Glycolytic lactylation modulates cell death decisions in diabetic kidney disease: Metabolic-epigenetic interplay between ferroptosis and autophagy in fibrotic remodeling (Review)

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Abstract. Diabetic kidney disease (DKD), a predominant contributor to end-stage renal disease, is distinguished by its intricate pathogenesis and constrained therapeutic interventions. The present review discusses the role of glycolytic flux-mediated protein lactylation, an emerging epigenetic modification, in the progression of DKD. Under conditions of hyperglycemia and hypoxia, renal cells undergo a metabolic shift towards glycolysis, resulting in the accumulation of lactate. Beyond its role as a metabolic byproduct, lactate functions as a signaling molecule that facilitates the lactylation of both histones and non-histone proteins. The present review discusses how lactylation has been implicated in key pathological mechanisms in DKD, including ferroptosis, dysregulated autophagy and fibrosis. The interplay between lactylation and other posttranslational modifications is also discussed, along with the therapeutic potential of targeting the glycolysis-lactylation axis. By highlighting this metabolic-epigenetic crosstalk, the present review proposes a conceptual framework that may inform the development of diagnostic and therapeutic strategies targeting lactylation in DKD.

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1. Introduction

According to the 11th edition of the International Diabetes Federation Diabetes Atlas, the global prevalence of diabetes is projected to increase substantially (1). Diabetic kidney disease (DKD), a microvascular complication of diabetes, occurs in ~40% of individuals with diabetes and represents a predominant cause of end-stage renal disease (2). Despite its clinical importance, the pathogenesis of DKD remains incompletely understood, with contributing factors including hyperglycaemia, inflammatory injury, metabolic dysregulation, oxidative stress and haemodynamic alterations (3-5). Current therapeutic strategies in clinical practice are limited to glycemic, lipid and blood pressure management, as no effective disease-modifying treatments are available (6). Consequently, early detection of DKD is important, as timely intervention can notably mitigate associated morbidity and mortality.

Recent advances have highlighted the pivotal role of metabolic reprogramming and epigenetic modifications in the progression of DKD (7-9). Within the hyperglycemic and hypoxic microenvironment characteristic of DKD, renal cells undergo considerable metabolic alterations, preferentially utilizing glycolysis for energy production and generating excessive lactate even under normoxic conditions,

a phenomenon analogous to the 'Warburg effect' observed in cancer cells (10-12). Once regarded merely as a metabolic byproduct of hypoxia, lactate is now recognized to perform essential physiological functions (13,14). Accumulating evidence suggests that lactate serves as a key signalling molecule, modulating gene expression and cellular functions through a novel epigenetic mechanism involving posttranslational modification (PTM) known as lactylation (9,15-17).

Emerging evidence implicates cell death pathways, particularly autophagy and ferroptosis, in the pathogenesis of DKD (18-20). Notably, lactylation has been identified as a potential regulatory mechanism in cell death processes (21). Renal fibrosis, a hallmark pathological feature of advanced kidney disease with various etiologies, carries out a pivotal role in driving the progression of DKD to renal functional decline (22,23). In addition to the well-established TGF-β signalling pathway (24,25), previous investigations have revealed substantial contributions of epigenetic modifications to the pathogenesis of renal fibrosis (26-28). However, the precise regulatory mechanisms of lactylation in diabetic kidney fibrosis, particularly its integration with dysregulated ferroptosis, autophagy, and fibrotic processes, remain poorly understood. Elucidating these mechanisms could provide key insights into the transition from metabolic dysregulation to irreversible organ damage in DKD. While individual studies have implicated lactylation in fibrotic or inflammatory pathways (29,30), a cohesive framework integrating ferroptosis and autophagy remains to be established (31).

Based on current evidence, the present review proposes the concept that lactylation is a key modulator of cell death decisions in DKD. The present review synthesizes current evidence on the complex metabolic-epigenetic interplay between ferroptosis and autophagy, to explore how their concurrent and synergistic interactions may contribute to fibrotic remodeling and DKD progression. The present review aims to propose novel targeted therapeutic strategies and foster interdisciplinary research at the nexus of metabolic and epigenetic regulation.

2. The glycolytic-lactate axis: A metabolic signature of the DKD microenvironment

Glycolysis in DKD. Local tissue oxidative stress has been identified as a key factor in the development and progression of DKD. Multiple pathways generating reactive oxygen species, including glycolysis and the polyol pathway, have been implicated in the pathogenesis of DKD (32). Glycolysis, a fundamental metabolic pathway conserved across organisms, generates pyruvate and two ATP molecules through the catabolism of glucose. This pathway represents the initial stage of glucose catabolism, comprising ten enzymatic reactions. While the majority of these reactions are reversible, the three steps catalyzed by hexokinase (HK), phosphofructokinase-1 (PFK1) and pyruvate kinase (PK) are irreversible, with the activity of these key enzymes playing a key role in regulating the overall rate of glycolytic flux (33,34). The transport of glucose across the cell membrane, facilitated by glucose transporter proteins, is a key regulatory step that governs cellular glucose uptake (35).

Within the cytoplasmic compartment, HK catalyzes the phosphorylation of glucose to glucose-6-phosphate, representing both the initial committed step and the first rate-limiting reaction in the glycolytic pathway (36). Among the four HK isoforms (HK1, HK2, HK3 and HK4), HK2 exhibits superior glycolytic promotion efficiency, with its renal activity being markedly diminished in diabetic animal models, suggesting its potential therapeutic relevance in DKD (37,38). PFK1 governs the second rate-limiting step, facilitating the conversion of fructose-6-phosphate to fructose-1,6-bisphosphate, thereby serving as a key regulatory node in glycolytic flux (39). PK, the terminal rate-limiting enzyme, catalyzes the transformation of phosphoenolpyruvate to pyruvate, influencing both glycolytic flux and energy metabolism through pyruvate fate determination (40). The mammalian PK system comprises four isoforms: Erythrocyte PK, liver PK and muscle isoforms PKM1 and PKM2 (41). Emerging evidence suggests that PKM2 is a potential biomarker for early DKD detection and a potential therapeutic target (42,43). Elevated plasma lactate levels, a glycolytic byproduct, are observed in diabetic patients (44), with lactate dehydrogenase (LDH) isoforms mediating the reversible conversion between pyruvate and lactate: LDHA catalyzes pyruvate-to-lactate conversion, and LDHB facilitates the reverse reaction (45,46). This conserved energy pathway is precisely regulated by its rate-limiting enzymes (HK, PFK1 and PKM2), with LDHA-mediated pyruvate-to-lactate conversion representing the terminal regulatory hub.

The lactate shuttle mechanism and its signaling role. Lactate, a pivotal metabolite generated through the Warburg effect, has dual functions as both an energy substrate and a metabolic byproduct (47). The lactate shuttle theory elucidates the mechanisms by which lactate operates within biological systems. This theory, which involves both intercellular and intracellular lactate shuttling, delineates the comprehensive process of lactate transmembrane transport (48). The intercellular lactate shuttle was initially proposed and systematically articulated by Brooks in 1985 (49). This concept posits that lactate, which functions as a metabolic intermediate, traverses the interstitium and vascular system, supplying carbon sources for gluconeogenesis and bio-oxidation, thereby fostering the progressive recognition of the novel biological roles of lactate (14,48). Brooks further advanced the intracellular lactate shuttle theory in 1998 (50), which posits that lactate produced in the cytosol via glycolysis or glycogenolysis can directly enter the mitochondria of the same cell for oxidation, bypassing the need for prior conversion to pyruvate in the cytosol. This theory is underpinned by studies on LDH enzyme kinetics (51,52). Brooks also introduced the mitochondrial lactate oxidation complex model, which reinforces this theoretical framework (14,48). Nevertheless, the intracellular lactate shuttle theory remains a subject of debate and warrants further in-depth investigation (53-55).

The transport of lactate across cell membranes is facilitated by the monocarboxylate transporter (MCT) protein family (56). The MCT family, classified within the solute carrier family 16 (SLC16), carries out a key role in human pathophysiology by regulating the bidirectional transport of key metabolites in fundamental metabolic processes (57). The MCT family comprises 14 proteins, each exhibiting distinct tissue distributions that reflect their specific roles in

various metabolic and physiological contexts. Among these, MCT1, MCT2 and MCT4 are widely expressed and catalyze the coupled, bidirectional transport of protons and monocarboxylates, including lactate (58). Under normal physiological conditions, the coordinated activity of MCT1, MCT2 and MCT4 collectively maintains systemic lactate homeostasis. Specifically, MCT1 and MCT2 primarily mediate lactate influx into cells, whereas MCT4 is predominantly responsible for lactate efflux (59,60).

Lactate, which is traditionally regarded as a metabolic byproduct of anaerobic glycolysis, has emerged as a multifunctional signalling molecule that carries out pivotal roles in both physiological and pathological processes (13,14,61). Mechanistically, lactate serves as a substrate for gluconeogenesis, which is mediated by LDHB, thereby contributing to energy homeostasis (62). Furthermore, lactate functions as a key regulator of the cellular redox balance by modulating the intracellular ratio of reduced to oxidized nicotinamide adenine dinucleotide ($NADH/NAD^+$), thereby stabilizing the redox state through its involvement in alternative metabolic pathways (63). Additionally, lactate accumulation has been shown to facilitate intracellular fatty acid synthesis, a key process for maintaining cellular membrane integrity, signal transduction and energy storage (14,64). Notably, lactate has been identified as a regulator of gene expression through lactylation, a novel epigenetic modification mechanism (15). These findings collectively challenge the conventional view of lactate as a metabolic waste product, instead positioning it as a central signalling molecule within the lactate shuttle framework, with the capacity to modulate gene expression networks. Notably, lactate has been demonstrated to activate TGF-β through a pH-dependent mechanism, thereby promoting fibrotic processes (65). Concurrently, lactate induces a mild reactive oxygen species burst that triggers nuclear factor erythroid 2-related factor 2 activation, enhancing antioxidant defenses and cell survival (66,67). These dual signaling roles, which are intricately linked to lactate metabolism and transport, are summarized in Fig. 1 and will be further discussed in the context of DKD pathogenesis in subsequent sections.

Dysregulated glycolysis and lactate accumulation in DKD. Metabolic reprogramming is increasingly recognized as a key feature of DKD, primarily driven by enhanced glycolysis and subsequent lactate accumulation. The sustained renal hypoxia observed during the initial stages of the pathological progression carries out a particularly key role in this process. Clinical investigations have established that elevated lactate concentrations and diminished redox potential are closely associated with this hypoxic state, a phenomenon analogous to, yet distinct from, the Warburg effect observed in malignant cells (11,68).

Substantial evidence indicates that under diabetic conditions, renal cells exhibit increased dependence on glycolysis despite sufficient oxygen availability, resulting in notable lactate production and accumulation. Srivastava *et al* (69) demonstrated that sirtuin (SIRT) 3 deficiency is associated with aberrant glycolytic activation in diabetic renal fibrosis, characterized by the upregulation of key glycolytic enzymes (HK2 and PKM2), elevated lactate levels and the activation of hypoxia-inducible factor 1α (HIF-1α), which subsequently perpetuates dysregulated glycolysis. These findings are corroborated by Liu *et al* (70) Park *et al* (71) and Jain *et al* (72). These findings collectively establish that disrupted PKM2 tetramer-dimer ratios and HIF-1α accumulation under hyperglycemic conditions promote pathological glycolytic activation and accelerate renal fibrotic progression. Consequently, these findings suggest that therapeutic targeting of aberrant glycolysis warrants further investigation as a potential strategy for DKD intervention.

HIF-1, a heterodimeric transcription factor comprising an oxygen-sensitive α-subunit and a constitutively expressed β-subunit, is ubiquitously expressed in hypoxic cellular environments (73). The pathogenesis of renal injury in DKD is driven primarily by chronic exposure to hyperglycemia and hypoxia, with HIF-1α serving as a central mediator of the adaptive hypoxic response (74). HIF-1α exerts its regulatory functions through binding to hypoxia-response elements (5'-RCGTG-3') within the promoter regions of target genes, thereby modulating critical processes, including glycolysis and angiogenesis (75). Experimental evidence has demonstrated that dysregulated HIF-1α activation in DKD promotes renal interstitial fibrosis and is associated with pathological structural alterations and proteinuria (76,77). Furthermore, HIF-1α orchestrates the downregulation of oxidative phosphorylation through hypoxia-mediated signalling pathways while simultaneously enhancing the expression of key glycolytic enzymes (HK, PFK, PKM2 and LDHA), thereby augmenting glycolytic flux (78,79). These mechanistic insights position HIF-1α as a potential therapeutic target for DKD management.

