It can associate with several proteins, including CD44, CD43, L-selectin, ICAM-1, ICAM-2, PSGL-1 and the death receptor CD95/Fas, thereby engaging in cell adhesion and apoptosis (174). Ezrin is expressed in multiple tissues, with elevated expression in the small intestine, stomach, lung, pancreas and kidney (175). It functions as a linker between the membrane and microfilaments, facilitating interactions between the cytoplasmic membrane and the actin cytoskeleton while preserving structural integrity, such as maintaining the integrity of the cellular epithelium and mediating intracellular transduction of extracellular mechanical signals. As a membrane-microfilament-linking protein, ezrin can generate membrane protrusions, regulating cellular remodeling, including cell proliferation, deformation, migration and adhesion, thereby playing key roles in sustaining cell shape and modulating cell movement. Ezrin comprises 586 amino acids and contains phosphorylation sites, including Tyr145, Tyr353 and Ser66.

Furthermore, Ezrin contains two cysteine residues, which are considered to undergo nitration modification (176). Ezrin serves as a key crosslinker protein within this complex, facilitates the development of elongated projections of the

podocyte slit diaphragm and controls several cellular activities, for example, adhesion and mobility. Disrupted ezrin/actin complexes have been detected in animal models of podocyte injury, for example, in rats administered puromycin aminonucleoside and the amount of podocyte ezrin is inversely associated with the severity of proteinuria-related kidney disease in pediatric patients (177).

Regarding lactylation, Qiao *et al* (178) partially clarified the association between elevated blood lactate levels and the increased incidence and unfavorable prognosis of SAKI. The increase in Ezrin may further exacerbate inflammatory responses, primarily through its interactions with MYD88 and IRAK1, thereby activating the NF-κB pathway. Histone H3K18 lactylation (H3K18la) is increased in SAKI. Moreover, this lactate-induced histone modification is enriched at the promoter of Ras homolog gene family member A (RhoA) and is positively associated with transcription. Rectification of altered lactate levels reversed atypical histone lactylation at the RhoA promoter. Investigation of the associated mechanisms revealed that histone lactylation stimulated the RhoA/Rho-associated protein kinase (ROCK)/Ezrin signaling pathway and activated NF-κB, the inflammatory response and apoptotic cell death, exacerbating impaired kidney function. Additionally, ezrin can undergo lactylation as a non-histone protein. Mutation of the K263 site (K263R) was found to counteract the regulatory effects of lactate on ezrin-mediated renal injury.

HIF-1α. HIF-1 is a heterodimeric protein containing α and β subunits, and the α and β subunits can operate as transcription factors only following dimerization. HIF-1α represents the functional subunit of HIF-1, while HIF-1β serves as the structural subunit of HIF-1 and is expressed at relatively stable levels within cells. Under normoxia, synthesis of the HIF-1α subunit occurs concurrently with its degradation via the UPS, resulting in minimal detection. However, under hypoxia, HIF-1 breakdown is suppressed, promoting the accumulation and nuclear translocation of HIF-1α, where it binds to HIF-1β for the generation of HIF-1 complexes (179). Under hypoxia, HIF-1α upregulation stimulates the expression of numerous target genes, regulating cellular proliferation, neovascularization and remodeling, programmed cell death, energy metabolism and iron transport.

There is tissue-specific expression of HIF-1α in the kidneys. Elevated glucose levels enhance HIF-1α expression and activity in human mesangial cells, thereby inducing glomerulosclerosis. Conversely, high glucose can also diminish the stability and function of HIF-1α in the proximal tubular HK-2 cell line, exacerbating DN tubulointerstitial injury (180). Another perspective suggests that under conditions of low oxygen and high glucose, high HIF-1α expression in cells renders kidney tissue and cells more susceptible to fibrosis (181). Prolonged activation of HIF-1α in proximal tubules can promote TIF. Inhibition of HIF-1α attenuates fibronectin expression associated with low oxygen in high-glucose cells, thereby mitigating fibrosis (182). Throughout DN progression, elevated glucose alters HIF-1α stability and activity, influencing vascular endothelial growth factor (VEGF) transcription in renal cells, leading to decreased VEGF production and promoting TIF (183). Another investigation revealed that in DN, during the compensatory phase, the upregulation of HIF-1α expression under hypoxic conditions can also inhibit apoptosis and ROS formation through the induction of mitochondrial autophagy, providing a protective effect (184). However, a sustained high-glucose and low-oxygen environment disrupts HIF-1α stability and inhibits mitochondrial autophagy (185). Impaired mitochondrial autophagy further exacerbates mitochondrial damage, ROS imbalance and disrupted intracellular homeostasis, thereby promoting the progression of DN. Additionally, HIF-1α is implicated in DN-associated inflammation, stimulating the production of various cytokines involved in immune responses. Under high-glucose conditions, high HIF-1α expression increases the levels of inflammation- and fibrosis-associated cytokines, for example, TGF-1β, endothelin and fibronectin, in mesangial cells, exacerbating the incidence of interstitial fibrosis in DN (186).

Regarding the lactylation of HIF-1α in prostate cancer (PCa), Luo *et al* (187) demonstrated that HIF-1α serves as a transcriptional inducer of KIAA1199, which is involved in pathways such as glycolysis, hypoxia and angiogenesis. Given that lactylation has been identified as a key mechanism of posttranscriptional regulation initiated by lactate, the potential for lactate to stimulate HIF-1α lactylation in PCa cells was further examined. Initially, in PCa cells treated with varying lactate amounts for 72 h under normoxic conditions, increased HIF-1α lactylation was observed. Following 72 h of culture with 10 mM lactate, substantial HIF-1α lactylation was noted in both the PC-3 and DU145 cell lines. Additionally, immunofluorescence revealed that lactate administration under normoxic conditions enhances colocalization of lactylation and HIF-1α in the PC-3 cell line, an effect reversed by MCT1 silencing. These findings indicate that lactate augments HIF-1α expression through its lactylation.

