

Lactate Metabolism and Protein Lactylation in Diabetic Kidney Disease: A Narrative Review

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Abstract: Diabetic Kidney Disease (DKD) is one of the common and serious microvascular complications of diabetes, and the pathogenesis is complex and incompletely understood. Recent studies have shown that lactylation, as a novel form of protein post-translational modification, has been increasingly involved in the progression of DKD through the specific binding of lactate molecules to protein amino acid residues, particularly involving important pathological processes such as inflammatory regulation, cell death-related signaling pathways and fibrotic remodeling. This review summarizes current evidence on abnormal lactate metabolism in DKD and the mechanisms by which lactate-driven lactylation regulates signaling pathways associated with kidney injury. It further evaluates the potential of lactate as a clinical biomarker and discusses intervention strategies targeting lactate metabolism as well as enzymes involved in lactylation and delactylation. These findings provide new insights and future research directions for the prevention and treatment of DKD.

Plain Language Summary: Diabetic kidney disease is a major cause of chronic kidney failure in people with diabetes, yet current treatments do not fully prevent disease progression. Understanding the biological mechanisms that drive kidney damage remains essential for developing better therapies. This review examines how changes in cellular metabolism contribute to diabetic kidney disease, with a focus on lactate, a key product of glucose metabolism. Beyond its traditional role in energy production, lactate can modify proteins through a process known as lactylation, which influences gene activity and cellular behavior. Recent studies suggest that abnormal lactate metabolism and protein lactylation may promote inflammation, tissue scarring, and cell dysfunction in the diabetic kidney. We summarize current evidence from experimental and clinical studies linking lactate-related pathways to kidney injury and disease progression. We also discuss the limitations of existing research and highlight important gaps that require further investigation. By clarifying how metabolic signals influence kidney pathology, this review provides insight into potential therapeutic targets and supports future research aimed at improving outcomes for people with diabetic kidney disease.

Keywords: diabetic kidney disease, lactate, lactate metabolism, glycolysis, post-translational modification, protein lactylation, renal fibrosis

Introduction

Diabetic kidney disease is a serious complication of diabetes, which often develops into end-stage kidney disease, thus significantly reducing the life expectancy of patients.¹ According to recent estimates from the International Diabetes Federation (IDF), the global prevalence of diabetes is approximately 583 million and is expected to rise to 853 million by 2050, with the majority of cases occurring in low- and middle-income countries. Among these individuals, approximately 40% may develop diabetic kidney disease, which is recognized as the leading cause of chronic kidney disease (CKD)

worldwide.^{2,3} The pathogenesis of DKD is multifactorial, and it is generally believed that it involves hemodynamic changes, metabolic disturbances and signaling pathway disorders of the renin-angiotensin-aldosterone system.⁴ Although mineralocorticoid receptor antagonists (MRAs), RAAS inhibitors, and glucagon-like peptide-1 receptor (GLP-1R) agonists have been incorporated into standard clinical practice, their efficacy in delaying the progression of DKD remains limited, and they are unable to prevent progression to end-stage renal disease (ESRD).⁵ Therefore, there is an urgent need to explore novel therapeutic targets and intervention strategies. In 2019, Zhang et al identified a characteristic mass shift on lysine residues of proteolytic peptides using mass spectrometry, thereby revealing lysine lactylation as a novel protein post-translational modification (PTM), a finding that has expanded our understanding of epigenetic regulation.⁶ Subsequent studies have shown that lactate induces histone lactylation which accelerates epithelial-mesenchymal transition (EMT) in DKD, thus linking lactylation to DKD pathogenesis.⁷ Moreover, other epigenetic mechanisms, including DNA methylation, post-translational modifications (such as acetylation, methylation, ubiquitination, and phosphorylation), and non-coding RNAs, have also been implicated in DKD-related renal injury (Table 1).^{8–13} In addition, these epigenetic modifications exhibit dynamic crosstalk. For example, histone lactylation and acetylation competitively target lysine residues, with their relative levels determined by the intracellular balance of lactate and acetyl-CoA.¹⁴

As an emerging epigenetic modification, lactylation provides a mechanistic framework linking aerobic glycolysis-driven lactate accumulation to renal injury in DKD. Accumulating evidence has implicated lactylation not only in the development of diabetes but also in the progression of associated complications, including diabetic kidney disease and diabetic retinopathy.¹⁵ As a metabolite-derived epigenetic modification driven by intracellular lactate accumulation, lactylation links cellular metabolic states to gene regulation. Epigenetic modifications can be stably maintained as a form of cellular memory and exert long-term effects in DKD, thereby constituting a key pathological basis of the “metabolic memory” phenomenon.¹⁶ Metabolic memory refers to the persistence of renal injury in DKD despite subsequent normalization of glycemic levels.¹⁷ Epigenetic regulation contributes to this process by modulating chromatin accessibility and sustaining the activation of genes involved in inflammation, fibrosis, and apoptosis.^{18,19} In this context, lactylation may serve as a mechanistic link between transient metabolic disturbances and persistent transcriptional reprogramming. Moreover, a potential positive feedback loop between lactate accumulation and lactylation may further amplify lactylation-dependent transcriptional programs. Collectively, lactylation may function as a molecular bridge connecting metabolic reprogramming with epigenetic memory, thereby contributing to the sustained progression of renal injury. Emerging evidence suggests that modulation of lactate metabolism and lactylation-related pathways may represent a potential therapeutic strategy. Pharmacological interventions targeting key regulators of lactate production, transport, and lactylation may influence disease progression. However, its clinical translation remains limited due to the lack of standardized detection methods and targeted therapeutic strategies, with current evidence largely confined to preclinical studies. Addressing these gaps will be essential to establish clinical relevance and unlock the potential of lactylation for precision diagnostics and therapeutics in DKD. Accordingly, this review summarizes the current evidence implicating protein lactylation in the pathogenesis of DKD and highlights recent advances in lactylation-based therapeutic strategies and detection approaches.