A substantial body of clinical evidence has reported an association between the activation of glycolytic pathways and the pathogenesis of DKD. In a large-scale cohort study involving 4,888 patients, Tang *et al* (80) observed a positive association between LDH levels and DKD incidence in patients with type 2 diabetes mellitus (T2DM). Furthermore, Lee *et al* (51) in both human and animal models of DKD, disease progression is mechanistically associated with LDHA-mediated lactic acidosis under hypoxic conditions, which subsequently induces fibrotic changes and mitochondrial dysfunction. Through comprehensive integration of clinical data, multiomics analyses and *in vivo*/*in vitro* experimental models, Darshi *et al* (81) reported that lactate functions not only as a biomarker for progressive renal functional decline but also as a pivotal pathogenic metabolite in DKD development. These findings are corroborated by multiple animal studies (44,82), which collectively highlight the key regulatory role of LDH activity in glycemic homeostasis and DKD progression.

The intracellular accumulation of lactate disrupts renal acid-base homeostasis, and persistent metabolic acidosis can lead to progressive renal damage and irreversible nephron injury (83). Renal tubular epithelial cells play an important role in systemic pH regulation through precise modulation of proton secretion (84). TGF-β, a well-established central mediator of fibrotic processes, is implicated in of DKD pathogenesis (85). In pulmonary fibrosis models, lactate has been reported to activate TGF-β in a pH-dependent manner, subsequently promoting fibrogenesis and upregulating HIF-1α expression, thereby establishing a positive feedback loop that enhances lactate production (65,86,87). While this specific mechanism

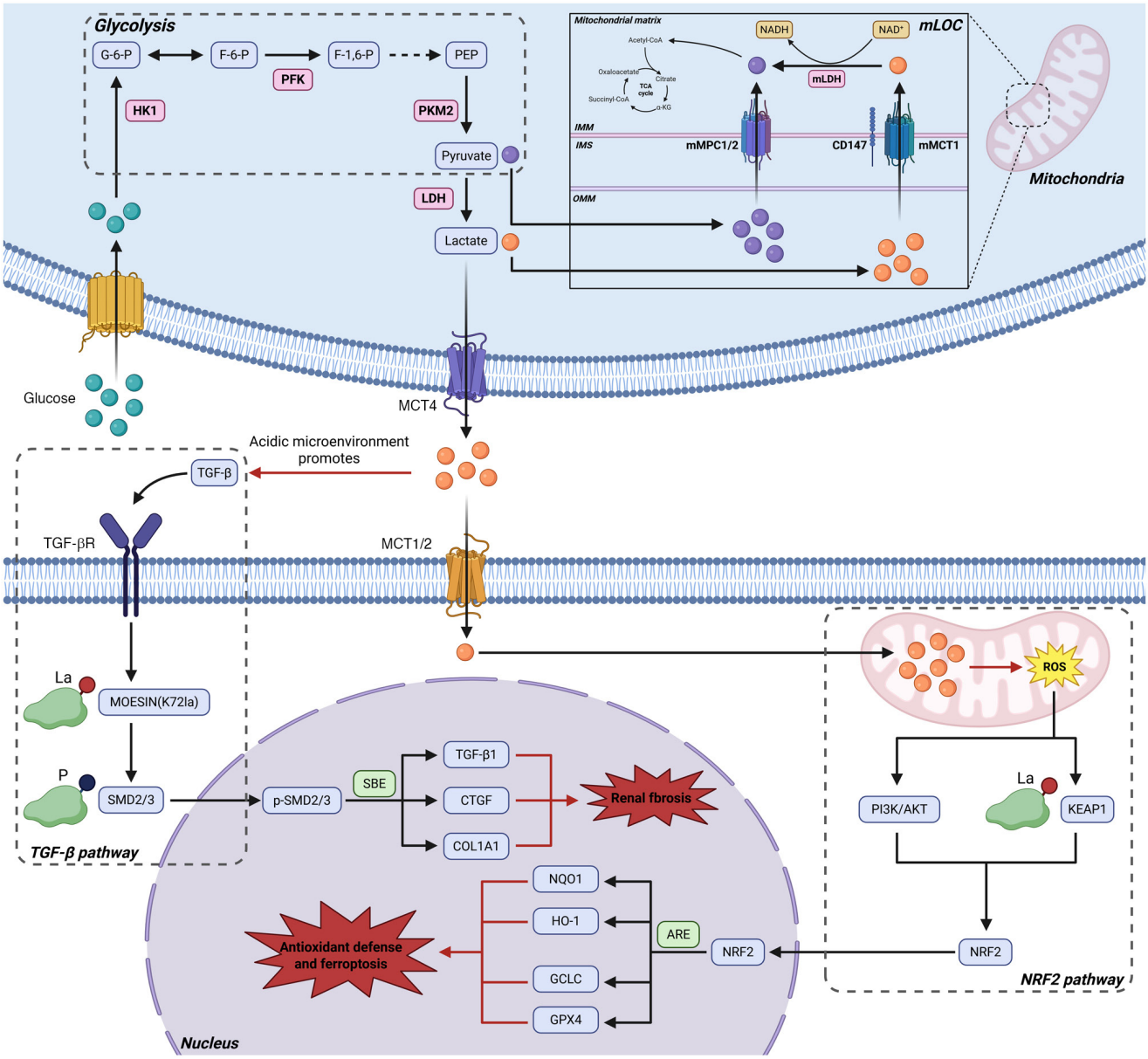

Figure 1. Lactate shuttling and its dual signaling roles in DKD. This schematic integrates intercellular lactate transport (mediated by MCT1/MCT4), mitochondrial lactate oxidation complex (mLOC)-mediated intracellular lactate metabolism, along with lactate-induced activation of pro-fibrotic TGF-β signaling via a pH-dependent mechanism and the activation of the antioxidant NRF2 response through a mild ROS burst. HK1: Hexokinase 1; G-6-P, Glucose-6-phosphate; F-6-P, Fructose-6-phosphate; PFK, Phosphofructokinase; F-1,6-P, Fructose-1,6-bisphosphate; PEP, Phosphoenolpyruvate; PKM2, Pyruvate kinase M2; LDH, Lactate dehydrogenase; mLOC, Mitochondrial lactate oxidation complex; IMM, Inner mitochondrial membrane; IMS, Intermembrane space; OMM, Outer mitochondrial membrane; NAD^+, Nicotinamide adenine dinucleotide; NADH, Nicotinamide adenine dinucleotide hydrogen; mLDH, Mitochondrial lactate dehydrogenase; TCA cycle, Tricarboxylic acid cycle; α-KG, α-ketoglutarate; mMPC1/2, Mitochondrial pyruvate carrier 1/2; CD147, Cluster of Differentiation 147; mMCT1, Mitochondrial monocarboxylate transporter 1; MCT1/2, Monocarboxylate transporter 1/2; MCT4, Monocarboxylate transporter 4; TGF-β, Transforming growth factor β; TGF-βR, Transforming growth factor β receptor; La, Lactylation; P, Phosphorylation; MOESIN, Membrane-organizing extension spike protein; SMD2/3, Mothers against decapentaplegic homolog 2/3; p-SMD2/3, Phosphorylated mothers Against decapentaplegic homolog 2/3; SBE, SMAD binding element; CTGF, Connective tissue growth factor; COL1A1, Collagen type 1 α chain; ROS, Reactive oxygen species; PI3K, Phosphoinositide 3-kinase; AKT, AKT serine/threonine kinase; KEAP1, Kelch-like ECH-associated protein 1; NRF2, Nuclear factor erythroid 2-related factor 2; ARE, Antioxidant Response Element; NQO1, NADP-quinone oxidoreductase; HO-1, Heme oxygenase 1; GCLC, Glutamate-cysteine ligase catalytic subunit; GPX4, Glutathione peroxidase 4.

has not been directly demonstrated in renal fibrosis, emerging evidence suggests a robust interplay between the lactate and TGF-β signalling pathways in the kidney: Lactate promotes renal fibrosis through activation of the transient receptor potential vanilloid 4 channel and the TGF-β/Smad2/3 signalling axis (88), with lactate accumulation exacerbating renal fibrosis in DKD animal models (77,89,90). These findings suggest that lactate and TGF-β may act synergistically to drive fibrotic processes in the kidney, although the precise molecular mechanisms warrant further experimental investigation.

The DKD microenvironment is shaped by three interconnected pathological factors: Hyperglycemia, hypoxia and acidosis. These elements form a self-amplifying feedforward cycle that drives glycolytic flux and lactate accumulation. Within the distinct metabolic landscape of DKD, lactic acid emerges as a key metabolic byproduct, serving as both a pathogenic

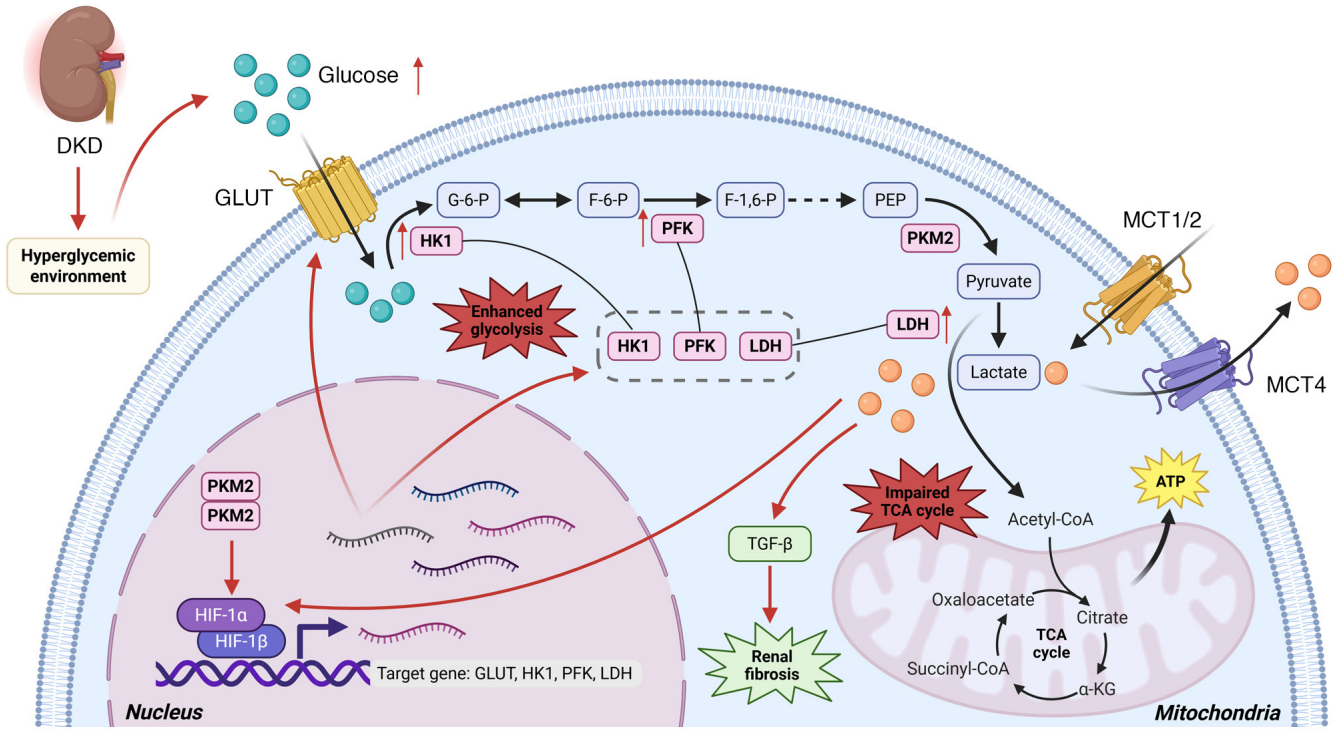

Figure 2. Hyperglycemia-induced metabolic reprogramming fosters a microenvironment conducive to lactylation in DKD. In diabetic kidneys, the synergistic effects of hyperglycemia and hypoxia induce excessive glycolysis, resulting in aberrant lactate accumulation. Under diabetic conditions, impaired lactate homeostasis leads to both intracellular and extracellular lactate accumulation. This lactate surplus triggers the activation of TGF-β signaling pathways, thereby promoting fibrotic processes, while simultaneously stabilizing HIF-1α in the nucleus, which upregulates glycolytic enzyme expression and establishes a self-perpetuating glycolytic loop. Furthermore, the diversion of pyruvate from mitochondrial oxidative phosphorylation to lactate production exacerbates energy deficits and mitochondrial dysfunction. DKD, Diabetic kidney disease; GLUT, Glucose transporter; HK1, Hexokinase 1; G-6-P, Glucose-6-phosphate; F-6-P, Fructose-6-phosphate; PFK, Phosphofructokinase; F-1,6-P, Fructose-1,6-bisphosphate; PEP, Fructose-1,6-bisphosphate; PKM2, Pyruvate kinase M2; LDH, Lactate dehydrogenase; MCT1/2, Monocarboxylate transporter 1/2; MCT4, Monocarboxylate transporter 4; HIF-1α, Hypoxia-inducible factor 1-α; HIF-1β, Hypoxia-inducible factor 1-β; ATP, Adenosine triphosphate; TGF-β, Transforming growth factor β; TCA cycle, Tricarboxylic acid cycle; α-KG, α-ketoglutarate.

signaling molecule and a precursor for lactylation. A key question is how this persistent metabolic stress translates into sustained pathological gene expression and cellular fate determination. It is plausible that lactylation may act as a regulator in this process, potentially associating enhanced glycolytic flux with stable epigenetic modifications and PTMs. Elucidating the intricate mechanisms underlying these processes may provide novel insights into the pathogenesis of DKD and inform innovative therapeutic strategies (Fig. 2) (25,91).