PFKP. Phosphofructokinase-1 (PFK-1) converts fructose-6-phosphate into fructose-1,6-bisphosphate and is modulated by fructose-2,6-bisphosphate(188). PFK-1 is the principal rate-limiting enzyme in glycolysis and represents an important juncture in this metabolic process. There are three variants of PFK-1 in vertebrates, designated PFKM (muscle-specific), PFKL (liver-specific) and PFKP (platelet-specific), based on their discovery locations, with PFKP assumed to play a pivotal role in the kidneys (189). PFKP, a predominant PFK-1 isoform involved in tumor cell glycolysis, has emerged as a promising anticancer target. The kidney ranks among the human organs with the greatest metabolic rates, primarily driven by tubular epithelial cells. The kidney needs to maintain energy homeostasis, as disruptions in energy metabolism may cause cellular dysfunction, cell death and multiple renal pathologies. In diabetic patients, alterations in metabolic substrates and oxygen delivery lead to hypoxia, enhanced glycolysis and lipid accumulation in tubules, culminating in elevated amounts of ROS, proinflammatory mediators and profibrotic molecules, as well as increased PTEC apoptosis and kidney fibrosis. Lang *et al* (190) reported that PFKP is highly expressed and is markedly upregulated in glomerular tissues from db/db mice. Similarly, PFKP is upregulated in samples from patients with DN compared with control kidney tissue samples from patients with cancer.

Furthermore, elevated ACR levels, increased mortality, and more pronounced foot process fusion were observed in db/db

mice treated with CTZ, a PFKP suppressor (191). Additionally, the application of FBP, a product of PFKP, ameliorated proteinuria and kidney damage in a db/db mouse model. PFKP inhibition exacerbates diabetic kidney injury and cytoskeletal remodeling in podocytes (192). These findings suggest that PFKP may function as an endogenous protective factor in DN.

PFKP may also be modified by lactylation. Cheng *et al* (193) noted that lactate could induce PFKP lactylation, which diminishes its enzymatic activity in the fetal human colon (FHC) cell line from the colon of a 13-week-old embryo. They reported that the FHC cell line uses a negative feedback mechanism in which lactate suppresses PFKP in glycolysis, highlighting the importance of deregulated lactate and PFKP lactylation in colorectal cancer development. However, the mechanisms by which PFKP lactylation levels are decreased following DCA administration and by which PFKP activity is modulated by lactylation require further exploration.

SOX9. SOX9 is an essential transcription factor within the SOX family. The name of the SOX family derives from its homology to the SRY gene found on the male Y chromosome. It is widely expressed across various developing organs, including the kidney, cartilage, pancreas, liver, heart valves, testicles and other organs (194). SOX9 primarily consists of four domains: An HMG box (N-terminal) that binds to DNA, a dimerization domain (N-terminal) and two transcription activation domains (C-terminal), one of which is rich in proline (Pro)/glutamine (Gln)/alanine (Ala), whereas the other transcription activation domain is enriched in Pro/Gln/serine (Ser). SOX9 predominantly binds and activates target genes via the HMG box, thereby fulfilling its role as a transcription factor. Its activation domain is located at amino acids 402-509 at the C-terminal end of SOX9 (195,196). Increasing evidence suggests that SOX9 is pivotal in embryonic development, organ tissue development and differentiation, and is extensively implicated in the onset and progression of tumors affecting multiple organs, including the kidney, prostate, lung, liver, pancreas, skin, breast and ovary (197). In the context of DN, a study by Kishi *et al* (198) revealed that SOX9 can prompt mesangial cells to undergo chondrogenic phenotype transformation, thereby promoting the progression of DN.

Furthermore, SOX9 overexpression led to increased ectopic levels of proteoglycans and COL2 in mesangial cells. SOX9 partially colocalized with HIF-1α and BMP4 in diabetic glomeruli. It may be because HIF-1α and BMP4 can upregulate SOX9 and induce subsequent chondrogenic phenotype transformation in DN (198). Given that renal fibrosis is a notable pathophysiological mechanism in DN, SOX9 also contributes to it. Research by Li *et al* (199) revealed that SOX9 silencing alleviated TGF-β induced renal fibrosis. When renal fibroblasts are stimulated with TGF-β *in vitro*, the TGF-β/Smad complex binds to the conserved enhancer region of SOX9, considerably upregulating SOX9 and thereby promoting cellular fibrosis.

In addition, SOX9 expression in the tumor microenvironment can be controlled by non-coding RNAs, RNA methylation and PTMs (for example, phosphorylation and lactylation). In non-small cell lung cancer, Yan *et al* (200) reported that hypoxia enhances SOX9 expression and lactylation and that these effects are reversed by suppressing glycolysis. In addition, SOX9 silencing blunted the malignant features of these cells. In tumor-bearing mice, SOX9 overexpression promoted tumor growth, which was attenuated by glycolysis suppression.