Methodology

Literature for this review was identified through searches of major scientific databases, including PubMed, Web of Science, Scopus, and Google Scholar. The search strategy combined keywords related to lactylation, diabetic kidney disease, epigenetic regulation, metabolic reprogramming, and lactate using Boolean operators (AND/OR), as exemplified by the following query: (diabetic kidney disease OR DKD OR diabetic nephropathy OR DN) AND (lactylation OR histone lactylation OR protein lactylation) AND (epigenetic regulation OR epigenetics OR histone modification) AND (metabolic reprogramming OR glycolysis) AND (lactate OR lactate metabolism). The search was limited to articles published in English up to March 2026. Relevant studies were screened based on their relevance to the topic and their contribution to understanding the role of lactylation in DKD. Given the narrative nature of this review, study selection was not conducted according to a predefined systematic protocol, which may introduce potential selection bias.

Table 1 Epigenetic Modifications Involved in the Pathogenesis of DKD

Epigenetic Modification Types		Cell Types	Target	Molecular Mechanism	Pathophysiological Outcome	Ref
DNA methylation		Immune cells	Cytosines	DNMT1↑→Cytosines methylation↑→mTOR↑	Inflammation	[8]
PTMs	Lactylation	Renal epithelial cells	H3K14	Lactate↑→H3K14la↑→KLF5↑	EMT	[7]
	Acetylation	Podocyte	MPC2	SIRT3↓→MPC2 acetylation↑→ROS↑/ATP↓/MMP↓	Podocyte apoptosis	[9]
	Methylation	Mononuclear cells	H3K4	Set7↑→H3K4me1↑→NF-kB p65↑	Endothelial dysfunction	[10]
	Ubiquitination	Macrophage	H2AK119	USP21/USP19↓→H2AK119Ub↑→Macrophage infiltration↑	Fibrosis	[11]
	Phosphorylation	Glomerular endothelial cells	H3Ser10	CCL2/CCR2↑→p38 MAPK/MSK1/2↑→VCAM-1↑→H3Ser10 phosphorylation↑	Glomerulosclerosis	[12]
Non-coding RNAs		Podocyte	lncRNA ENST00000436340	FTO↑→ENST00000436340↑→PTBPI↑→RAB3B↓→GLUT4↓	Podocyte injury	[13]

Notes: This table summarizes major epigenetic regulatory mechanisms, including DNA methylation, post-translational modifications (PTMs), and non-coding RNAs, across different renal and immune cell types. Representative molecular targets, signaling pathways, and their associated pathological processes—such as inflammation, epithelial–mesenchymal transition (EMT), apoptosis, endothelial dysfunction, fibrosis, and glomerulosclerosis—are presented. Arrows (↑/↓) indicate upregulation or downregulation, respectively.

Abbreviations: DNMT1, DNA methyltransferase 1; mTOR, mammalian target of rapamycin; H3K18la, histone H3 lysine 18 lactylation; EMT, epithelial–mesenchymal transition; MPC2, mitochondrial pyruvate carrier 2; SIRT3, sirtuin 3; ROS, reactive oxygen species; MMP, mitochondrial membrane potential; Set7, SET domain-containing lysine methyltransferase 7; H3K4me1, monomethylation of histone H3 lysine 4; USP21, ubiquitin-specific peptidase 21; H2AK119Ub, monoubiquitination of histone H2A lysine 119; CCL2, C-C motif chemokine ligand 2; CCR2, C-C motif chemokine receptor 2; p38 MAPK, p38 mitogen-activated protein kinase; MSK1/2, mitogen- and stress-activated protein kinases 1/2; VCAM-1, vascular cell adhesion molecule 1; lncRNA, long non-coding RNA; FTO, fat mass and obesity-associated protein; PTBPI, polypyrimidine tract binding protein 1.

Lactate Metabolism and Protein Lactylation

Lactate metabolism represents a central metabolic process linking glucose utilization to cellular energy balance and signaling pathways. In the human body, lactate exists in the form of two stereoisomers, namely L-lactate and D-lactate, of which L-lactate is the main form of glycolysis.²⁰ The traditional view is that lactate is only a metabolic waste of anaerobic glycolysis. However, with the introduction of the Warburg effect, the physiological function of lactate has been reconsidered. The Warburg effect was first found in tumor cells. Even under aerobic conditions, cells can produce lactate through glycolysis.²¹ Lactate is now increasingly considered to be involved in the pathological processes of various diseases, including inflammation, tumor progression, sepsis, and wound healing.²² In 2019, Zhang et al first reported the existence of lysine lactylation as a novel PTM of proteins.⁶ Lactylation is a new form of PTM derived from lactyl-CoA, which is characterized by the covalent connection of lactate and lysine residues in proteins.²³ Although the Warburg effect does not directly regulate lactylation, the increase in glycolytic flux associated with this metabolic state will produce a large amount of lactate, and lactate can be used as a substrate for histone lactylation (Figure 1). Through this mechanism, lactate-associated lysine lactylation is believed to link metabolic reprogramming with epigenetic regulation, which represents an emerging focus of metabolic–epigenetic research.²⁴ Studies have found that lysine lactylation is widely involved in the pathogenesis of a variety of kidney diseases, including renal cell carcinoma, acute kidney injury, diabetic kidney disease, and renal fibrosis.²⁵

Altered Lactate Metabolism in Diabetic Kidney Disease

The kidney plays an essential role in systemic lactate homeostasis, and alterations in renal lactate metabolism have been increasingly recognized in diabetic kidney disease. The kidneys are the second most important organ for lactate metabolism after the liver. The clearance of lactate by the kidneys depends on the functional division and coordination