3. Molecular mechanisms of lactylation in DKD

In 2019, a research team led by Yingming *et al* (15) at the University of Chicago first reported a novel PTM termed lysine lactylation (Kla). This modification involves the transfer of lactyl groups to specific amino acid residues, particularly lysine, on target proteins, thereby modulating the expression of associated genes and proteins (14,47). This seminal discovery opened new avenues for lactylation research, positioning lactate as a key mediator in epigenetic regulatory pathways (92). The distinctive metabolic milieu characteristic of DKD provides an optimal biochemical environment for lactylation modifications. The next section will discuss the mechanistic pathways through which metabolic stress in DKD may be linked to functional epigenetic and post-translational signaling networks.

Enzymatic and non-enzymatic lactylation modifications. Lactylation modifications can be classified into two distinct mechanisms: Enzymatic and non-enzymatic processes. While lactate serves as the primary substrate in both pathways, its stereochemical configuration differs between the two mechanisms. Specifically, L-lactate is utilized in enzymatic lactylation, whereas D-lactate is implicated in nonenzymatic lactylation (93).

Enzymatic lactylation modification. Enzymatic lactylation constitutes a reversible, enzyme-regulated dynamic process, which is orchestrated by three principal functional components: Writers, erasers and readers (94). The dysregulation of this intricate regulatory system, particularly within the distinct metabolic milieu of DKD, is postulated to constitute a fundamental mechanistic pathway underlying the pathogenesis of pathological hyperlactylation.

Writers. The enzymatic addition of lactyl groups to specific protein residues is mediated by a class of enzymes referred to as 'writers' (95). Current evidence suggests that this catalytic activity may occur through at least two distinct biochemical pathways: The L-lactyl-CoA pathway and the lactate-AMP pathway (96). DKD microenvironment displays features that may favor the activation of these pathways. Chronic hyperglycemic conditions coupled with hypoxia can increase lactate

production, thereby providing a substantial substrate pool for these enzymatic reactions.

In the L-lactyl-CoA pathway, lactate is enzymatically converted into the high-energy donor lactyl-CoA by acetyl-CoA synthetase 2 (ACSS2) and GTP-specific succinyl-CoA synthetase (GTPSCS) within the nucleus, which serve as substrates for subsequent lactylation modifications. Zhu *et al* (97) reported that ACSS2 facilitates histone lactylation, tumor growth and immune evasion through its interaction with lysine acetyltransferase 2A (KAT2A), thereby identifying ACSS2 and KAT2A as previously unrecognized lactyl-CoA synthetases and lactyltransferases, respectively. In a separate study, Liu *et al* (98) showed that GTPSCS translocates to the nucleus and cooperates with p300 to increase histone lactylation without concurrent succinylation, establishing GTPSCS as the first enzyme that catalyzes lactyl-CoA synthesis for epigenetic histone lactylation. Collectively, these findings suggest that both ACSS2 and GTPSCS may functional 'lactyl-CoA synthetases' in the conversion of lactate to lactyl-CoA.

While the complete repertoire of lactylation writers has not been fully elucidated, current evidence points to functional overlap with enzyme families that mediate other PTMs, including histone acetyltransferases (HATs), such as CBP/p300, GCN5, KAT5, KAT7 (HBO1) and KAT8, as well as other modifiers, such as α-tubulin acetyltransferase 1 and histone deacetylase (HDAC) 6 (99). CBP and p300, ubiquitously expressed paralogues essential for animal development, function as transcriptional coactivators for numerous transcription factors, including nuclear receptors (100). These proteins contain multiple core domains, such as the HAT domain, bromodomain and ZZ-type zinc finger domain, and regions rich in cysteine and histidine residues [encompassing the plant homeodomain and really interesting new gene (RING) domains], which facilitate acyl group transfer to diverse substrates (101). Notably, p300 was the first protein identified to exhibit lactylation writer activity (15). CBP/p300 mediates the L-lactyl-CoA pathway by utilizing its bromodomain to recognize lactyl-CoA and catalyze the transfer of the lactyl group to lysine residues on target proteins, thereby influencing chromatin remodelling and the transcription of pro-oncogenic genes. This process requires lactyl-CoA as a high-energy donor substrate rather than free lactate directly (102,103). Notably, lactyl-CoA originates from lactate, which is itself produced from pyruvate through LDH catalysis, linking this pathway and glycolytic flux. The activation of CBP/p300 has been associated with reactive oxygen species production, inflammation and extracellular matrix (ECM) protein synthesis in DKD. The hyperglycemic and hypoxic conditions characteristic of DKD further amplify lactate generation, potentially intensifying these pathological processes (104,105). Elevated reactive oxygen species levels and inflammation are known contributors to renal fibrosis (106). To the best of our knowledge, while no studies have explicitly demonstrated CBP/p300-mediated lactylation in DKD, based on parallels with acetylations, it is plausible that this process is likely to occur under DKD-specific conditions. If confirmed, this would position CBP/p300 as a promising therapeutic target for DKD intervention.

The lactate-AMP pathway involves aminoacyl-tRNA synthetases 1 and 2 (AARS1/2) in lactylation. AARS1 is predominantly localized in the cytoplasm, whereas AARS2 is primarily located in the mitochondria. These enzymes employ an ATP-dependent mechanism to directly convert lactate and ATP into a lactyl-AMP intermediate, which subsequently transfers the lactyl group to lysine residues on substrate proteins, resulting in lactylation (107-109). In human embryonic kidney cells, the knockdown of AARS1 expression suppresses lactylation, whereas its overexpression increases lactylation levels (107,110), suggesting that AARS enzymes may function as lactyltransferases in this process. This regulatory mechanism may also be operative in the kidney, potentially offering new insights for DKD prevention and treatment. The discovery of the lactate-AMP pathway, in contrast to the first pathway, points to a potentially more direct cellular response to intracellular lactate levels. In the context of DKD, renal cells experience chronic lactate overload, which may induce persistent activation of AARS1/2, resulting in extensive lactylation of both cytoplasmic and mitochondrial proteins. This process could directly disrupt cellular functions, thereby exacerbating the mitochondrial dysfunction and metabolic inflexibility characteristic of DKD. Further studies investigating whether the expression or activity of AARS1/2 is modulated in renal cells could provide valuable insights and potentially identify novel therapeutic targets.

Erasers. The elimination of lactylation modifications plays a pivotal role in dynamic cellular signalling and is regulated by specific enzymatic erasers (95). To date, two primary classes of erasers have been reported in lactylation regulation: Class I HDAC1-3 and SIRT deacetylases 1-3 (111,112). These erasers are considered to function in opposition to lactylation writers to maintain metabolic homeostasis. It has been hypothesized that in DKD, dysregulation of epigenetic modifications, characterized by diminished eraser activity in conjunction with heightened writer function, may contribute to a pathological state of lactylation.

In vitro studies have demonstrated that class I HDAC1-3 considerably reduce lysine lactylation levels on histones, with HDAC1 and HDAC3 exhibiting distinct site-specific activity in histone delactylation (113-115). Additionally, Du *et al* (116) established through overexpression and knockout experiments that SIRT1 and SIRT3 serve as potent erasers in mammalian cells, modulating lactylation across both histone and non-histone protein substrates. Notably, SIRT2 has been shown to carry out a key role in non-histone protein delactylation, specifically by removing lactylation modifications from METTL16, thereby influencing cuproptosis regulation (117).

The activity of these erasers appears to be context dependent and potentially influenced by factors such as expression levels, PTMs, subcellular localization and the availability of cofactors and coenzymes (118). It remains unclear whether such regulatory mechanisms operate within the metabolically dysregulated environment of DKD to prevent excessive lactylation accumulation. HDACs and SIRTs have been the subject of extensive investigation in the context of renal pathology. Current evidence implicates HDACs in DKD pathogenesis, particularly through their association with pathological processes, including fibrosis, oxidative stress and inflammation (119). Daude *et al* (120) demonstrated that reduced HDAC2 activity attenuates renal injury in diabetic model rats. While HDAC inhibitors have demonstrated some efficacy in

improving renal function in DKD animal models, clinical trials have identified notable toxic and off-target effects, highlighting the need for the development of agents with improved safety profiles (121). Among the SIRT family members, SIRT1 is predominantly expressed in the nucleus and widely expressed in renal tubular cells and podocytes, SIRT2 is uniquely expressed in the cytoplasm and SIRT3, which is localized to the mitochondrial matrix, serves as a key regulator of organelle acetylation (122,123). SIRT1 is the most extensively studied member of this family, with the SIRT family collectively participating in diverse biological processes, including the oxidative stress response, cell cycle regulation, metabolism and apoptosis (124). Current research indicates that SIRT1-3 contribute to renal homeostasis maintenance, with the upregulation of SIRT1, SIRT2 and SIRT3 demonstrating protective effects against renal injury and fibrosis in DKD (125-128). However, the potential role of HDAC1-3 and SIRT1-3 in lactylation erasure within the context of DKD remains unexplored. If their delactylase activity is preserved in the DKD microenvironment, this could imply novel functional roles for these enzymes and may advance the understanding of DKD pathophysiology.

Readers. The biological consequences of lactylation are mediated by specialized 'reader' proteins that specifically recognize and interpret lactylated amino acid residues, subsequently recruiting downstream effector complexes to modulate gene expression or protein function (96). Although research on enzyme-catalyzed lactylation readers is still in its nascent stages, considerable progress has been made. For instance, Hu *et al* (129) identified Brg1 as a reader of H3K18la, demonstrating its accumulation at promoter regions of genes associated with pluripotency and epithelial junctions, thereby playing a pivotal role in induced pluripotent stem cell reprogramming. Additionally, recent studies have revealed that TRIM33β functions as a reader of H3K18la, regulating the TGF-β signalling pathway (130), whereas DPF2, a reader of H3K14la, is important for chromatin remodelling and gene expression modulation in cancer (131).

In the context of DKD, it remains an open question whether specific epigenetic readers are recruited by lactylation to drive fibrotic progression. Notably, the reader protein TRIM33β, which recognizes H3K18la and modulates TGF-β signaling, represents a promising candidate. Within the unique microenvironment of DKD, lactate-induced H3K18la could facilitate the recruitment of TRIM33β to the promoters of profibrotic genes, potentially activating their transcriptional. If confirmed, this would establish a mechanistic association between glycolytic flux and fibrotic pathogenesis. The identification and functional characterization of such DKD-specific epigenetic readers are key to elucidating the molecular mechanisms by which lactylation signaling contributes to disease progression.

In summary, enzymatic lactylation serves as an active regulatory interface that associates metabolic processes with cellular functions. In DKD, the accumulation of excess substrates (lactic acid) and activated writers, coupled with impaired erasers, leads to the saturation of cellular environments with lactylation markers. These markers are subsequently recognized by specific reader proteins, which initiate downstream signaling cascades promoting fibrosis and programmed cell death. The dysregulation of these three key molecular components suggests a shift of lactylation from a dynamic regulatory mechanism toward a contributor to pathology, thereby influencing cellular fate decisions and fibrotic remodeling in DKD.