Mecp2. Methyl-CpG binding protein 2 (MeCP2) represents an important DNA methylation binding protein belonging to the methyl-CpG binding domain (MBD) family. Presently, the majority of fundamental studies on MeCP2 have focused on neurological diseases, for example, Rett syndrome and MeCP2 duplication syndrome (201). The biological function of MeCP2 primarily lies in its capacity as a DNA methylation-binding protein. Previous investigations have established that MeCP2 possesses six structural domains, the most important of which are the MBD and the transcriptional repressor domain. These two structural domains predominantly facilitate the interaction of MeCP2 with methylated DNA sites and recruit additional factors to form transcriptional repression complexes, thereby executing transcriptional repression functions (202). MeCP2 can also recruit histone deacetylase complexes. MeCP2 modulates gene expression posttranslationally by inhibiting nuclear miRNA processing. Studies of Mecp2 PTMs revealed that phosphorylated MeCP2 (p-MeCP2) directly interacts with DiGeorge syndrome critical region 8 (DGCR8), a vital factor in nuclear micro RNA processing and disrupts the Drosha-DGCR8 complex (203). Conversely, homeodomain interacting protein kinase 2 (HIPK2), which regulates gene expression by phosphorylating transcription factors, phosphorylates MeCP2 at Ser80, with p-MeCP2 produced by HIPK2 contributing to apoptotic cell death (204). p-MeCP2, HIPK2 and NOX4 are upregulated in animal and cell models of diabetes. Notably, the mechanism outlined by these studies may be relevant to DN and other renal disorders in humans, as renal Mecp2 is upregulated in clinical CKD, lupus nephritis, focal segmental glomerulosclerosis, IgA nephropathy and DN (205).

Lactylation is considered a novel form of PTM of Mecp2. Given that exercise generates the lactate used in lactylation, Wang *et al* (206) first explored the fundamental role of exercise in atherosclerotic cardiovascular disease (ASCVD) via Mecp2 k271 lactylation. They demonstrated that exercise markedly elevated Mecp2k271la levels in an ASCVD mouse model, resulting in diminished inflammation in endothelial cells and suppressed ASCVD progression. In the inflammatory state, Mecp2k271la suppresses Ereg expression, which modulates Egfr/MAPK signaling, thereby upregulating IL-1β, IL-6, Icam-1, Vcam-1 and Mcp-1 and downregulating Enos in endothelial cells, thereby mitigating plaque progression in ASCVD. Specifically, increased Mecp2k271la expression decreased ASCVD by downregulating adhesion (Vcam-1, Icam-1 and Mcp-1) and proinflammatory (IL-1β and IL-6) factors, while increasing Enos in ECs.

Neuronal precursor cell expressed, developmentally downregulated 4 (NEDD4). NEDD4 represents a variant of E3 ubiquitin ligase that can bind to lysine residues associated with the upstream ubiquitin-activating enzyme E1 and conjugating enzyme E2, resulting in the ubiquitination of its substrate proteins. NEDD4 enzymes are broadly expressed in yeast and mammalian cells (207). NEDD4 can exert antiapoptotic effects through various mechanisms. Research has demonstrated that NEDD4 can specifically

interact with PTEN to facilitate its degradation by the neural proteasome system, thereby counteracting apoptosis (208). Additional findings indicate that NEDD4 activates PI3K/Akt signaling to diminish apoptosis in myocardial cells triggered by ischemia/reperfusion (209). Furthermore, NEDD4 expressed in vascular endothelial cells degrades VEGFR2, which is involved in endocytosis (210). In the kidney, NEDD4L is predominantly located in proximal tubules and is markedly upregulated in mice afflicted with DN. Co-immunoprecipitation experiments demonstrated that NEDD4L overtly interacts with Ca/calmodulin-dependent protein kinase β (CaMKKβ). Furthermore, NEDD4L suppression under high-glucose conditions inhibited the rapid degradation of CaMKKβ. Cell culture assays demonstrated that abnormal NEDD4L expression adversely affects CaMKKβ protein stability. Inhibition of NEDD4L results in a reduction in urinary protein excretion, TIF, oxidative stress and impaired mitochondrial function. Additional cell culture assays revealed that small interfering-Nedd4L curtails mitochondrial fusion and ROS accumulation and that these effects are counteracted by si-CaMKKβ (211). Another investigation indicated that mice lacking NEDD4L, particularly in renal tubular cells, had mild kidney disease because of ENaC upregulation (212), since NEDD4L potentially contributes to renal regulation of potassium (213) and sodium (214) balance.

Li *et al* (215) also reported that lactates modulate NEDD4 K33 lactylation, thereby inhibiting the interaction between Caspase-11 and NEDD4. Furthermore, inhibiting lactylation diminishes non-canonical pyroptosis in macrophages and alleviates hepatic damage. Their research connects lactate to the intricate modulation of non-canonical inflammasomes and establishes a foundation for targeting lactylation to address caspase-11-associated non-canonical pyroptosis and acetaminophen-dependent liver damage. Given that LPS enhances macrophage histone lactylation, the authors examined whether LPS affects NEDD4 lactylation. As anticipated, LPS could increase NEDD4 lactylation and synergize with exogenous lactate intake.

Transcription factor EB (TFEB). TFEB is a constituent of the microphthalmia-associated transcription factor/transcription factor E family, is widely expressed across various cell types, and regulates numerous cellular biological functions (216). The TFEB protein comprises 476 amino acid residues, including an acidic activation domain, a helix-loop-helix leucine zipper, a glutamate-rich domain and sequences rich in serine. Previous evidence revealed that TFEB can undergo phosphorylation at serine residue 142 (S142), serine residue 211 (S211) and the terminal serine-rich domain. It initiates transcription of corresponding genes by recognizing E-box and M-box sequences and engaging in various pathophysiological processes (217). Recent investigations have shown that TFEB can directly interact with the coordinated lysosomal expression and regulation network in the promoters of lysosome-related genes. Overexpression of TFEB induces expression of these genes, thereby augmenting lysosome biosynthesis and function (218). TFEB also interacts with the promoter regions of autophagy-related genes, regulating autophagy by facilitating autophagosome generation, autophagosome-lysosome fusion and the degradation of autophagic substrates (219). Furthermore, TFEB is important for modulating lipid metabolism, organelle autophagy, the immune response, inflammation and carcinogenesis (220).