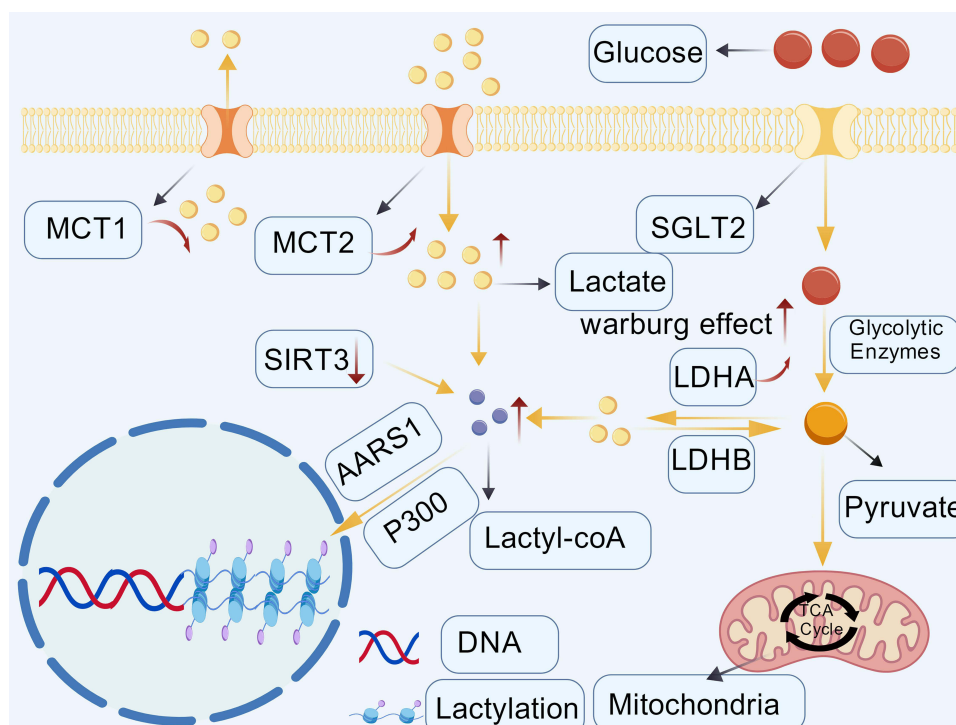


Figure 1 Schematic overview of lactate metabolism and protein lactylation. This schematic summarizes current understanding of the relationships among glucose metabolism, lactate production, transport, and protein lactylation. Enhanced glycolytic activity is shown to be associated with increased pyruvate-to-lactate conversion mediated by LDHA and LDHB, reflecting metabolic features commonly described as the Warburg effect. Lactate transport via MCT1 and MCT2, as well as its potential contribution to lactyl-CoA generation, are illustrated. Enzymes reported to participate in the regulation of protein lactylation, including the lactyltransferases p300 and AARS1, as well as the delactylase SIRT3, are indicated to highlight proposed regulatory nodes of this modification. Arrows represent proposed metabolic routes or reported associations rather than direct causal relationships. The figure was independently assembled by the authors using original graphical elements together with licensed BioGDP components. Created with BioGDP.com.²⁶

between the renal cortex and the renal medulla. The renal medulla mainly produces lactate through glycolysis, while the renal cortex efficiently absorbs and oxidizes lactate to meet energy requirements. Both are involved in regulating the glucose-lactate cycle.²⁷ Under physiological conditions, lactate is freely filtered by the glomerulus and is almost completely reabsorbed in the proximal tubules, resulting in minimal urinary excretion and contributing to the maintenance of metabolic and acid–base homeostasis.²⁸ In DKD, persistent hyperglycemia is accompanied by changes in cell metabolism, which is characterized by increased glycolysis dependence and reduced mitochondrial oxidative phosphorylation. These metabolic changes occur simultaneously with the increase in lactate levels in the renal tissue and are related to the progressive impairment of renal function.²⁹ In the kidneys, the maintenance of lactate homeostasis depends on the synergy of lactate dehydrogenase (LDH), pyruvate dehydrogenase (PDH) and monocarboxylate transporters (MCTs) (Figure 2). The three together form a dynamic balance system, which regulates the concentration and distribution of lactate in the kidney.³⁰ The production and utilization of lactate in renal tissue are mainly regulated by LDH and PDH. LDH is a core enzyme in glycolysis, which directly affects the production of lactate.³¹ Within the nephron, lactate dehydrogenase A (LDHA) is mainly located in proximal tubular cells, where it promotes the reduction of pyruvate to lactate. In contrast, lactate dehydrogenase B (LDHB) is higher in the distal segments of the nephron and participates in the reconversion of lactate into pyruvate.³² Evidence from