Non-enzymatic lactylation modification. Non-enzymatic lactylation, which is distinct from its enzymatic counterpart, occurs independently of enzymatic catalysis in metabolic regulation. This process is predominantly mediated by D-lactate, which undergoes lactylation through a nucleophilic substitution reaction between S,D-lactoylglutathione (LGSH) and lysine residues (132). LGSH is synthesized by glyoxalase 1 (GLO1), which catalyzes the reaction between methylglyoxal (MGO), a byproduct of glycolysis and glutathione (GSH) (133). MGO, a well-characterized metabolic byproduct of glycolysis, is generated from glycolytic intermediates such as dihydroxyacetone phosphate and glyceraldehyde 3-phosphate (134). Under physiological conditions, MGO is detoxified by the GLO system, which comprises GLO1 and GLO2. GLO1 converts MGO into stable LGSH, whereas GLO2 hydrolyses LGSH to yield D-lactate and regenerate GSH (135).

In DKD, the endogenous protective mechanisms may become compromised. Chronic hyperglycemia markedly elevates the generation of glycolytic intermediates, resulting in the pathological accumulation of MGO. MGO serves as a key precursor for the formation of advanced glycation end products, which are strongly implicated in the pathogenesis and progression of DKD (136,137). A causal relationship between GLO1 and DKD has been established, particularly in tissues such as the skin and salivary glands, raising the possibility of its utility as a DKD biomarker (138). Consequently, impaired MGO clearance resulting from glycolytic overflow or dysfunctional GLO activity promotes the diversion of MGO into the non-enzymatic lactylation pathway, leading to the production of D-lactate and LGSH.

Non-enzymatic lactylation predominantly targets lysine residues, whose reactive ε-amino groups exhibit increased susceptibility to modification under conditions of metabolic stress. Elevated lactate concentrations, particularly within the acidic pH environment associated with DKD-induced metabolic acidosis, can facilitate the protonation of carboxyl groups of lactate. This protonation markedly enhances the reactivity of lactate, enabling a direct nucleophilic attack on the ε-amino groups of lysine to form stable amide bonds, thereby generating Kla. This 'mass effect'-driven mechanism differs from the tightly regulated process of enzymatic lactylation and has been proposed as a potential indicator of metabolic dysregulation (93,135,139).

In summary, the DKD microenvironment may be subject to both enzymatic and non-enzymatic lactylation modifications, which may transition from regulatory mechanisms to contributors to pathogenesis. These modification pathways may function in a coordinated manner: Non-enzymatic lactylation induces widespread, stochastic protein damage, establishing the foundational pathological conditions. Within this framework, signal-driven enzymatic lactylation may contribute to specific pathological programs, including the transcriptional activation of fibrotic genes and the direct suppression of autophagy and ferroptosis. This synergistic interplay facilitates the efficient

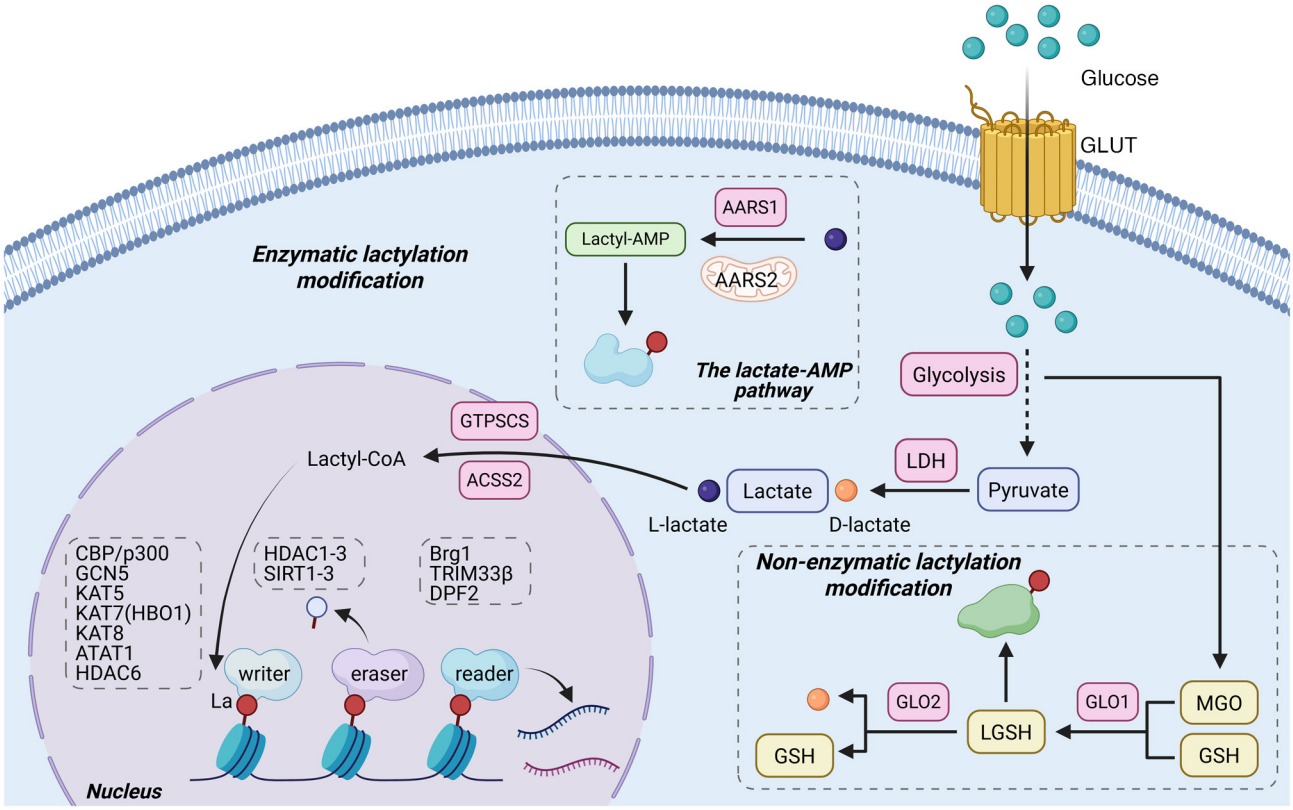

Figure 3. Molecular mechanisms of lactylation, enzymatic and non-enzymatic pathways. Lysine lactylation is mediated through two distinct biochemical pathways, the enzymatic and non-enzymatic mechanisms. The enzymatic pathway is characterized by a highly regulated process involving three functional protein classes, writers catalyze the addition of lactate groups, erasers facilitate their removal and readers recognize the modification to propagate downstream signaling. By contrast, the non-enzymatic pathway directly modifies lysine residues through D-lactate derived from the glycolytic MGO pathway in a stochastic, concentration-dependent manner, independent of enzymatic catalysis. This non-enzymatic modification serves as a molecular indicator of severe metabolic dysregulation. GLUT, Glucose transporter; AARS1, Alanyl-tRNA synthetase 1; AARS2, Alanyl-tRNA synthetase 2; Lactyl-AMP, Lactoyl adenosine monophosphate; LDH, Lactate dehydrogenase; GTPSCS, GTP-specific succinyl-coA synthetase; ACSS2, Acyl-coA synthetase short-chain family member 2; Lactyle-CoA, Lactyl-coenzyme A; La, Lactylation; CBP, CREB-binding protein; p300, E1A binding protein p300; GCN5, General control nonderepressible 5; KAT5, Lysine acetyltransferase 5; KAT7 (HBO1), Lysine acetyltransferase 7; KAT8, Lysine acetyltransferase 8; ATAT1, α-tubulin N-acetyltransferase 1; HDAC6, Histone deacetylase 6; HDAC1-3, Histone deacetylase 1-3; SIRT1-3, Sirtuin 1-3; Brg1, Brahma-related gene 1; TRIM33β, Tripartite motif-containing protein 33 β; DRF2, D4-related factor 2; LGSH, Lactoylglutathione; GLO2, Glyoxalase 2; GSH, Glutathione; GLO1, Glyoxalase 1; MGO, Methylglyoxal.

conversion of high-throughput glycolytic states into the precise execution of cellular damage and death pathways, potentially contributing to fibrotic remodeling (Fig. 3).

Histone and non-histone lactylation: Functions and implications. Lactylation modifications can be classified into two distinct categories on the basis of their protein targets: Histone lactylation and non-histone lactylation. Histone lactylation predominantly involves the modification of lysine residues on histones by L-lactate, whereas non-histone lactylation primarily targets glycolytic enzymes through D-lactate, thereby regulating glycolysis via a negative feedback mechanism (47). Although these two forms of lactylation operate through distinct mechanisms, they may together link metabolic signals into functional outputs, potentially playing synergistic roles in the pathogenesis of DKD.

Histone lactylation. Histones, as the most extensively characterized and earliest identified lactylated proteins, have served as prototypical models for investigating the functional mechanisms of Kla. The process of histone lactylation entails the covalent attachment of a lactyl group to lysine residues, which directly modulates chromatin architecture and transcriptional regulation (12,15,140). This PTM has been proposed as a molecular link between aberrant lactate accumulation in DKD and the transcriptional activation of genes implicated in fibrotic processes and oxidative stress responses.

In DKD, renal fibrosis is primarily driven by the activation of myofibroblasts and excessive accumulation of ECM, processes associated with various fibrotic and growth factors (141). Metabolic dysregulation and chronic hyperglycemia-induced inflammatory damage are intricately linked, operating both independently and synergistically to exacerbate renal injury (142,143). Emerging evidence suggests that histone lactylation is an epigenetic mechanism that links hyperlactate signaling in DKD to sustained activation of fibrotic and inflammatory gene programs. It is plausible that in renal cells, hyperglycemia-induced glycolytic flux and subsequent lactate accumulation may lead to histone lactylation, which localizes to the promoters of key pathogenic genes, potentially contributing to the initiation and persistence of fibrotic states.

Consistent with this hypothesis, experimental findings have identified specific histone lactylation sites that may be implicated in DKD. Recent investigations have identified multiple

lactylation sites on histones H3 and H4, specifically at H3K9, H3K14, H3K18, H3K27, H3K56, H4K8, and H4K12 (140,144). Notably, lactylation at H3K14 and H3K18 has been implicated in the pathological progression of DKD. Zhang *et al* (7) demonstrated that H3K14la promotes epithelial-mesenchymal transition (EMT) by activating the fibrotic transcription factor KLF5 in renal tubular epithelial cells. Similarly, Hu *et al* (142) reported that H3K18la facilitates renal fibrosis and endothelial-mesenchymal transition (EndoMT) by modulating *insulin-like growth factor-binding protein 5* (*IGFBP5*). Importantly, H3K18la activates the NLRP3 inflammasome, establishing a direct molecular association between lactate accumulation, chronic inflammation and tissue remodeling in DKD (142). These findings suggest that histone lactylation may represent a regulatory mechanism contributing to fibrosis in DKD. While the roles of other lactylation sites in DKD have not been fully investigated, their potential involvement in the diabetic milieu through alternative PTMs (Table I) (7,145-159) raises the possibility of complex epigenetic crosstalk.

Histone lactylation has been proposed as an epigenetic mechanism that may link glycolytic flux to sustained pathological gene activation in DKD. However, several key questions remain unresolved. First, the functional roles of other histone lactylation sites in DKD require further investigation, as they could be involved in additional fibrotic and inflammatory gene programs. Second, the existence of cell-specific lactylation patterns remains unclear. Finally, the interplay between histone lactylation and other PTMs in reshaping chromatin landscapes merits further study to understand its potential role in disease progression. Determining whether histone lactylation plays a primary role or amplifies pre-existing fibrotic signals will be important for understanding its role in DKD pathogenesis.

Non-histone lactylation. Protein lactylation, which extends beyond histones, involves a diverse array of non-histone proteins, including metabolic enzymes, transcription factors, and signalling proteins. This post-translational modification exerts rapid and direct regulatory effects on protein activity, stability and molecular interactions, thereby facilitating precise and dynamic cellular responses to metabolic fluctuations (140,160,161). In the context of DKD, non-histone protein lactylation has been implicated in cellular injury, directly disrupting fundamental cellular processes and contributing to disease pathogenesis.