In DN progression, TFEB plays a key role. Yuan *et al* (221) reported that mesenchymal stem cells (MSCs) enhance lysosomal function by activating TFEB, augment autophagy and mitigate DN by promoting the M2 macrophage phenotype. Previous findings revealed that MSCs can bolster the anti-inflammatory response in M2 macrophages; downregulate TNF-α, monocyte chemotactic protein and IL-1β in DN mice; safeguard against kidney damage; increase the protein expression of tissue protease B, TFEB, LC3II and Beclin1 in macrophages; decrease the protein expression of P62; and increase lysosomal autophagy. Additional studies have also indicated that MSCs ameliorate lysosomal dysfunction in high-glucose-induced RAW264.7 cells, increase autophagic flux and alleviate cellular inflammation triggered by high glucose (222). Research by Zhao *et al* (223) revealed a notable reduction in the number of autophagic vesicles in podocytes of patients of DN, accompanied by diminished autophagy. In mice with late-stage diabetes AGEs activate mTOR, inhibiting TFEB translocation into the nucleus, thereby further downregulating lysosome-related genes and autophagy-related genes, obstructing autophagosome and autolysosome formation and impeding autophagic flux, thus contributing to the progression of DN.

Current evidence indicates that TFEB activation is predominantly regulated by PTMs, such as phosphorylation and acetylation (224,225). mTORC1-related phosphorylation plays a fundamental role by sequestering TFEB in the cytosol, while inactivating mTORC1 triggers TFEB dephosphorylation and translocation into the nucleus to initiate the transcription of target genes (226). A previous study also reported that the transcription of TFEB itself might be controlled by a positive feedback loop (227) and that STIP1 homology and U-box containing protein 1 (STUB1) directs TFEB for UPS-dependent breakdown (228). Huang *et al* (229) demonstrated that lactate covalently modifies TFEB, resulting in stable lactylation. Mechanistically, lactylation at K91 prevents TFEB interaction with the E3 ubiquitin ligase WWP2, thereby inhibiting TFEB ubiquitination and proteasomal degradation, increasing TFEB activity and enhancing autophagy. Using specific antibodies targeting lactylated K91, augmented TFEB lactylation was detected in human pancreatic cancer specimens. These findings indicate that lactylation represents a new regulatory mechanism for TFEB and that TFEB lactylation may associate with increased autophagy in fast-growing cells, including malignant cells.

P53. P53 is a key tumor suppressor gene located at 17p13.1 on the human chromosome and encodes the 43.7-kDa p53 protein. p53 is involved in and regulates multiple pathophysiological processes, for example, controlling the cell cycle in tissues, facilitating apoptosis, preserving genetic stability and suppressing tumor angiogenesis (230-232). Furthermore, increasing evidence indicates that p53 contributes to and modulates the physiological and pathological mechanisms underlying kidney disease. Under physiological conditions, renal p53 protein levels remain low and are primarily maintained at a minimal level through ubiquitination and degradation pathways (233). However, when cells encounter

stress conditions such as elevated glucose, the p53 protein can rapidly accumulate and affect downstream targets, producing corresponding biological effects (234). Increased p53 levels and phosphorylation are observed in both tubular cells and podocytes in chronic DN. Nuclear p53 content is markedly elevated in DN and IgA nephropathy cases compared with control cases with minimal change disease, confirming p53 activation in the context of progressive kidney damage in humans (235). STZ-induced diabetic mice, along with db/db mice, showed elevated kidney levels of p53, BAX and Puma, as well as increased apoptotic death of epithelial cells (236). Mitigating oxidative stress through catalase overexpression reduced p53 levels and alleviated diabetic kidney damage (237). Human kidney allograft rejection is associated with tubular damage, ongoing fibrosis and induction of p53 and p21. Indeed, p53 and p21 levels in allografts are positively associated with creatinine levels and negatively associated with the eGFR (238), underscoring the clinical importance of p53 hyperactivation in transplantation failure. However, the extent to which p53 contributes to the progression of human nephropathies remains to be explored, as extensive p53 activation has been observed in various *in vivo* models of kidney disease. The aggravation of I/R injury in diabetes also results in a p53-mediated increase in serum creatinine levels, increased tubular damage and increased apoptotic cell death. DN-related AKI, triggered by both diabetes and ischemia, is also alleviated by pifithrin-α administration and PTC p53 ablation (234). By contrast, global p53 knockout mice develop more severe AKI than their wild-type counterparts after I/R due to heightened inflammation, indicating that p53 may, under specific conditions, also protect the kidney (239).

In a recently published study, proteomics revealed multiple AARS1 targets, for example, p53 with lactylated K120 and K139 (DNA binding domains). The use of p53 variants harboring constitutively lactylated lysine moieties demonstrated that AARS1 lactylation of p53 suppresses its liquid-liquid phase separation, DNA binding and transcriptional activation. AARS1 levels and p53 lactylation were markedly associated with poor survival in patients with breast cancer harboring wild-type p53. β-alanine disrupts the interaction between lactate and AARS1, reduces p53 lactylation and alleviates tumorigenesis in model animals, indicating that AARS1 is involved in tumorigenesis by associating metabolic events to proteome changes in tumor cells (240).

AMPKα. Adenosine monophosphate-activated protein kinase (AMPK) is a heterotrimer consisting of one catalytic (α) and two regulatory (β and γ) subunits. AMPK-α1 and α2 have tissue-specific distributions: α1 is predominantly expressed in the kidney, liver, lung, heart and brain, whereas α2 is primarily expressed in the heart, liver, skeletal muscle and brain neuronal cells. The α subunit of AMPK is the essential catalytic component that contains a conventional serine/threonine kinase domain. Furthermore, the central region of the α subunit also functions as an autoinhibitory domain that interacts with the kinase domain in the absence of a notable activator of the AMPK signaling pathway, AMP, thereby hindering activation of the active site (241). In the context of metabolic stress, hypoxia, ischemia and similar conditions, AMPK is activated as the concentration of AMP rises and the AMP/ATP ratio increases, thereby increasing ATP consumption. Activating agents for AMPK include liver kinase B1 (LKB1), CaMKKβ and TGF-β-activating kinase (242).