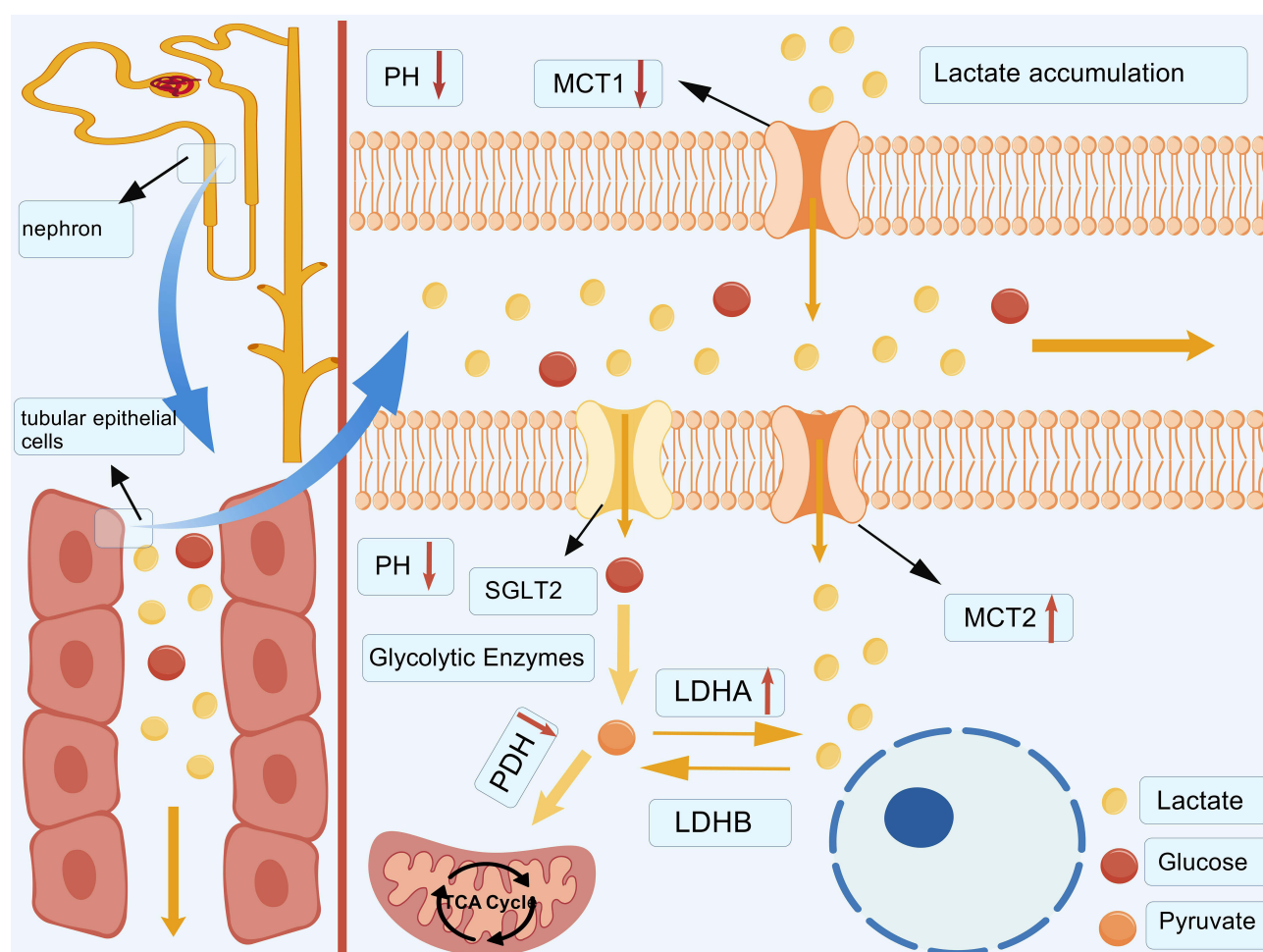


Figure 2 A schematic diagram of lactate metabolism in renal tubular epithelial cells under diabetic kidney disease. In diabetic kidney disease, glucose uptake by renal tubular epithelial cells via sodium–glucose cotransporter 2 (SGLT2) is associated with enhanced glycolytic activity and increased pyruvate generation. Pyruvate is preferentially converted to lactate by upregulated LDHA, while reduced activity of LDHB and PDH has been reported in association with further lactate accumulation. Intracellular lactate may be transported across the plasma membrane via monocarboxylic acid transporters, with altered MCT1- and MCT2-mediated fluxes described in diabetic kidney disease. Excessive lactate accumulation has been associated with changes in the local microenvironment, including altered pH, as well as with tubular epithelial cell injury and impaired renal function. Arrows indicate proposed metabolic routes or reported associations rather than direct causal relationships. This diagram was independently created by the authors using original graphical elements together with licensed BioGDP components. Created with BioGDP.com.²⁶

kidney injury research shows that the concentration of lactate dehydrogenase in plasma and urine is increased. Therefore, lactate dehydrogenase can be used as a potential indicator to reflect the damage of specific nephron segments. In addition, persistent hyperglycemia can activate the polyol metabolic pathway, upregulate the expression of lactate dehydrogenase, and promote the accumulation of lactate in the renal tissue.³³ PDH reduces lactate levels by facilitating the entry of pyruvate into mitochondrial oxidative metabolism, which is a key node for regulating cell energy metabolism and lactate homeostasis.³⁴ Inhibiting PDH activity will enhance aerobic glycolysis, increase lactate generation, and may impair lactate clearance, thereby contributing to lactate accumulation in tissues.^{35,36} The transmembrane transport of lactate is another important mechanism to maintain its steady-state distribution, which is mainly mediated by the monocarboxylic acid transport protein family. In the kidney, MCT1 is mainly located in proximal tubular cells, while MCT2 is mainly expressed in the thick ascending branch and distal tubule, which participates in lactate transport together.³⁷ It is reported that changes in MCT expression will affect glycolysis metabolism and cellular redox homeostasis.³⁸ Under the condition of DKD, proximal renal tubular cells showed a decrease in MCT1 expression and an increase in MCT2 expression, which is associated with an increase in intracellular lactate levels.³⁹ When lactate accumulation occurs in cells, the activity of MCT will be inhibited, thus hindering the transport of lactate from the inside of the cell to the outside of the cell, resulting in the further accumulation of lactate in the cell.⁴⁰