Emerging evidence underscores the pivotal role of non-histone lactylation in the pathogenesis of DKD. A key mechanism involves the suppression of protective autophagy, wherein lactylation of lysine 970 in Lysyl-tRNA synthetase 1 (LARS1) activates the mTORC1 signaling pathway, thereby inhibiting autophagy and contributing to podocyte injury (162). Furthermore, non-histone lactylation exacerbates metabolic dysregulation and oxidative stress. Specifically, lactylation of lysine 182 in acyl-CoA synthetase family member 2 compromises its enzymatic activity, aggravating mitochondrial dysfunction and impairing HK-2 cell viability under hyperglycemic conditions (163). Additionally, lactylation has been associated with apoptotic pathways, as demonstrated by the lactylation of lysine 206 in E3 ubiquitin ligase TRIM65. This modification attenuates its catalytic activity, resulting in the accumulation of ferroportin 2 (IREB2) and phosphodiesterase 4, which subsequently induces ferroptosis in renal tubular epithelial cells and exacerbates aberrant glycolysis (164). Collectively, these findings suggest that non-histone lactylation may represent a regulatory mechanism that can influence the pathological and physiological functions of key metabolic and signaling nodes in DKD.

Emerging evidence indicates that non-histone lactylation modifications may be involved in modulating the activity of key glycolytic enzymes, with potential implications for disease pathogenesis. Specifically, mannose has been demonstrated to inhibit lactylation at lysine 433 of the PKM2 protein while facilitating its nuclear translocation, resulting in the suppression of both lactate production and glycolytic flux (165). In the context of DKD, lactylation of PKM2 may establish a positive feedback mechanism that amplifies glycolytic activity and lactate accumulation, thereby exacerbating metabolic dysregulation. Furthermore, lactylation modifications of key signaling molecules, including HIF-1α and mTOR, have been shown to enhance their stability and functional activity, contributing to the reinforcement of pathological conditions (162,166).

In summary, non-histone lactylation has emerged as an important effector in mediating metabolic injury in DKD. Distinct from the regulatory role of histone lactylation, which orchestrates pathological processes through epigenetic modulation of gene expression, non-histone lactylation exerts direct functional impacts on cellular mechanisms. Specifically, it has been associated with cellular dysfunction through effects on autophagy, mitochondrial function and ferroptosis pathways. These mechanisms, in conjunction with fibrotic reprogramming, may collectively contribute to the progressive renal tissue damage observed in advanced stages of DKD.

Interplay between lactylation and other PTMs. PTMs form a complex and interconnected regulatory network that contributes to the regulation of cellular metabolism and function. Lactylation, a recently identified PTM (29,167,168), is an integral component of this network and interacts with other PTMs through mechanisms of competition, cooperation and functional collaboration, with potential implications for cell fate (93,99). Within the unique pathological microenvironment of DKD, aberrant lactate accumulation may disrupt the homeostatic balance among PTMs, leading to a comprehensive 'reprogramming' of the modification landscape. This molecular reprogramming has been associated with disease-specific alterations in both gene expression profiles and protein functional states, potentially influencing key cellular fate decisions.

Competitive interactions can occur when multiple PTMs target identical amino acid residues. Lactylation specifically targets the ε-amino group of lysine (Kla), but this site can also be modified by other modifications, including acetylation (169), crotonylation (170), phosphoglycerolation (171) and ubiquitination (172). The interplay between lactylation and acetylation has been implicated in the pathogenesis of DKD. HDAC1-3, which function as 'erasers' of lactylation, demonstrate dual enzymatic activities as both de-lactylases and de-acetylases (173). Their dysregulation in DKD may create a molecular milieu that favors PTM imbalances. Pyruvate, a key metabolic intermediate, undergoes conversion into either acetyl-CoA or lactyl-CoA through specific acyltransferases,

Table I. Histone lactylation in DKD and other histone modifications in the context of DM.

Histone site	Lactylation in DKD?	Known mechanism in DKD (via lactylation)	Known mechanism in DM (via other PTMs)	(Refs.)
H3K9	No	Not yet reported	Sodium butyrate activates p300, increases H3K9bu, suppresses expression of renal injury-related genes, and ameliorates nephropathy.	(145)
			In response to hyperglycaemia, TGF-β1 induces the nuclear redistribution of the repressive histone mark H3K9me3, promoting fibroblast activation and thereby contributing to DKD.	(146)
			ACSS2 promotes podocyte injury in diabetic kidney disease by catalysing H3K9ac, which activates the Raptor/mTORC1 pathway and subsequently suppresses podocyte autophagy.	(147)
			Exendin-4 alleviates diabetic kidney disease by activating SIRT1, which reduces H3K9ac levels at the *Txnip* promoter and thereby downregulates *Txnip* expression.	(148)
			SIRT2 downregulation exacerbates oxidative stress and inflammation in diabetic osteoarthritis by compromising H3K9 deacetylation.	(149)
H3K14	Yes	H3K14la activates KLF5 expression, promoting EMT in renal tubular cells.	Downregulation of SIRT2 exacerbates diabetic osteoarthritis by promoting H3K14 deacetylation, which in turn amplifies oxidative stress and inflammatory responses.	(7,149)
H3K18	Yes	H3K18la facilitates *IGFBP5*-mediated renal fibrosis and EndoMT. Also implicated in NLRP3 inflammasome activation.	The elevation of H3K18cr represents a key mechanism through which NaCr mediates its renoprotective effects.	(141,150)
H3K27	No	Not yet reported	EZH2 and JMJD3 cooperatively drive fibroblast activation and renal fibrosis in DKD via the coordinated regulation of H3K27me3 and pro-fibrotic signalling.	(146)
			Advanced glycation end products AGEs may alter the H3K27me3 landscape in podocytes, contributing to DKD progression.	(151)
H3K56	No	Not yet reported	SIRT6-mediated β-catenin signalling deacetylates it, thereby preventing renal fibrosis.	(152)
			In diabetic retinopathy, the hyperglycaemic milieu induces SIRT6 downregulation, which relieves the repression of HIF-1α and is accompanied by increased H3K56ac, thereby driving the upregulation of *VEGF* gene expression.	(153)
			Deficiency of SIRT6 in pancreatic β-cells elevates H3K56ac, contributing to glucose intolerance and impaired glucose-stimulated insulin secretion in mice.	(154)

Table I. Continued.

Histone site	Lactylation in DKD?	Known mechanism in DKD (via lactylation)	Known mechanism in DM (via other PTMs)	(Refs.)
			In diabetic OA, hyperglycaemia suppresses SIRT2 and increases H3K56ac, contributing to diabetic oxidative stress and inflammatory responses.	(149)
			Extensive H3K56 acetylation in human adipocytes is associated with the KEGG T2DM pathway.	(155)
			H3K56 deacetylation, mediated by SIRT1, is involved in oxidative stress processes in diabetes.	(156)
H4K8	No	Not yet reported	Activation of NF-κB and TGF-β signalling, along with increased PCAF/CBP expression, elevates H4K8ac levels, upregulating ANP, BNP and NEP expression in diabetic hearts and kidneys.	(157)
			In diabetic cardiomyopathy, pharmacological reversal of H4K8ac helps alleviate the inflammatory (NF-κB/MCP-1), pro-fibrotic (TGF-β/Smad7), and apoptotic (PARP/Caspase-3) cascades. pro-fibrotic (TGF-β/Smad7), and apoptotic (PARP/Caspase-3) cascades.	(158)
H4K12	No	Not yet reported	In diabetic mice, the upregulation of HDAC2 and HDAC3 leads to reduced levels of histone H4K12ac, which consequently suppresses the expression of memory-associated proteins (BDNF, SYP, PSD-95) and leads to cognitive dysfunction.	(159)

DKD, Diabetic kidney disease; DM, Diabetes mellitus; PTMs, Post-translational modifications; H3K9, Histone H3 lysine 9; H3K9bu, Histone H3 lysine 9 butyrylation; TGF-β1, Transforming growth factor β 1; H3K9me3, Histone H3 lysine 9 trimethylation; ACSS2, Acyl-CoA synthetase short-chain family member 2; H3K9ac, Histone H3 lysine 9 acetylation; mTORC1, Mechanistic target of rapamycin complex 1; SIRT1, Sirtuin 1; *Txnip*, Thioredoxin-interacting protein; SIRT2, Sirtuin 2; H3K14, Histone H3 lysine 14; H3K14la, Histone H3 lysine 14 lactylation; KLF5, Krüppel-like factor 5; EMT, Epithelial-mesenchymal transition; H3K18, Histone H3 lysine 18; H3K18la, Histone H3 lysine 18 lactylation; *IGFBP5*, Insulin-like growth factor-binding protein 5; EndoMT, Endothelial-mesenchymal transition; NLRP3, NLR family pyrin domain containing 3; H3K18cr, Histone H3 lysine 18 crotonylation; H3K27, Histone H3 lysine 27; EZH2, Enhancer of zeste homolog 2; JMJD3, Jumonji domain-containing protein 3; H3K27me3, Histone H3 lysine 27 trimethylation; AGEs, Advanced glycation end products; H3K56, Histone H3 lysine 56; SIRT6, Sirtuin 6; HIF-1α, Hypoxia-inducible factor 1-α; H3K56ac, Histone H3 lysine 56 acetylation; *VEGF*, Vascular endothelial growth factor; KEGG, Kyoto Encyclopedia of Genes and Genomes; T2DM, Type 2 diabetes mellitus; H4K8, Histone H4 lysine 8; NF-κB, Nuclear factor kappa-B; PCAF, p300/CBP-associated factor; CBP, CREB-binding protein; H4K8ac, Histone H4 lysine 8 acetylation; ANP, Atrial natriuretic peptide; BNP, B-type natriuretic peptide; NEP, Neprilysin; MCP-1, Monocyte chemoattractant protein-1; Smad7, Mothers against decapentaplegic homolog 7; PARP, Poly(ADP-ribose) polymerase; H4K12, Histone H4 lysine 12; HDAC2, Histone deacetylase 2; HDAC3, Histone deacetylase 3; H4K12ac, Histone H4 lysine 12 acetylation; BDNF, Brain-derived neurotrophic factor; SYP, Synaptophysin; PSD-95, Postsynaptic density protein 95.

mediated by enzymatic or non-enzymatic reactions (174). While acetyl-CoA serves as the acyl donor for acetylation, lactyl-CoA functions as the substrate for lactylation. In the hyperlactatemic environment characteristic of DKD, the increased lactyl-CoA to acetyl-CoA ratio may function as a molecular switch, preferentially promoting lactylation over acetylation. This metabolic shift potentially redirects transcriptional regulation from homeostatic maintenance toward the activation of pro-inflammatory and pro-fibrotic gene networks, thereby influencing cellular fate decisions between pathological activation and programmed cell death.

Dynamic interactions between cooperation and synergy are considered to be important in cellular processes (175-177). Proteins exhibit collaborative behavior through PTMs,

wherein distinct modification mechanisms may synergistically influence functional outcomes. Phosphorylation represents a prominent example of such cooperative interactions. In the context of DKD, TGF-β-mediated Smad phosphorylation constitutes the central mechanism underlying fibrotic progression (178). Cappelli *et al* (179) elucidated that phosphorylated Smad2/3 recruits the transcriptional coactivator p300, establishing a molecular platform for histone lactylation at TGF-β target genes, thereby potentiating their transcriptional activation. This cooperative interplay may initiate a signaling cascade that exacerbates fibrotic programming. Moreover, functional synergy can occur when multiple PTMs collectively modulate protein stability. As the principal regulator of hypoxia response in DKD, HIF-1α lactylation has been demonstrated to impede Von Hippel-Lindau recognition, consequently inhibiting ubiquitin-mediated proteasomal degradation and augmenting HIF-1α stability (166). This mechanism could contribute to a robust positive feedback loop: HIF-1α can promote glycolytic flux and lactate production, which in turn stabilizes HIF-1α through lactylation, further amplifying glycolytic activity and creating a self-perpetuating cycle that contributes to metabolic dysregulation and its associated pathological consequences (65,78,79).

In conclusion, the interplay between lactylation and other PTMs is not only of biochemical interest but also represents a regulatory mechanism that may be dysregulated in DKD. The competition for lysine residues can reshape the epigenetic landscape, while the cooperation with phosphorylation could enhance pro-fibrotic signaling pathways. Additionally, the synergistic stabilization of pivotal factors such as HIF-1α can entrench cells in a pathological metabolic state. This complex regulatory network may help explain how the initial metabolic perturbations induced by hyperglycemia and hypoxia could lead to a robust and coordinated pathological program, linking the intricate interplay among ferroptosis, autophagy and fibrosis that underlies the progression of DKD. Future investigations should be aimed at delineating these interaction networks within relevant renal cell populations to help identify key therapeutic targets for intervention.