AMPKα is prominently expressed in various kidney cell types, for example, mesangial cells, glomerular endothelial cells and podocytes. Impaired AMPKα signaling, podocyte damage, metabolic dysregulation, insulin resistance and reduced adiponectin levels are notably associated with DN initiation and progression. AMPKα serves as a pivotal modulator of energy metabolism in cells. AMPKα activation can trigger the activation of insulin receptor tyrosine kinases, inducing the phosphorylation of downstream effector proteins, further phosphorylation, and the activation of Akt, ultimately facilitating GLUT4 transport to the plasma membrane, which considerably enhances glucose uptake in skeletal muscles, improves insulin sensitivity, augments fatty acid oxidation and modulates gene transcription (243). Presently, AMPKα is considered a beneficial regulator of insulin sensitivity. Knockout of the AMPKα gene can induce insulin resistance in mice, whereas AMPKα overexpression or targeted activation of AMPKα exerts insulin-sensitizing effects, reducing podocyte injury, diminishing proteinuria and deferring the onset and progression of DN (244). Moreover, AMPKα is also an upstream regulatory factor of SIRT1, elevating the AMP/ATP ratio, particularly the NAD+/NADH ratio, to boost SIRT1 activity or increasing nicotinamide phosphoribosyl transferase to increase NAD+ levels, further enhancing SIRT1 activity (245). SIRT1 can also deacetylate the upstream kinase LKB1 of AMPKα, promoting LKB1 translocation to the cytoplasm and activating AMPKα. The interplay between AMPKα and SIRT1 is underscored by these findings, suggesting that they confer protective effects in damaged kidneys by affecting the renal filtration barrier and alleviating renal pathology. Furthermore, AMPKα activators can restore Thr172 phosphorylation of the AMPKα subunit, decrease mTORC1 phosphorylation induced by elevated glucose levels, reduce podocyte apoptosis and reduce proteinuria (246). Research on podocytes in DN has demonstrated that upregulating AMPKα expression can increase the levels of the Nephrin and Podocin proteins within cells, effectively ameliorating podocyte injury (247).

A recent investigation demonstrated that glutamine concentrations are decreased in human and aged Sprague-Dawley rat nucleus pulposus (NP) tissues with severe degeneration, whereas lactate levels and lactylation are increased. Exogenous glutamine curtails glycolysis and increases lactate levels, downregulating AMPKα lactylation and increasing AMPKα phosphorylation. Furthermore, glutamine administration mitigated senescence in NP cells and promoted autophagy and ECM production by suppressing glycolysis and AMPKα lactylation; impaired glycolysis also suppressed lactylation. These findings suggest that glutamine may prevent intervertebral disc degeneration by suppressing glycolysis and AMPKα lactylation, thereby fostering autophagy and curtailing NP cell senescence (248).

Limitations. Several non-histone lactylation events discussed in the present review have been characterized in non-DN contexts, and their relevance to DN is mechanistically plausible but still requires direct validation. For instance, in pro-inflammatory macrophages, lactate-induced PKM2 K62

lactylation stabilizes the tetrameric (high-activity) form, reduces nuclear translocation and attenuates the Warburg effect as a negative-feedback 'metabolic brake'. Because podocytes and mesangial cells in DN also display tumor-like aerobic glycolysis, it is tempting to speculate that PKM2 lactylation might similarly restrain excessive glycolytic flux and toxic metabolite accumulation in early DN, a concept that aligns with the current interest in PKM2 tetramerizing agonists; however, no study has yet directly mapped PKM2 K62la in diabetic kidneys, making this a hypothesis that warrants targeted metabolic and lactyl-proteomic validation in DN models (70,78,122,249).

Likewise, YY1 K183 lactylation in microglia has been shown to enhance its DNA binding and transcriptional activation of FGF2, thereby promoting angiogenesis under hypoxia, and this effect is driven by p300 and can be blocked by the p300 inhibitor A-485. Given that YY1 is upregulated in DN mesangial cells and acts as an important co-factor for TGF-β-induced profibrotic gene expression, high lactate levels in the diabetic microenvironment may reasonably be hypothesized to amplify TGF-β signaling through YY1 K183 lactylation, increasing mesangial 'sensitivity' to fibrogenic cues and fueling a metabolism-epigenetics vicious cycle; however, direct evidence for YY1 lactylation in DN kidneys is still lacking and should be a focus of future work (152,250,251).

In SAKI, lactate-driven H3K18 and Ezrin K263 lactylation promote RhoA/ROCK/Ezrin signaling, NF-κB activation, inflammation and renal dysfunction, with Ezrin K263la enhancing Ezrin-MYD88 interaction. Because Ezrin is a core linker between the podocyte slit diaphragm and the actin cytoskeleton, it is plausible that chronic lactate elevation in DN could induce similar Ezrin lactylation, simultaneously promoting NF-κB-mediated inflammation and destabilizing cytoskeletal anchoring, thereby contributing to foot process effacement and proteinuria; this mechanism has not yet been directly demonstrated in DN and represents an important hypothesis connecting 'inflammation-to-structure' damage at the molecular level (24,178,251,252).