Enzymatic Regulation of Protein Lactylation

The dynamic control of histone lactylation is achieved through the coordinated actions of three functional classes of enzymes, conventionally referred to as writers, erasers, and readers.⁴¹ Writers and erasers are responsible for catalyzing the installation and removal of lactyl groups on lysine residues of histones. Through these reversible modifications, they influence chromatin organization and subsequently regulate gene transcription. In contrast, reader proteins recognize lactylated lysine sites and facilitate downstream transcriptional responses. It is reported that acetyltransferase p300 can directly catalyze histone lactylation.⁶ Emerging evidence further suggests that these regulatory enzymes may exhibit cell-specific functions within the kidney, particularly in renal tubular epithelial cells, where metabolic reprogramming and lactate accumulation are prominent features of kidney injury. In sepsis-associated acute kidney injury, lactate induces H3K18la through the acetyltransferase p300. The elevated H3K18la subsequently promotes the transcription of sphingosine kinase 1 (SPHK1), which in turn mediates the phosphorylation of sirtuin 1 (SIRT1) and accelerates its degradation. The reduction of SIRT1 further enhances H3K18la accumulation, forming a positive feedback regulatory loop that ultimately drives tubular epithelial cell death. These findings reveal that p300 and SIRT1 cooperatively participate in tubular epithelial cell injury.⁴² In addition, alanyl-tRNA synthetase 1 (AARS1) has been identified as a lactyltransferase, which can directly catalyze histone lactylation, and its upregulation has been associated with aggravated renal dysfunction in DKD models.⁴³ Recent studies further indicate that AARS1-mediated lactylation occurs predominantly in renal epithelial cells, where AARS1 mediates lactylation of STAT3 and p65, thereby regulating abnormal proliferation and fibrotic processes in renal tubular epithelial cells and ultimately promoting the progression of autosomal dominant polycystic kidney disease.⁴⁴ Erasers, including histone deacetylases 1–3 (HDAC1–3) and sirtuins 1–3 (SIRT1–3), have been reported to remove lactyl modifications and dynamically regulate lactylation levels.⁴⁵ Among these enzymes, the mitochondrial deacylase SIRT3 appears to play a particularly important role in proximal tubular epithelial cells, where mitochondrial metabolism is tightly coupled to lactate production and fibrotic signaling. In DKD, the impairment of SIRT3 function is associated with abnormal lactate accumulation and enhanced fibrotic reaction.⁴⁶ In DKD, down-regulation of SIRT3 in renal tubular cells promotes lactate accumulation, which subsequently enhances RUNX1 transcription through H4K12la, thereby inducing fibrotic responses in tubular epithelial cells.⁴⁷ Furthermore, SIRT3 contributes to the maintenance of mitochondrial metabolic homeostasis in renal tubular epithelial cells by deacetylating Lys385 of pyruvate dehydrogenase E1 α (PDHE1 α), thereby preventing mitochondrial protein hyperacetylation, limiting metabolic reprogramming, and suppressing renal fibrosis.⁴⁸ Collectively, these findings suggest that enzymes regulating protein lactylation exert cell-type-specific effects within the kidney and modulate renal cell injury by either delaying or promoting lactylation at specific target sites.

Enzymes involved in lactylation also play critical roles in other post-translational modifications, particularly acetylation, highlighting their dual regulatory functions.⁴⁹ For example, p300 serves as a writer protein for lactylation and

catalyzes lysine acetylation through its intrinsic HAT (histone acetyltransferase) domain, thereby modulating both modifications in response to the concentrations of various acyl-CoAs.^{50,51} HDAC1–3 and SIRT1–3 have been identified as dual-function deacetylases that remove both lysine acetylation and lactylation. SIRT1–3 exhibit broad-spectrum deacetylase activity, enabling the removal of multiple acyl modifications.⁵² It was found that SIRT1 is predominantly localized to the nucleus and cytoplasm, where it regulates both lactylation and acetylation, whereas SIRT3 is mainly localized to the mitochondria and modulates the same modifications on mitochondrial proteins.⁵³ Similarly, HDAC1–3 function as both deacetylases and delactylases in mammals.⁵⁴ Overall, these dual-function enzymes couple lactate metabolism to epigenetic regulation by utilizing shared catalytic domains and metabolite-dependent substrate selection, thereby coordinating acetylation and lactylation to modulate chromatin accessibility and transcription factor activity. Dynamic regulation of protein lactylation by these enzymes has been implicated in the modulation of protein function and transcriptional activity. However, the specific involvement of lactylation-related enzymes in the pathogenesis of DKD is not completely understood and requires further investigation.

Lactylation-Associated Pathological Mechanisms in Diabetic Kidney Disease

Inflammatory Activation

Inflammation is widely recognized as a central pathological feature of DKD.⁵⁵ Lactate generated through glycolysis can modulate the release of immune cell activation, inflammatory mediators, and intracellular signaling pathways.⁵⁶ Lactate metabolism has been shown to play a key role in driving macrophage polarization through mitochondrial pyruvate metabolism, a process central to the inflammatory response in DKD.⁵⁷ In DKD, polarized macrophages accumulate in the glomerulus, amplifying renal inflammation and fibrosis through the release of pro-inflammatory cytokines.^{58,59} Lactate metabolism induces macrophage polarization by promoting H4K12 lactylation, further accelerating CKD progression.⁶⁰ Meanwhile, macrophage polarization enhances glycolysis via the HIF-1 α -HK2 signaling pathway, forming a positive feedback loop.⁶¹ These findings highlight a reciprocal interaction between lactate metabolism and macrophage polarization, linking metabolic reprogramming to inflammatory responses in DKD pathogenesis. Furthermore, epigenetic modifications such as histone acetylation and methylation regulate macrophage polarization and synergize with lactylation to drive macrophage-mediated inflammatory responses.⁶² Lactate produced by the metabolic conversion of pyruvate can activate the NLRP3 inflammasome through protein kinase R (PKR) phosphorylation. This activation pathway has been demonstrated to have pathological relevance and can significantly promote renal inflammatory responses and fibrosis.^{63,64} As research has progressed, the role of histone lactylation in the regulation of inflammatory responses has gradually been elucidated. In patients with infectious shock, high serum lactate levels and lactate-mediated histone H3 lysine 18 lactylation (H3K18la) can promote the release of procalcitonin (PCT) and a variety of inflammatory factors, suggesting that lactylation may be important in the regulation of systemic inflammation.⁶⁵ The increase in H3K18la also facilitates binding to the promoters of NF- κ B1 (p50) and RelA (p65), thus affecting NF- κ B pathway activity and cytokine expression.⁶⁶ Insulin-like growth factor binding protein 5 (IGFBP5) has been implicated in tissue inflammation by enhancing glycolysis and lactate production.⁶⁷ Evaluation of renal tissues indicated that diabetic mice displayed substantially increased expression of endothelial–mesenchymal transition (EndoMT)–related markers along with IGFBP5 relative to control animals. In this context, loss of IGFBP5 was associated with a delayed course of renal injury progression. Further mechanistic studies found that IGFBP5 may promote lactate production by enhancing glycolytic activity, thereby inducing increased lactylation levels, among which H3K18la was the most prominent. Increased levels of H3K18la have been linked to enhanced activation of the NLRP3 inflammasome, accompanied by greater release of interleukin-1 β , a process that appears to aggravate renal inflammation.⁶⁸ Collectively, these observations suggest that histone lactylation is involved in DKD and may contribute to renal damage in association with heightened inflammatory responses. In addition, previous work has highlighted the glycolytic regulator PFKFB3 as a contributor to metabolic reprogramming in renal tubular cells. This shift is accompanied by increased lactate accumulation and elevated H4K12la, changes that coincide with transcriptional activation of NF- κ B–related signaling and a heightened inflammatory state in the kidney.⁶⁹ Lactate not only participates in the regulation of inflammation in DKD but also activates the NLRP3