Comparative insights: Lactylation in cancer vs. DKD. Lactylation, a previously identified PTM (14,15), was initially discovered in oncology research, revealing how the Warburg effect drives tumor progression and immune evasion through lactate. In both cancer and DKD, lactate accumulation can drive histone and non-histone lactylation; however, due to differences in the microenvironment and cellular lineages, the functional outcomes and regulatory contexts differ substantially. In tumors, lactylation is generally associated with promoting cell proliferation and immune suppression (180). In contrast, in DKD, lactylation is primarily linked to fibrotic remodeling, metabolic dysfunction, and the modulation of cell death pathways (181,182).

A potential distinction may lie in the concept of the 'lactate clock', referring to the duration and intensity of lactate exposure. In cancer, intermittent hypoxia and lactate shuttling between glycolytic and oxidative zones contribute to a dynamically fluctuating lactylation landscape, which may facilitate tumor cell adaptation to microenvironmental changes. In comparison, DKD is characterized by persistent hyperglycemia and chronic hypoxia, leading to sustained lactate overload. This results in a relatively static and pathologically fixed lactylation state, which might explain why lactylation in DKD is more frequently associated with irreversible tissue damage and fibrosis rather than adaptive growth (182,183).

From a molecular perspective, common 'writers' and 'erasers' appear to exert context-dependent regulatory roles in different disease settings. For example, p300/CBP, as canonical lactylation writers, primarily promote oncogene expression in cancer (184), whereas in DKD, they amplify pro-fibrotic and pro-inflammatory transcriptional programs (181). Specifically, p300-mediated H4K12 lactylation has been shown to suppress ferroptosis by upregulating GCLC in colorectal cancer stem cells, thereby promoting chemotherapy resistance (185). In the context of DKD, however, the same p300/H4K12la axis has been implicated in renal injury through the regulation of AKR1B1 (30). Similarly, HDAC1-3 and SIRT1-3 function as lactylation erasers in both diseases, yet their regulatory targets and biological effects appear distinct: Inhibition of these erasers is often associated with suppressed tumor growth in cancer (180), whereas their activation in DKD has been associated with renoprotective effects through the restoration of autophagic flux and attenuation of fibrosis (181).

These comparative observations suggest that therapeutic strategies targeting the lactylation axis may need to account for disease-specific contexts. Thus, while lactylation represents a conserved metabolic-epigenetic regulatory mechanism, its pathological consequences in cancer vs. DKD appear to be substantially shaped by the distinct microenvironment and cellular background (186). Elucidating these differences may not only deepen the understanding of DKD pathogenesis but also provide a rationale for the development of context-selective intervention strategies.

4. Deciphering the regulatory nexus of lactylation in cell death pathways and fibrotic tissue remodeling

Ferroptosis and lactylation. Ferroptosis, an iron-dependent, regulated cell death mechanism mediated by lipid peroxidation, has been increasingly recognized as a notable contributor to the pathogenesis of DKD. The distinctive DKD microenvironment, marked by hyperglycemia, hypoxia and oxidative stress, fosters conditions conducive to ferroptosis through the inhibition of the cystine/glutamate antiporter (system Xc-), depletion of GSH and subsequent accumulation of cytotoxic lipid peroxides in renal cells (187-189). Recent studies have suggested that lactylation may serve as a metabolic regulator that influences the activation of this cell death pathway (190,191).

The role of glycolytic flux and lactate in this regulatory mechanism has been explored in recent studies. Yang *et al* (164) demonstrated that lactate promotes ferroptosis through lactylation at K206 of TRIM65, which inhibits its E3 ubiquitin ligase activity, thereby suppressing the degradation of IREB2. This results in IREB2 accumulation, dysregulated iron metabolism, enhanced lipid peroxidation and ultimately ferroptosis in renal tubular epithelial cells, exacerbating kidney injury. IREB2 modulates intracellular free iron levels by regulating the mRNA expression of the transferrin receptor (192). These findings suggest a potential connection wherein lactylation may be involved in the modulation of pro-ferroptotic signaling

pathways in a context-dependent manner (31,193). In addition to its regulatory role in iron homeostasis, lactylation may also affect the antioxidant defense system. Specifically, lactylation of GPX4, a pivotal enzyme responsible for the detoxification of lipid peroxides, has been experimentally validated to facilitate ferroptosis in models of cardiac injury (194,195). This evidence strongly suggests that in DKD, GPX4 lactylation likely suppresses its enzymatic activity, thereby compromising cellular capacity to eliminate lipid peroxides and consequently enabling the progression of ferroptosis.

Furthermore, lactylation may facilitate ferroptosis induction through the modulation of systemic metabolic homeostasis. In DKD, the characteristic glycolytic shift accompanied by lactate accumulation has been associated with the suppression of the pentose phosphate pathway, a key cellular source of NADPH. This metabolic perturbation compromises the regeneration of reduced GSH, thereby attenuating the GPX4-mediated antioxidant defense system and establishing a cellular milieu conducive to ferroptosis (196,197). Moreover, the elevated lactate environment is associated with a reduction in the NAD^+/NADH ratio, which may disrupt cellular redox homeostasis and contribute to the oxidative stress conditions that can lead to ferroptotic cell death (198).

In conclusion, lactylation emerges as a key regulatory mechanism in DKD-associated ferroptosis, potentially affecting key executioner proteins such as TRIM65 and potentially GPX4, while also influencing cellular antioxidant defenses through metabolic reprogramming. Several key questions remain to be addressed: What is the complete repertoire of ferroptosis-related proteins undergoing lactylation across diverse renal cell populations? How does the interplay between lactylation and other PTMs influence ferroptotic susceptibility? Furthermore, elucidating the integration of the lactylation-ferroptosis axis with other cell death pathways will be essential for understanding the complex regulatory networks governing cell fate determination in diabetic nephropathy.

Autophagy and lactylation. Autophagy, a fundamental cellular process essential for maintaining homeostasis, demonstrates a complex dualistic role in DKD. Dysregulation of autophagy, manifesting either as excessive activation or, more frequently, as impaired function, has been extensively implicated in the pathogenesis of renal injury (199,200). Under hyperglycemic conditions, activation of energy-sensing pathways such as AMP-activated protein kinase can stimulate autophagy; however, the prevailing metabolic milieu in DKD paradoxically results in autophagic suppression. Furthermore, the phosphorylation of various oxidases enhances key metabolic processes, including glycolysis, glucose transport and fatty acid metabolism, thereby exerting additional influence on cellular homeostasis (201). Notably, the glycolysis-lactylation axis has recently emerged as a key regulatory mechanism that may affect autophagic flux, potentially influencing cell fate decisions.

The relationship between lactylation and autophagy has been explored through several studies. Sun *et al* (202) demonstrated that lactate serves as a key metabolic signal connecting glycolysis to autophagy. The suppression of autophagy by lactylation has been linked to the mTORC1 signaling pathway. Experimental evidence derived from DKD models indicates that lactylation of LARS1 at K970 may contribute to mTORC1 activation, suggesting a potential regulatory role in autophagic flux. This activation has been associated with inhibition of autophagosome formation and disruption of autophagic flux, ultimately resulting in podocyte injury and apoptosis (162,203). This mechanistic pathway provides an example of how a specific lactylation event may influence a key regulatory node and affect a cytoprotective cellular process.

Beyond mTORC1 signaling, lactylation is poised to directly target the core autophagic machinery. Key proteins involved in autophagosome formation and degradation, including LC3, ATG5 and p62, have been identified as potential lactylation substrates. Specifically, lactylation of LC3 may interfere with its lipidation process or receptor binding capacity, while lactylation of p62 could impair its functional activity or degradation, potentially leading to its pathological accumulation and subsequent disruption of selective autophagy. Although direct evidence linking these mechanisms to DKD remains limited, studies in other biological contexts offer relevant insights. Notably, lactylation of RUBCN at K33 under high-lactate conditions has been reported to enhance LC3-associated phagocytosis, illustrating the ability of lactate to directly modify and functionally regulate autophagy-related proteins (204).

Lactylation exerts deleterious effects on mitophagy, a key process for the selective elimination of damaged mitochondria. The impairment of mitophagy exacerbates mitochondrial dysfunction, potentially amplifying oxidative stress and establishing a self-perpetuating cycle of cellular damage. This phenomenon is evidenced by studies in acute kidney injury models, where lactylation of aldehyde dehydrogenase 2 has been associated with reduced mitophagy and mitochondrial dysfunction (95,182,205). A comparable mechanism is postulated to occur in the energetically compromised microenvironment of DKD, where lactylation-induced mitophagy failure would further deplete cells of functional mitochondria, potentially impairing the energy-demanding autophagy process itself.

In conclusion, the glycolysis-lactate axis has been implicated in multifaceted regulatory effects on autophagy in DKD through three principal mechanisms: Modulation of key signaling pathways, regulation of core autophagy-related proteins and selective elimination of damaged organelles via mitophagy. This coordinated dysregulation compromises essential cellular defense mechanisms, thereby increasing renal cell susceptibility to secondary injuries. The dual role of lactate in both suppressing autophagy and promoting ferroptosis may represent a regulatory node in determining cellular fate, collectively contributing to the progression of renal injury. Future investigations aimed at comprehensive profiling of the lactate-modified autophagy proteome in DKD and precise characterization of the regulatory mechanisms underlying these modifications could provide valuable insights.

Lactylation as an epigenetic contributor to renal fibrosis. The early phases of DKD are characterized by mild renal inflammation, which progresses to renal fibrosis and sclerosis, culminating in end-stage renal disease (206). Renal fibrosis is characterized by the activation and proliferation of myofibroblasts and excessive ECM deposition (141), with TGF-β serving as a pivotal profibrotic mediator (85). Consequently, protein

lactylation, driven by glycolytic flux, has been proposed as a key epigenetic mechanism. This process may contribute to the conversion of metabolic signals into a sustained fibrotic program across diverse renal cell populations, potentially serving as a metabolic mediator for the establishment of pathological memory.

Lactylation has been associated with direct regulatory effects on fibrotic phenotypes in renal cells through distinct molecular mechanisms across different cell types. In renal tubular epithelial cells, H3K14la functions as a key mediator of myofibroblast differentiation via EMT, facilitating ECM production. This process is mechanistically associated with the *KLF5* gene activation, which drives mesenchymal matrix secretion and contributes to tubulointerstitial fibrosis (7). In glomerular endothelial cells, hyperglycemic conditions upregulate *IGFBP5*, enhancing glycolytic flux and subsequent lactic acid production. The resulting H3K18la binds to the promoter regions of NLRP3 and IL-1β, initiating pyroptosis and promoting EndoMT (142). Furthermore, in podocytes, lactylation targets non-histone proteins, specifically modifying K970 in the LARS1 protein, which activates mTORC1 signaling, impairs autophagy flux and exacerbates podocyte injury and detachment, ultimately contributing to glomerulosclerosis (162). Collectively, these findings suggest that lactylation may represent an epigenetic mechanism that can influence transcriptional networks and cellular functions in renal cells, associating transient metabolic stress with persistent fibrotic pathology.

The fibrotic cascade in DKD is intricately associated with chronic inflammation, where macrophages have been recognized as central mediators in this process (142,207). Lactate metabolism has been implicated in macrophage polarization, with H4K12la associated with M2 phenotype acquisition. This polarization has been associated with activation of genes involved in glycolysis and oxidative phosphorylation, potentially contributing to renal fibrosis (208,209). Additionally, H3K18la in macrophages upregulates *Tgfb1* expression, which in turn activates the TGF-β1/Smad3 signaling pathway. This activation drives macrophage-to-myofibroblast transition, potentially contributing to fibrotic progression (89). Collectively, lactate-mediated immune modulation may contribute to a renal microenvironment characterized by both immunosuppressive and pro-fibrotic features.

Lactation has also been implicated as a key function in intercellular signaling mechanisms. The metabolic reprogramming of renal tubule epithelial cells and podocytes has been associated with both autonomous fibrotic changes and increased lactate efflux into the extracellular milieu. This extracellular lactate may function as a paracrine signaling molecule that can be taken up by adjacent cells, including fibroblasts and macrophages. Within these recipient cells, lactate-mediated lactylation, such as H4K12la in (myo)fibroblasts, has been associated with NF-κB pathway activation and enhanced pro-inflammatory and pro-fibrotic gene expression (210). This process may contribute to a feedback loop: M2 macrophages secrete TGF-β, which can enhance glycolytic activity and lactate production in renal tubule cells, potentially perpetuating the cycle.