Finally, recent work identifies AARS1 as a lactate-responsive lactyltransferase that modifies p53 at K120 and K139, impairing its DNA binding, liquid-liquid phase separation and transcriptional activation of canonical target genes, and associating with poor outcomes in patients with breast cancer with wild-type p53. Because p53 hyperactivation is a major driver of podocyte apoptosis and tubular cell senescence in DN, AARS1-mediated p53 lactylation raises the possibility of a stage-dependent 'protective vs. pathogenic' switch: Early in DN, elevated lactate might transiently dampen p53 transcriptional activity and delay cell death, whereas in advanced disease, disruption of lactate handling or dominance of other PTMs (for example, acetylation and phosphorylation) could override this brake, leading to overt apoptosis and fibrosis. This dynamic model is conceptually attractive but remains speculative until p53 K120/K139 lactylation is quantified across DN stages in animal models and in human kidney tissue (240,253,254). Overall, while extrapolating non-histone lactylation data from macrophage, microglial, angiogenesis and sepsis-induced AKI models provides a coherent mechanistic framework for DN, these assumptions must be explicitly labeled as hypotheses and systematically tested in diabetic kidney models using site-specific lactyl-proteomics and functional assays.

4. Prospect of lactylation as a therapeutic target for DN

Drugs targeting lactylation. Given that previous studies have shown that lactylation can contribute to the development of DN by regulating multiple key signaling pathways, for example, ROS, inflammation, mitochondrial dysfunction, autophagy, apoptosis and ferroptosis, effective therapeutic strategies based on lactylation regulation are promising but currently lacking. Owing to the incomplete elucidation of the roles of lactate and lactylation in DN, this therapeutic approach may attract increasing interest. With respect to therapeutic applications, a series of drugs have been shown to affect lactylation, focusing mainly on lactate production or inhibition.

First, LDHA drives pyruvate conversion to lactate, and LDHA inhibitors such as oxamate, (R)-GNE-140, and fargesin effectively inhibit lactylation. Oxamate has been studied in depth for its mechanism and value in lactylation and has been shown to inhibit LDHA activity and, subsequently, affect histone Kla expression, particularly H3K18la (255). Oxamate is a classical isosteric and isoelectronic analogue of pyruvate that mimics the carboxyl and carbonyl groups of α-keto acid, allowing it to bind in the LDHA active site and competitively interfere with the conversion of pyruvate to lactate. Structure-activity studies indicate that maintaining the pyruvate-like α-keto-carboxylate pharmacophore is key for LDHA binding, while prodrug strategies, such as esterification of the carboxyl group, can improve membrane permeability and may enhance uptake across RTECs before intracellular hydrolysis regenerates the active inhibitor (256-259). Oxamate is a polar pyruvate analogue with poor oral bioavailability and requires relatively high systemic doses (often administered intraperitoneally or intravenously in animals) to achieve meaningful LDH inhibition *in vivo*. Newer LDH inhibitors (such as N-hydroxyindole LDH-A inhibitors, NCI-006, GNE-140 and pyrazole-based LDH inhibitors) with improved potency and lipophilicity show improved tissue penetration but still display relatively short half-lives and are primarily cleared renally and hepatically, which is relevant in DN with impaired kidney function (257,260-265). Preclinical studies show that oxamate can suppress whole-body glycolytic flux, lower ATP production and increase ROS, which is beneficial against tumors but may compromise energy homeostasis in high-demand tissues such as the kidney, heart and brain. At high concentrations, oxamate and related compounds may inhibit other glycolytic enzymes (for example, PK or enolase), raising concerns regarding systemic fatigue, hypoglycemia-like symptoms and worsening of ischemic injury in DN, especially in patients with already reduced renal reserve (260,261,266,267).

Second, lactate transporters are important for increasing lactate transport; MCT suppressors, for example, AZD-3965, α-cyano-4-hydroxycinnamate, lonidamine, AR-C155858, the MCT1/4 inhibitor syrosingopine, MCT1 inhibitors (meplazumab, phloretin and thalidomide) and derivatives (lenalidomide and pomalidomide), can also be used to alter lactate levels, regulating lactylation (268). In addition, drugs that target SMCT are scarce. Common drugs used in the clinic may exert suppressive effects on MCT/SMCT, for example, the non-steroidal

anti-inflammatory drugs ibuprofen and salicylic acid (269,270). Some aforementioned drugs are being examined in ongoing clinical trials. AZD3965 is a potent, nanomolar inhibitor that selectively targets MCT1 and competes with endogenous monocarboxylates (such as lactate) at the substrate-binding site, locking the transporter in a non-productive conformation and thereby blocking bidirectional lactate transport across the plasma membrane. The compound contains an acidic or pseudo-acidic scaffold that forms hydrogen bonds and ionic interactions in the central cavity of MCT1, a feature identified as a key SAR element for high-affinity binding and effective inhibition of lactate flux (271-274). AZD3965 is an oral, selective MCT1 inhibitor with dose-dependent target engagement demonstrated in phase I oncology trials, and its pharmacokinetic profile supports once-daily dosing at a maximum tolerated dose of ~20 mg in adults. It achieves substantial inhibition of lactate transport in high-MCT1-expressing tissues, including tumor, heart and retina, which is central to both its efficacy and toxicity (275-277). The main dose-limiting toxicities of AZD3965 are on-target, reversible ocular events (retinal functional changes) and potential cardiac effects in tissues with high MCT1 expression, alongside common low-grade symptoms such as nausea and fatigue. In DN, where cardiometabolic comorbidities and microvascular eye disease are prevalent, MCT1/4 inhibition might aggravate retinal or cardiac stress if not carefully monitored, although kidney-focused delivery or intermittent dosing could leverage renal benefits (reduced lactate influx and lactylation) while minimizing systemic risks (24,276,277).