inflammasome and the NF- κ B pathway through histone lactylation, thereby promoting the release of inflammatory mediators and exacerbating inflammatory responses. This process links glycolytic metabolic reprogramming with renal inflammation and provides new insight into the interplay between metabolism and inflammation in DKD.

Cell Death

In the pathogenesis of DKD, programmed cell death of kidney cells induced by persistent hyperglycemic conditions is implicated in the occurrence and development of DKD.⁷⁰ Under elevated glucose or pathological conditions, glucose metabolism in renal tubular cells is reprogrammed, tending towards the glycolysis pathway, leading to a large accumulation of lactate.⁷¹ This accumulated lactate can downregulate the expression of SIRT3 and AMP-activated protein kinase (AMPK) in renal tubular epithelial cells, thereby favoring the initiation of apoptotic processes.⁷² Lactate also exacerbates renal cell death by inducing protein lactylation. For example, lactate-associated histone lactylation is related to the activation of the RhoA/ROCK/NF- κ B signaling pathway, which is associated with inflammatory responses and apoptosis.⁷³ Moreover, lactate can promote abnormal mitochondrial fission by mediating lactylation of the mitochondrial fission-related protein Fis1, thereby inducing cell death and worsening renal dysfunction.⁷⁴ ACSF2 is a ferroptosis-associated protein primarily localized in mitochondria in renal tubular cells. In DKD, enhanced glycolysis leads to lactate accumulation, which contributes to increased global lysine lactylation in renal tissues. Notably, lactylation of ACSF2 at lysine 182 (K182) has been shown to exacerbate mitochondrial injury. This modification promotes excessive accumulation of reactive oxygen species (ROS) and impairs mitochondrial function. The resulting oxidative stress may further drive ferroptosis, thereby contributing to tubular damage.⁷⁵ In podocytes, lactate accumulation has been linked to the activation of mTORC1 signaling through lactylation of LARS1 at lysine 970, leading to impaired autophagy and increased apoptosis, thereby aggravating podocyte injury and proteinuria.⁷⁶ Ferroptosis has also been implicated in DKD pathophysiology.⁷⁷ Lactylation of proteins such as TRIM65 K206 has been reported to modulate the ubiquitination of iron response element-binding protein 2 (IREB2) and pyruvate dehydrogenase kinase 4 (PDK4), thereby facilitating ferroptotic responses and glycolytic dysfunction in renal tubular cells.⁷⁸ In addition, AARS1 can induce H3K181a and STAT1, regulate the transcriptional expression of elongase-5 (ELOVL5), thus contributing to the process of ferroptosis and aggravating DKD-related renal dysfunction.⁴³ Lactylation can also promote the expression of apoptosis-promoting genes by regulating gene transcription. Specifically, lactate from glycolysis can promote the lactylation of p53 and enhance its transcriptional activity, which further accelerates cell apoptosis.⁷⁹ It is worth noting that the role of lactate-driven cell apoptosis is not limited to kidney disease, but has also been verified in other disease systems. For example, the increase in glycolysis reprogramming and the production of lactate in crystalline silicosis promotes the level of lactylation to drive the death of NLRP3-dependent cells, and inhibiting this reprogramming can significantly alleviate the occurrence of cell death.⁸⁰ By modifying key proteins such as histones and mitochondrial factors, lactate has been implicated in the regulation of diverse programmed cell death processes, among them apoptosis, ferroptosis, and autophagy-related damage, changes that may contribute to ongoing renal parenchymal injury in DKD.

Fibrosis

Renal fibrosis is the core pathological feature of the progression of DKD. Its essence lies in the excessive deposition of the extracellular matrix, which eventually leads to renal failure.⁸¹ Aerobic glycolysis enhancement has been proven to promote collagen synthesis in fibroblasts and is closely linked to tissue fibrosis.⁸² As a prominent metabolite generated through glycolytic flux, lactate has been implicated in the activation of fibroblasts and the establishment of hypoxic, acidic microenvironments. Alongside these changes, lactate has been linked to enhanced transforming growth factor- β 1 (TGF- β 1) activity, a combination of effects that is thought to favor myofibroblast differentiation and drive fibrogenic responses.^{83–85} Lactate-induced protein lactylation has been implicated in EMT, a process associated with podocyte dysfunction and proteinuria in DKD.⁸⁶ Increased lactate levels have been reported to correlate with the extent of podocyte EMT under hyperglycemic conditions.⁸⁷ Experimental studies suggest that hyperglycemia-associated lactate accumulation promotes lactylation and EMT-related gene expression, which is associated with fibrotic remodeling and renal functional decline.⁸⁸ Lactylation has also been reported to modulate transcription factors involved in EMT.⁸⁹ In DKD, H3K141a has been linked to increased expression of the transcription factor KLF5 and enhanced EMT in renal