In conclusion, lactylation has been implicated as a key regulatory mechanism contributing to fibrotic processes across diverse renal cell populations. This phenomenon involves direct cellular reprogramming, immune microenvironment remodeling and the modulation of metabolic-epigenetic crosstalk. As summarized in Table II (89,142,162-164,208-212), lactylation targets in various renal cell types have been associated with fundamental pathological pathways, including ferroptosis, autophagy suppression and inflammatory activation, potentially contributing to fibrotic progression.

The elucidation of lactylation mechanisms presents both a considerable scientific challenge and a therapeutic opportunity. As depicted in Fig. 4, the intricate lactylation networks highlight the need for highly targeted intervention strategies. Future research should prioritize the development of cell-specific delivery systems to precisely modulate pathogenic lactylation events while preserving physiological homeostasis. Furthermore, elucidating the temporal dynamics of these modifications during DKD progression and investigating their interplay with other PTMs are essential. Current evidence suggests that targeted disruption of this coordinated lactylation network may represent a promising therapeutic approach to attenuate the progressive fibrotic cascade in DKD.

5. Clinical translational potential of glycolysis and lactylation in DKD

The rapidly advancing field of DKD research underscores the importance of therapeutic interventions that target fundamental pathogenic mechanisms rather than merely addressing symptomatic manifestations. While current standard-of-care approaches, primarily focused on glycemic, lipid and blood pressure regulation, have shown limited efficacy in halting disease progression, they highlight a need for additional therapeutic options. The identification of the glycolysis-lactylation axis as a key contributor to DKD pathogenesis has opened a new avenue for therapeutic intervention.

Therapeutic strategies targeting the glycolysis, lactylation axis can be categorized into three distinct intervention levels based on their mechanism of action: i) Inhibition of lactate generation (upstream metabolic enzymes), ii) blockade of lactate transport (MCT inhibitors) and iii) direct modulation of the lactylation machinery (writers, erasers and readers). A summary of representative agents targeting each level is provided in Table III (70,72,104,105,125-128,130,213-228). This section discusses the potential of targeting the glycolysis-lactylation axis, reviews strategies for modulating lactylation modifications and considers translational challenges, providing a perspective on emerging therapeutic strategies for DKD.

Targeting the glycolytic-lactate axis

Inhibitors of key glycolytic enzymes. Accumulating evidence indicates that dysregulation of PKM2 is associated with the pathogenesis and progression of DKD (229). PKM2 exists in a dynamic equilibrium between its highly active tetrameric form and less active dimeric state, with the latter serving as a nuclear transcription co-activator. In the context of DKD, the shift toward the dimeric form facilitates PKM2 nuclear translocation, where it interacts with HIF-1α to upregulate glycolytic gene expression, thereby perpetuating a metabolic regulatory feedback loop (70,230,231). Pharmacological activation of PKM2 using compounds such as TEPP-46 promotes

Table II. Lactylation targets, functional outcomes, and signalling pathways across different renal cell types.

Cell type	Lactylation target	Functional outcome	Involved pro-fibrotic pathway/gene	(Refs.)
Tubular epithelial cells	ACSF2(K182la)	Mitochondrial ROS accumulation and dysfunction in HK-2 cells under hyperglycaemic conditions.	Therapeutic targeting of mitosis and ferroptosis	(163)
	TRIM65	TRIM65 confers protection against ferroptosis and suppresses excessive glycolysis by mediating the ubiquitination and degradation of IREB2 and PDK4.	Ferroptosis	(164)
	Tsc1	Activated mTORC1 signalling, triggered by Tsc1 loss, acts as a master driver of this metabolic switch, ultimately leading to aberrant tubular epithelial cell proliferation, cyst formation, and renal fibrosis.	mTORC1	(214)
Podocytes	LARS1	mTORC1 activation drives DKD progression by inhibiting autophagic activity, a process that accelerates podocyte apoptosis and injury.	mTORC1, autophagy	(162)
Glomerular endothelial cells	H3K18la	Promotes NLRP3 inflammasome-induced EndoMT and renal fibrosis, accelerating the progression of DKD.	EndoMT/*IGFBP5*	(141)
Macrophages	H4K12la	Enhances HIF-1α transcription and augments PA-induced inflammatory responses in macrophages.	*Slc16a3*	(212)
		Stimulates macrophage M2 polarization and exacerbates renal tissue fibrosis.	TMAO, TGF-β/Smad, Wnt/β-catenin	(208,209)
	H3K18la	Activates *Tgfb1* expression, and the subsequent TGF-β1 activates the Smad3 pathway to drive the MMT process.	*Tgfb1*/TGF-β1/Smad3	(89)
(Myo) fibroblasts	H4K12la	Lactate, produced by PFKFB3-driven glycolysis, mediates H4K12la to activate the transcription of NF-κB pathway genes, including *Ikbkb*, *Rela* and *Relb*.	PFKFB3/ NF-κB	(210)

ACSF2, Acyl-coA synthetase family member 2; K182la; ROS, Reactive oxygen species; HK-2, Human kidney 2; TRIM65, Tripartite motif-containing 65; IREB2, Iron-responsive element-binding protein 2; PDK4, Pyruvate dehydrogenase kinase 4; mTORC1, Mechanistic target of rapamycin complex 1; Tsc1, Tuberous sclerosis complex 1; LARS1, Leucyl-tRNA synthetase 1; DKD, Diabetic kidney disease; NLRP3, NLR family pyrin domain containing 3; H3K18la, Histone H3 lysine 18 lactylation; EndoMT, Endothelial-mesenchymal transition; *IGFBP5*, Insulin-like growth factor-binding protein 5; H4K12la, Histone H4 lysine 12 lactylation; HIF-1α, Hypoxia-inducible factor 1-α; *Slc16a3*, Solute carrier family 16 member 3; TMAO, Trimethylamine N-oxide; TGF-β, Transforming growth factor β; Smad, Mothers against decapentaplegic homolog; Wnt, Wingless-related integration site; H3K18la, Histone H3 lysine 18 lactylation; MMT, Macrophage-to-myofibroblast transition; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; *Ikbkb*, Inhibitor of nuclear factor kappa-B kinase subunit β; *Rela*, v-rel reticuloendotheliosis viral oncogene homolog A; *Relb*, v-rel reticuloendotheliosis viral oncogene homolog B.

tetramer formation, which inhibits its nuclear function, restores metabolic homeostasis, attenuates fibrotic progression and preserves renal function (213). Notably, Jian *et al* (72) identified a novel imidazopyrimidine derivative, 15n, which exhibits mechanisms of action analogous to TEPP-46 and demonstrates efficacy in mitigating renal fibrosis in preclinical

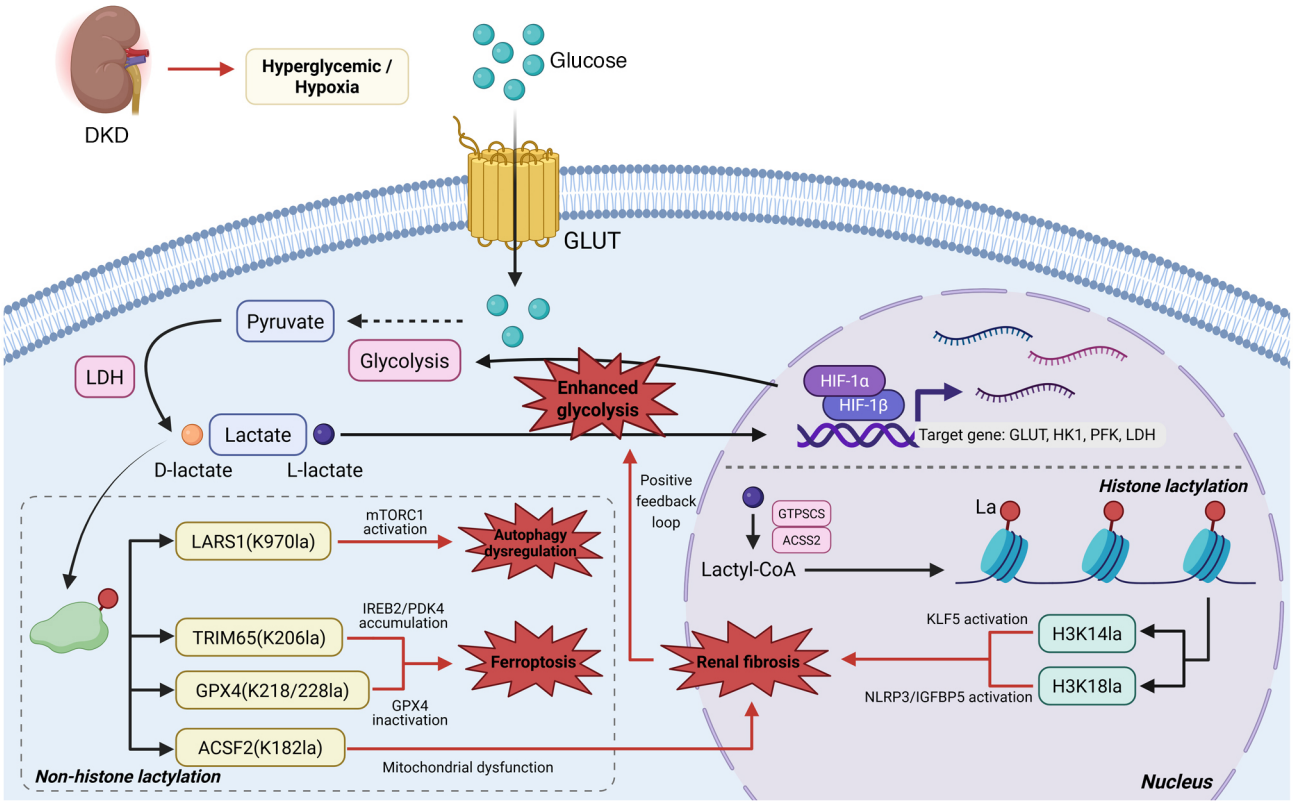

Figure 4. The glycolytic-lactate axis orchestrates fibrotic remodeling in DKD through lactylation-mediated modulation of ferroptosis and autophagy. Elevated lactate concentrations induce cellular dysfunction through non-histone lactylation, suppress cytoprotective autophagy and initiate ferroptosis, thereby activating key pathways associated with cellular damage and death. Concurrently, lactylation drives renal fibrosis via a dual regulatory mechanism, histone modification-mediated activation of profibrotic gene expression and signaling protein alteration-induced functional impairment. The resultant fibrotic tissue remodeling exacerbates hypoxic conditions and inflammatory responses, establishing a self-perpetuating cycle that progressively amplifies disease pathogenesis. DKD, Diabetic kidney disease; GLUT, Glucose transporter; LDH, Lactate dehydrogenase; LARS1, Mechanistic target of rapamycin complex 1; K970la, Lysine 970 lactylation; mTORC1, Mechanistic target of rapamycin complex 1; TRIM65, Tripartite motif-containing 65; K206la, Lysine 206 lactylation; IREB2, Iron-responsive element-binding protein 2; PDK4, Pyruvate dehydrogenase kinase 4; GPX4, Glutathione peroxidase 4; K218/228la, Lysine 218/228 lactylation; ACSF2, Acyl-coA synthetase family member 2; K182la, Lysine 182 lactylation; HIF-1α, Hypoxia-inducible factor 1-α; HIF-1β, Hypoxia-inducible factor 1-β; HK1, Hexokinase 1; PFK, Phosphofructokinase; GTPSCS, GTP-specific succinyl-coA synthetase; ACSS2, Acyl-coA synthetase short-chain family member 2; Lactyle-CoA, Lactyl-coenzyme A; La, Lactylation; H3K14la, Histone H3 lysine 14 lactylation; H3K18la, Histone H3 lysine 18 lactylation; KLF5, Krüppel-like factor 5; NLRP3, NLR family pyrin domain containing 3; IGFBP5, Insulin-like growth factor-binding protein 5.

models. This therapeutic strategy exemplifies a targeted approach to modulating underlying metabolic dysregulation in DKD.

Direct inhibition of lactate production has been proposed as a therapeutic approach. Pharmacological inhibitors of LDHA, such as oxamate and FX11, have been reported to reduce intracellular lactate concentrations and attenuate protein lactylation (218). This strategy is of interest given the evidence associating LDHA activity with DKD pathogenesis (44,51,80,81). By targeting LDHA, this approach may influence lactate accumulation, metabolic acidosis and the formation of a lactate-enriched microenvironment. These strategies for inhibiting lactate production that represent distinct intervention points within the upstream metabolic cascade (Table III). However, the systemic administration of these metabolic enzyme inhibitors presents challenges, as they could affect energy homeostasis in non-target tissues, underscoring the need for kidney-specific delivery strategies.