Additionally, studies on other targets have yielded encouraging findings (262,278-285). Since p300/CBP regulates lactylation as a writer, its inhibitors have therapeutic potential; C646, a small-molecule inhibitor designed to inhibit p300 HAT activity, was experimentally validated for targeting histone lactylation (278). A-485 is a highly selective, competitive small-molecule inhibitor that targets the catalytic domain of p300/CBP by occupying the acyl-CoA (such as acetyl-CoA or lactyl-CoA) binding pocket and structurally mimicking key interactions of the CoA thioester scaffold. By blocking the CoA-binding channel, A-485 prevents transfer of acyl groups, including lactyl moieties, to lysine residues on histone and non-histone substrates, thereby suppressing lactylation-dependent transcriptional programs (21,262). A-485 is an orally bioavailable, small-molecule CBP/p300 HAT inhibitor with moderate plasma half-life and good tissue distribution in rodents, achieving sustained suppression of histone acetylation at tolerable doses. Because p300/CBP is ubiquitously expressed, systemic exposure to A-485 affects multiple organs, including bone, liver, the immune system and potentially the kidney (279-283). In preclinical models, A-485 and related CBP/p300 HAT inhibitors can cause hematologic changes (transient leukocytosis), alter osteoclast/osteoblast balance and modulate inflammatory signaling, reflecting broad epigenetic reprogramming. For DN, this implies that while p300 inhibition might reduce pathogenic histone and non-histone lactylation in renal cells, long-term systemic blockade could interfere with normal repair, immune responses and bone metabolism, necessitating kidney-targeted delivery or carefully titrated dosing regimens (279-281,283). HDAC suppressors enhance histone lactylation. For example, mouse P19 Embryonal Carcinoma cells-derived Neural Stem/Progenitor Cells treated with the HDACi MS275 (entinostat) presented increased global histone Kla levels; in addition (284), apicidin, a specific suppressor of HDAC1-3, also increased histone Kla levels (30). As SIRTs act as dehydrogenases, strategies for the use of epigenetic small molecules to upregulate sirtuins at the gene and protein levels represent promising options; currently available SIRT-activating compounds include piceatannol, resveratrol, SRT1720, SRT2104, ADTL-SA1215, honokiol and UBCS039 (285). However, it is still necessary to explore whether these inhibitors affect lactylation and related diseases in future studies. The majority of the aforementioned drugs have been studied in oncology and have been shown to exert antitumor effects; thus, drugs targeting lactylation might provide new therapeutic options for DN in the future.

Other therapeutic methods targeting lactylation. The regulation of lactate, histone lactylation and non-histone protein lactylation can be epigenetically modulated by microRNAs (miRNAs). miRNAs are 18-25 nucleotide-long non-coding RNAs that regulate target genes posttranscriptionally by generating incomplete complementary base pairs at the 3' untranslated regions (3' UTRs) of target mRNAs (286). Further evidence showed that the virus-encoded miR-N20 targets HIF-1α to suppress host glycolysis, leading to downregulation of H3K18la and H4K12la (287). In addition, exos, a current research focus in DN, have not been extensively investigated because of the notable role lactylation may carry out in their function. MSCs are highly valued for their multipotency, paracrine functions, immunomodulatory properties and tissue repair capabilities. In particular, the exos produced by MSCs (MSC-Exos) contain high amounts of bioactive compounds and promote intercellular communication, with key roles in multiple pathophysiological events. The evidence suggests that MSC-Exos effectively treat DN by improving tissue repair, inhibiting fibrosis and reducing the inflammatory response. Recent findings highlight the potential use of MSC-Exos, underscoring their wide therapeutic applicability in DN (288). Whether MSC-Exos can be administered and retreated by extracting exosomes from urine to alleviate DN progression via lactylation also deserves further examination.

5. Impact of infectious agents on lactate metabolism and DN

In the context of the COVID-19 pandemic, individuals with diabetes and obesity face a disproportionately higher risk of severe COVID-19, intensive care unit admission and AKI, and DN or obesity plus diabetes markedly increase COVID-19-related mortality (289-294). These observations support the classification of patients with COVID-19 who have underlying obesity or diabetes as a global high-risk group that warrants intensified renal monitoring and preventive strategies. SARS-CoV-2 infection is characterized by profound systemic inflammation and tissue hypoxia, which together enhance aerobic glycolysis, upregulate LDH expression, and lead to excessive lactate accumulation and lactic acidosis. Experimental and translational studies indicate that elevated intracellular lactate can promote histone and non-histone lactylation, thereby reprogramming immune and stromal cells and contributing to

organ fibrosis in various inflammatory settings (295-297). It is therefore plausible that, in patients with pre-existing diabetes or obesity, COVID-19-induced lactate overload may exacerbate renal inflammation and fibrosis through lactylation-mediated pathways, further accelerating the progression of DN and long-term kidney dysfunction (67,74,290,298-302). These data highlight the urgency of elucidating lactate-lactylation signaling in high-risk populations with COVID-19, which may uncover novel targets to mitigate post-infectious renal fibrosis in patients with metabolic comorbidities.

Beyond SARS-CoV-2, emerging evidence suggests that a broad spectrum of infectious agents, including both bacteria and other viruses, can perturb host lactate metabolism via metabolic reprogramming, potentially exacerbating the progression of DN. During bacterial infections or sepsis, pathogen-associated molecular patterns such as LPS induce a 'Warburg-like' metabolic shift in both immune and renal cells, leading to excessive lactate accumulation (58,138). This hyperlactatemic microenvironment triggers both histone and non-histone lactylation. For instance, in SAKI, lactate-driven lactylation of H3K18 and Ezrin has been shown to activate the RhoA/ROCK pathway, amplifying inflammatory responses and destabilizing the podocyte cytoskeleton (178). Similarly, other viral infections, such as influenza A, have been reported to upregulate LDH activity, where lactate-mediated signaling can suppress type I interferon production, thereby impairing host immunity and magnifying tissue damage (303). Given that patients with DN are highly susceptible to recurrent infections, these infection-induced alterations in the lactylation landscape may serve as a 'second hit' that accelerates the deterioration of renal function.