epithelial cells, whereas inhibition of LDHA or KLF5 deficiency has been associated with reduced H3K14la levels and attenuation of fibrotic progression.⁷ In addition, H3K18la has been strongly associated with renal fibrosis in DKD. Downregulation of Glis1 weakens its interaction with the lactyl transferase KAT5, thus enhancing the level of H3K18la, promoting tubular epithelial cell senescence, and contributing to fibrosis.⁹⁰ As a key glycolytic enzyme, the upregulation of pyruvate kinase M2 (PKM2) is linked to increased lactate production and H3K18la, and its expression level is correlated with the severity of fibrosis.⁹¹ During kidney stone development, increased galectin-3 (LGALS3) expression has been linked to PKM2 activation, accompanied by a shift toward enhanced glycolysis and greater lactate production. Accumulating lactate is associated with elevated H3K18la, which correlates with increased fibroblast growth factor receptor 4 (FGFR4) expression. Together, these changes may facilitate stone formation while also contributing to the progression of renal fibrosis.⁹² In chronic kidney disease, increased PKM2 activity is accompanied by lactate accumulation and higher levels of H3K18la, together with enhanced TGF- β 1 transcription. In this setting, macrophages tend to adopt a profibrotic M2-like phenotype and participate in macrophage–fibroblast transition via Smad3 signaling, a pattern that parallels the development of renal fibrosis.⁹³ Taken together, the available evidence supports an important involvement of H3K18la in processes underlying renal fibrotic remodeling. The development of renal fibrosis in DKD is closely related to disorders of lactate metabolism. Lactate-mediated protein lactylation regulates key pathways, including epithelial–mesenchymal transition, cell senescence, and fibrosis-related gene expression, thus activating fibrotic signaling pathways. Targeting lactate generation and its lactylation signaling pathways may provide new treatment strategies to slow down the progression of DKD fibrosis.

Lactate and Lactylation in DKD: Biomarkers and Therapeutic Implications

Lactate-Related Biomarkers

Lactate is an important metabolite, and its levels show significant changes in diabetic conditions.⁹⁴ There is a clear positive correlation between the level of lactate and lactylation. Studies show that the increase in lactate levels in blood plasma, urine, and kidney tissue in diabetes is closely related to the decrease in glomerular filtration rate and proteinuria. Therefore, lactate can be used as a new biomarker to reflect the rate of decline in glomerular filtration and predict the risk of kidney disease.^{95,96} Lactate metabolism-related enzymes are also involved in disease progression and prognostic markers of DKD. In DKD patients, the expression of LDHA in the glomerulus and renal tubular epithelial cells is significantly increased, accompanied by a decrease in glomerular filtration rate (eGFR) and an increase in the expression of the fibrosis marker α -SMA.⁹⁷ Elevated LDHA levels are not only an independent risk factor for the occurrence and development of DKD, but are also significantly associated with an increased risk of end-stage renal disease, increased cardiovascular mortality, and increased urinary albumin/creatinine ratio (ACR).^{98,99} It can be seen that the concentration of lactate and the expression of key metabolic enzymes are expected to be used as new biomarkers for the early diagnosis, disease assessment, progression prediction and monitoring of treatment response of DKD.

Detection and Clinical Potential of Protein Lactylation

Histone PTMs represent a central regulatory mechanism governing chromatin dynamics and gene transcription, and dysregulation of these modifications has been closely associated with the pathogenesis and progression of numerous human diseases. In 2019, the research group led by Yingming Zhao first identified lysine lactylation as a novel histone modification using a specific anti-H3K18la antibody combined with chromatin immunoprecipitation sequencing (ChIP-seq) and RNA sequencing analyses.⁶ Traditional methods for detecting histone PTMs, including Western blotting and ChIP-seq, rely largely on antibody-based recognition and are limited by relatively low throughput. Advances in high-resolution mass spectrometry have transformed the study of histone modifications, and mass spectrometry-based proteomics is now considered a powerful approach for identifying lactylation sites and performing global lactylome profiling.¹⁰⁰

Although standardized clinical assays for lactylation detection remain lacking, several studies have begun to explore its detection in human tissues using antibody-based approaches. For example, immunohistochemical and immunoblot analyses using a monoclonal antibody against H4K5la revealed significantly elevated H4K5la levels in breast cancer

tissues, with expression positively correlated with serum lactate and carcinoembryonic antigen levels.¹⁰¹ In parallel, label-free quantitative lactylome profiling strategies have been developed to systematically characterize lysine lactylation and investigate its metabolic regulation in diseases such as diabetes.¹⁰² Despite these advances, clinical detection of protein lactylation remains at an early stage. The development of high-sensitivity mass spectrometry platforms and highly specific anti-lactyllysine antibodies, together with optimized antibody-based detection protocols, will therefore be essential for establishing standardized assays and advancing lactylation as a clinically relevant biomarker.

Potential Therapeutic Strategies in DKD

With the deepening of the understanding of lactate metabolism and lactylation in DKD, the treatment strategies for these pathways have attracted increasing attention. Regulation of lactate production, related enzymes, and transport processes may provide potential opportunities for mechanism-based therapeutic intervention. Lactate production is closely associated with glomerular filtration, renal tubular sodium reabsorption, and urine flow. Loop diuretics can reduce lactate production by inhibiting the reabsorption of sodium in renal tubules.²⁷ A clinical study involving 39 patients with DKD demonstrated that Sodium-glucose cotransporter 2 (SGLT2) inhibition reduced lactate production and restored oxidative phosphorylation in human proximal tubular cells.³⁹ However, SGLT2 inhibitor use is associated with an increased risk of adverse events, particularly urinary tract infections, volume depletion, ketoacidosis, and fractures.¹⁰³ LDHA is a key enzyme involved in lactate production. Modulating LDHA activity has been shown to limit lactate generation, thereby reducing the severity of renal injury. In the DKD mouse model, intervention with the LDHA inhibitor sodium oxalate (Oxa) can significantly reduce the serum lactate levels in mice and inhibit histone lactylation.⁸⁸ Furthermore, research has also shown that angiotensin-receptor blocker (ARB) can reduce lactate accumulation by inhibiting the expression of LDHA in proximal renal tubules, thus exerting a protective role in the kidney.¹⁰⁴ Nevertheless, inhibition of LDH triggers metabolic reprogramming that increases fatty acid catabolism. This metabolic shift is coupled with ROS accumulation and ATP depletion, leading to exacerbated DNA damage and impaired DNA repair. Collectively, these effects ultimately enhance cellular susceptibility to oxidative stress and promote cell death.^{105–107} Modulation of MCT activity has been shown to influence renal lactate handling. For example, the MCT inhibitor syrosingopine can block the transport of lactate, the end product of glycolysis, thereby attenuating tubular injury and fibrosis in unilateral ischemia–reperfusion injury (IRI) mice.¹⁰⁸ Nevertheless, extensive inhibition of MCT expression may result in non-specific adverse effects. Clinical administration of the MCT1 inhibitor AZD3965 has been associated with adverse events, including retinopathy, cardiotoxicity, fatigue, gastrointestinal toxicities, and metabolic acidosis.¹⁰⁹ Therefore, the development of highly selective MCT-targeted inhibitors is of great research significance. Lactate exerts diverse functions in metabolism. It acts as a critical glycolytic intermediate supplying the TCA cycle, regulates immune responses, and serves as a signaling molecule. It modulates cellular functions through lactate shuttling and receptor-mediated pathways. Accordingly, widespread inhibition of lactate generation or metabolism may disrupt these processes and lead to metabolic dysregulation.^{110–112}