Lactate transporter inhibitors. The functional expression of MCT1 and MCT4 is essential for lactate transport, facilitated by their association with the ancillary protein Basigin (CD147) (232-236). In DKD, glomerular cells exhibiting a glycolytic phenotype predominantly utilize MCT4 for lactate efflux. Elevated MCT4 expression levels have been observed in patients with T2DM, suggesting a potential role in disease pathogenesis (237). Pharmacological inhibition of MCT4 may disrupt intracellular lactate efflux, potentially leading to autotoxicity and impairment of intercellular lactate shuttles, thereby attenuating fibrotic signaling in recipient cells, including fibroblasts and macrophages. While MCT4 inhibitors such as VB124 and AZD3965 have been primarily studied in oncological contexts (223,224), their application in DKD could provide key insights into their therapeutic potential by targeting pathological lactate-mediated cellular communication.

Notably, MCT4 inhibition represents a distinct intervention strategy targeting lactate transport rather than its generation, disrupting intercellular lactate shuttling and potentially attenuating fibrotic signaling in recipient cells such as fibroblasts and macrophages (Table III). Preclinical evidence in kidney injury models has demonstrated that the MCT4 inhibitor syrosingopine can restore adaptive kidney repair by suppressing proinflammatory endothelial activation, supporting the therapeutic relevance of targeting lactate transport in renal disease (226).

Table III. Summary of therapeutic agents targeting the glycolysis-lactylation axis in DKD.

Intervention level	Mechanism of action	Agent/compound	Key description	(Refs.)
Inhibition of lactate generation (upstream metabolic intervention)	PKM2 activator	TEPP-46	Promotes PKM2 tetramer formation, inhibits its nuclear pro-glycolytic function, restores metabolic homeostasis.	(70,213)
			Suppresses apoptosis and fibrosis.	(214)
			Reduces nuclear PKM2 translocation, downstream LDHA and GLUT1 transcription and lactate production.	(215)
		15n	Novel imidazopyrimidine derivative with a similar mechanism to TEPP-46, attenuates renal fibrosis.	(72)
	PKM2 inhibitor	LncRNA *ARAP1*	Promotes aberrant glycolysis and fibrosis in DKD via the EGFR/PKM2/HIF-1α pathway.	(216,217)
	LDHA inhibitor	Oxamate	Directly inhibits LDHA activity, reduces lactate production and protein lactylation.	(218)
		FX11	Directly blocks pyruvate-to-lactate conversion, reduces lactate concentration and downstream lactylation levels.	
	HIF-1α inhibitor	LW6	Inhibits central hypoxic signaling, downregulates glycolytic enzyme expression, fundamentally reduces lactate synthesis.	(219-222)
Blockade of lactate transport (intercellular communication intervention)	MCT4 inhibitor	VB124	Inhibits lactate efflux, disrupts intercellular lactate shuttling, potentially attenuates fibrotic signaling in recipient cells such as fibroblasts.	(223)
		Syrosingopine	Inhibits MCT4, restores adaptive kidney repair.	(223)
		AZD3965	Primarily studied in oncology; may provide insights into pathological cellular communication in DKD.	(224)
Direct modulation of lactylation machinery (epigenetic intervention)	CBP/p300 inhibitor	A-485 (HAT inhibitor)	Inhibits lactylation-writing enzymes; may delay disease progression by directly suppressing pro-fibrotic lactylation marks.	(104,105, 225)
		CPI644 (bromodomain inhibitor)		
		NEO2734 (Dual bromodomain inhibitor)		
		CCS1477 (PROTAC inhibitor)		
	AARS1 inhibitor	β-alanine	Inhibits novel lactylation writer, ameliorates renal injury and fibrosis.	(226)

Table III. Continued.

Intervention level	Mechanism of action	Agent/compound	Key description	(Refs.)
	SIRT1 agonist	Resveratrol	Enhances delactylase activity, removes pathological modifications, improves renal injury and fibrosis.	(125-128, 227,228)
		SRT2104		
	SIRT3 agonist	Picroside		
		Shennanone		
		Metformin		
Regulation of lactylation recognition (signal transduction intervention)	Reader protein inhibitor	TRIM33β inhibitor	Interferes with reader protein recognition of lactylation sites, blocks downstream pro-fibrotic signal transduction (for example, TGF-β)	(130)

DKD, Diabetic kidney disease; PKM2, Pyruvate kinase M2; LDHA, Lactate dehydrogenase A; GLUT1, Glucose transporter 1; *ARAP1*, ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 1; EGFR, Epidermal growth factor receptor; HIF-1α, Hypoxia-inducible factor 1-α; MCT4, Monocarboxylate transporter 4; HAT, Histone acetyltransferase; CBP, CREB-binding protein; p300, E1A binding protein p300; PROTAC, Proteolysis-targeting chimera; AARS1, Alanyl-tRNA synthetase 1; SIRT1, Sirtuin 1; SIRT3, Sirtuin 3; TRIM33β, Tripartite motif-containing protein 33 β; TGF-β, Transforming growth factor β.

HIF-1α inhibitors. As a central regulator of hypoxic responses and a key modulator of glycolytic flux in DKD, HIF-1α emerges as a promising therapeutic target. Pharmacological inhibition of HIF-1α, exemplified by the compound LW6, has been demonstrated to facilitate its proteasomal degradation, attenuate EMT, normalize aberrant glycolysis and mitigate renal fibrotic processes (219-221). These inhibitory agents have been associated with renoprotective effects, potentially through transcriptional downregulation of key glycolytic enzymes and reducing lactic acid production (222). Nevertheless, the therapeutic application of HIF-1α inhibitors is challenging due to their pleiotropic physiological functions, particularly in angiogenesis and erythropoiesis (238,239). Future research aimed at developing kidney-selective or microenvironment-responsive HIF-1α modulators could help reduce off-target effects and improve therapeutic efficacy in DKD.

Targeting lactylation modifications

Targeting writers. The inhibition of writers, particularly CBP/p300, emerges as a promising therapeutic strategy for mitigating pathogenic lactogenic processes. Current research has identified four distinct classes of CBP/p300 inhibitors: HAT domain inhibitors (for example, A-485), bromodomain inhibitors (for example, CPI644), dual inhibitors targeting both CBP/p300 and BRD4 bromodomains (for example, NEO2734) and proteolysis-targeting chimera inhibitors (for example, CCS1477) (225). Mechanistically, CBP/p300 activation has been shown to upregulate NADPH oxidase activity, fibrotic pathways and inflammatory responses in diabetic nephropathy (104,105), suggesting that its inhibition could potentially attenuate disease progression through direct suppression of fibrotic lactogenic markers. Although these compounds have been primarily studied in oncology, their application in DKD models warrants investigation as a potential therapeutic approach. Concurrently, targeting AARS1/2 within the lactate-AMP signaling pathway could offer an alternative approach to influencing lactylation in response to intracellular lactate levels. Recent studies have identified that AARS1 promotes glycolytic reprogramming in DKD by lactylating Akt and p65, and its pharmacological inhibition with β-alanine has been shown to ameliorate renal injury and fibrosis in preclinical models (240-242). This approach represents a distinct epigenetic intervention strategy, directly targeting the lactylation machinery rather than upstream lactate availability.

Targeting erasers. The augmentation of eraser activity represents a complementary therapeutic approach in disease management. SIRT1-3, which exhibit deacetylase activity, have been reported to be downregulated in DKD. Activation of these SIRTs has been empirically validated to ameliorate renal injury and fibrosis (125-128). SIRT1 agonists, including the naturally occurring compound resveratrol and the synthetic molecule SRT2104, have been investigated for their therapeutic potential. However, the clinical application of resveratrol is constrained by its limited bioavailability and off-target effects (227). Similarly, SIRT3 agonists such as picroside, shennanone and metformin have been shown to confer renal protection, potentially mediated through the restoration of deacetylation functions (228). The enhancement of eraser activity may offer the distinct advantage of modulating pathological modifications while preserving physiological signaling pathways.

Targeting readers. The targeted inhibition of reader proteins that specifically recognize lactylation marks offers a novel therapeutic strategy characterized by high specificity, potentially reducing off-target effects on other PTM pathways. For example, small-molecule inhibitors that selectively interfere with the interaction between the H3K18la reader TRIM33β and its lactylated histone substrate might allow modulation of its role in TGF-β signaling and fibrotic

processes (130). This approach could achieve higher specificity by interfering with signal interpretation rather than modification deposition. Nevertheless, this research area remains in its early stages of exploration. A pivotal research objective is the systematic identification and functional validation of pathogenic reader proteins specifically implicated in DKD, which would facilitate the development of a new class of therapeutic agents targeting the terminal step of lactylation-mediated signal transduction.

Therapeutic modulation of lactylation poses considerable challenges, primarily arising from its intricate biological mechanisms. The extensive structural and functional similarities between lactylation-regulating enzymes and those involved in other acylation processes (for example, acetylation) may increase the potential for off-target effects. Non-selective inhibition could inadvertently affect key physiological pathways. Therefore, the development of highly specific inhibitors capable of distinguishing Kla from Kac, coupled with the advancement of kidney-targeted drug delivery systems, is considered an essential prerequisite for successful clinical translation. Future progress in this field will likely require achieving a level of precision that corresponds to the complexity of the PTM network.

Challenges and future directions. The clinical translation of therapeutics targeting the glycolysis-lactylation axis encounters substantial challenges that warrant careful consideration. A primary obstacle is achieving pharmacological specificity, as systemic inhibition of core metabolic or epigenetic pathways could lead to off-target effects and toxicity, highlighting the need for kidney-selective drug delivery platforms. Furthermore, the functional roles of specific lactylation modifications in the pathogenesis of DKD remain incompletely characterized, highlighting the need for advanced spatial multi-omics approaches and cell-type-specific genetic tools to identify the most biologically relevant and therapeutically actionable targets. Additionally, while monotherapeutic strategies targeting this axis show potential, the complex, multifactorial pathophysiology of DKD may require rationally designed combination therapies that simultaneously modulate fibrosis, inflammation and metabolic dysregulation to achieve synergistic therapeutic efficacy and mitigate the emergence of treatment resistance.

6. Conclusion and perspectives

The present review synthesizes emerging evidence suggesting that glycolysis-driven lactylation may represent a key mechanism in DKD, though direct causal evidence remains limited and further experimental validation is required to establish definitive mechanistic links. The present review discussed how the hyperglycemic and hypoxic microenvironment can increase glycolytic flux, leading to lactate accumulation that may serve as a substrate for both enzymatic and non-enzymatic lactylation. This modification has been proposed to function as a regulatory bridge, linking metabolic states to epigenetic and post-translational signals. Specifically, how lactylation has been implicated in key pathological processes, affecting ferroptosis, influencing autophagic flux and contributing to pro-fibrotic gene programs across diverse renal cell types was explored. The intricate interplay between lactylation and other PTMs may further contribute to its impact, forming a complex regulatory network that could stabilize the pathological phenotype.

Looking ahead, this field holds considerable potential for advancing the understanding of DKD. Future research aimed at understanding the cell-specific and temporal dynamics of lactylation in the kidney could be important for defining its roles in disease initiation vs. progression. The identification of novel pathogenic 'reader' proteins and the exploration of crosstalk between lactylation and other metabolic signaling pathways may represent promising avenues for discovery. Additionally, while therapeutic targeting presents challenges, the continued development of highly specific agents and advanced delivery systems may offer potential for applying these mechanistic insights to therapeutic strategies.

In summary, lactylation represents an intersection of metabolic and epigenetic regulation in DKD. Despite the complexities and unresolved questions, further exploration of this pathway may not only advance the understanding of diabetic kidney injury but also reveal new therapeutic opportunities for managing DKD.

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All authors read and approved the final manuscript. TZ conceptualized and directed the research project, authored the initial manuscript draft and designed the graphical representations. XZ, YX, YL, SX and XY systematically gathered and organized scientific literature and associated datasets pertaining to diabetes and lactylation from publicly accessible repositories. TL and LL conducted comprehensive reviews of the manuscript, providing critical feedback and substantive revisions. Data authentication not applicable.

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Competing interests

The authors declare that they have no competing interests.

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