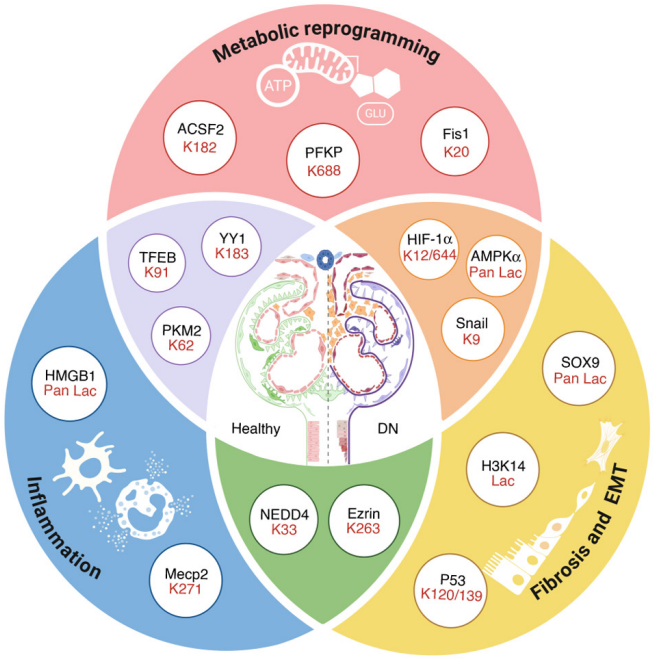

Figure 5. Possible mechanism of lactylation in diabetic nephropathy pathogenesis. The diagram illustrates the categorization of lactylated proteins based on their primary pathological impact in DN. Metabolic Reprogramming: Lactylation of ACSF2, PFKP, HIF-1α, Snail, AMPKα, Fis1, YY1, TFEB and PKM2. Inflammation: Lactylation of HMGB1, Mecp2, YY1, TFEB, PKM2, NEDD4 and Ezrin. Fibrosis and EMT: Lactylation of H3K14, P53, SOX9, NEDD4, Ezrin, HIF-1α, Snail and AMPKα. ACSF2, Acyl-CoA synthetase family member 2; PKM2, pyruvate kinase M2; HMGB1, high-mobility group box 1; YY1, yin yang 1; Fis1, fission 1; HIF-1α, hypoxia-inducible factor-1α; PFKP, platelet isoform of phosphofructokinase 1; Sox9, sex determining region Y (SRY)-related HMG-box gene 9; Mecp2, methylated CpG-binding protein 2; NEDD4, neuronally expressed developmentally downregulated 4; TFEB, transcription factor EB; AMPKα, adenosine monophosphate-activated protein kinase α; DN, diabetic nephropathy; ROS, reactive oxygen species; EMT, epithelial-mesenchymal transition. Figure created in Biorender.com.

6. Conclusion and prospects

Lactylation is associated with metabolic reprogramming, suggesting that dynamic changes in lactylation are linked to nutritional supply, oxygen levels and energy demand and can affect biological processes important in the pathogenesis of metabolic disorders. Whereas diabetes is a typical metabolic disorder, several aspects of lactylation modification, especially diabetic complications, remain unexplored. Non-histone lactylation, which is distinct from other PTMs, is still in its early stages of research but has already shown great potential in biomedical research and clinical applications. Although several DN-related non-histone proteins that can be lactylated and participate in numerous aspects of DN pathophysiology have been identified (Fig. 5), extensive research is imperative to elucidate the specific functions and regulatory mechanisms involved in DN. In addition, with rapid advances in sequencing techniques, several comprehensive databases for integrating and predicting PTM sites have been developed by collating data from high-throughput sequencing and experimental verification sources, providing comprehensive information and research tools for the study of protein PTMs. However, to the best of our knowledge, there are currently no available lactylation databases. Therefore, making full use of existing technologies, such as high-throughput sequencing, proteomics and bioinformatics tools, to systematically study lactylation is important for revealing its roles in cellular signal transduction, metabolic regulation, and disease pathogenesis. Such tools would help improve understanding of the importance of lactylation and reveal lactylation targeting as a new treatment approach for different stages of various diseases.

However, while targeting the lactate-lactylation axis holds therapeutic promise, several critical hurdles must be overcome before clinical translation. First, current evidence is predominantly derived from preclinical models; therefore, robust, large-scale clinical trials are urgently required to validate the safety and efficacy of lactylation-modulating agents specifically in patients with DN. Secondly, a major challenge in clinical studies is the lack of molecular specificity. Numerous 'writers' (for example, p300/CBP) and 'erasers' (for example, HDACs) of lactylation also regulate other post-translational modifications, such as acetylation. Consequently, systemic inhibition of these enzymes may lead to broad epigenetic off-target effects, potentially disrupting normal cellular homeostasis. Thirdly, as lactate serves as a vital energy substrate for high-demand organs such as the heart and brain, systemic interference with lactate metabolism could compromise metabolic homeostasis, leading to adverse effects such as systemic fatigue or organ dysfunction. Furthermore, dose-limiting toxicities observed in Phase I trials of MCT1 inhibitors (for example, AZD3965), underscore the necessity for developing kidney-targeted delivery systems to minimize systemic risks and improve the therapeutic index.

In conclusion, the present review summarizes lactylation and key regulatory molecules during the progression of DN, with a focus on the relationship between lactylated non-histone proteins and DN. Currently, few drugs target lactylation for the treatment of metabolic diseases, especially DN. The limited availability of potential treatments is related to the small numbers of druggable targets and drugs identified to date, as well as the incomplete understanding of lactylation or its regulatory mechanisms. Once these issues are effectively addressed, the use of lactylation as a target for DN treatment would be feasible.

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Authors' contributions

YYX was responsible for conceptualization, writing the original draft and visualization. YYX and YHX were responsible for literature collection and curation. NSW, DKG and YHX were responsible for supervision, writing, reviewing and editing. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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