Current research indicates that therapeutic modulation of lactylation may be achieved through pharmacological intervention targeting lactylation “writers.” A-485 is a selective inhibitor of p300 that binds to its catalytic site and competes with acetyl-CoA, thereby suppressing histone modifications.¹¹³ Moreover, “erasers” have also been shown to regulate lactylation dynamics. Nicotinamide adenine dinucleotide (NAD⁺) regulates the deacylase activity of the sirtuin family.¹¹⁴ Honokiol (HKL) functions as a SIRT3 activator that markedly suppresses Cyclin E2 (CCNE2) lactylation through SIRT3 activation, ultimately driving hepatocellular carcinoma progression.¹¹⁵ Although no therapeutic strategy currently exists that specifically targets individual lysine lactylation sites in DKD, recent studies have demonstrated that genetic code expansion enables the site-specific incorporation of lysine lactylation, thereby laying the groundwork for the future development of targeted inhibitory strategies against this modification.¹¹⁶ Notably, there are currently no clinically available therapeutic strategies that directly and specifically target protein lactylation at defined lysine residues in DKD. Although pharmacological modulation of lactate metabolism may indirectly influence lactylation levels, such approaches lack specificity and may disrupt physiological metabolic homeostasis. Emerging evidence suggests that enzymes involved in lactylation dynamics, including lactylation “writers” and “erasers”, may represent potential targets for more selective intervention. However, the development of such strategies remains in its early stages, and their feasibility,

specificity, and safety in the context of DKD require further investigation. In particular, whether targeting these enzymes can achieve site-specific modulation of lactylation without affecting other PTMs remains an important challenge.

Discussion

As a narrative review, this study may be subject to potential selection bias, and future systematic analyses are warranted to provide a more comprehensive and unbiased synthesis of the available evidence. This review synthesizes current evidence on the critical involvement of lactate metabolism and lactylation in the pathogenesis of DKD, and explores their promising implications for clinical diagnosis and treatment. Traditionally, lactate has been regarded as a metabolic end product. However, the recognition of the Warburg effect has redefined lactate as an active metabolic regulator, thereby expanding its functional role in cellular processes. Metabolic reprogramming under hyperglycemic conditions promotes lactate accumulation, which acts as a key metabolic signal linking disordered energy metabolism to renal injury. Notably, lactate can serve as a substrate for histone lactylation, extending its role in epigenetic regulation. Emerging evidence further indicates that lactylation functions as a metabolite-driven signaling mechanism. It translates glycolysis-derived lactate accumulation into epigenetic regulation by inducing lysine lactylation on both histone and non-histone proteins. This modification regulates chromatin accessibility and facilitates the recruitment of transcriptional machinery, thereby modulating gene expression programs associated with disease progression. Histone lactylation is involved in multiple signaling pathways related to inflammation, cell death, and fibrosis, thereby contributing to the pathogenesis of DKD. In addition, lactylation of non-histone proteins further broadens the regulatory landscape of this modification in DKD. Collectively, these findings position lactylation as a central mediator that integrates glycolytic reprogramming with transcriptional control, ultimately contributing to DKD progression (Table 2 and Figure 3). Notably, while most studies consistently support a deleterious role of lactylation in DKD, the underlying mechanisms remain incompletely understood and may vary depending on cell type, disease stage, and experimental conditions. In addition to mechanistic insights, this review addresses the dysregulation of lactate metabolism in DKD, explores the potential of lactate as

Table 2 Mechanistic Roles of Protein Lactylation in the Pathogenesis of DKD

Author	Mechanism	Model	Lactylation Target	Molecular Pathway	Ref
Xiaofang Hu	Inflammatory activation	STZ-induced mice	H3K18	IGFBP5↓→Lactate↑→H3K18la↑→NLRP3 inflammasome↑→IL-1β↑→Renal inflammation↑	[51]
Jingfang Chen	Cell death	db/db mice	ACSF2 K182	Lactate↑→ACSF2 K182la↑→Mitochondrial dysfunction↑→ROS↑→Renal tubular injury↑	[58]
Zhibin Fan		STZ-induced mice	LARS1 K970	Lactate↑→LARS1 K970la↑→mTORC1↑→Apoptosis↑→Podocyte injury and Proteinuria↑	[59]
Guangyan Yang		db/db mice	TRIM65 K206	Lactate↑→TRIM65 K206la↑→IREB2/PDK4 Ubiquitination↓→Ferroptosis/Glycolysis↑→Kidney injury↑	[61]
Jia Hong		STZ-induced mice	H3K18	AARS1↑→H3K18la/STAT1↑→ELOVL5↑→Ferroptosis↑	[38]
Ting Zheng	Fibrosis	STZ-induced mice	Histone	Lactate↑→Histone lactylation↑→Podocyte EMT↑	[71]
Xuanxuan Zhang		db/db mice	H3K14	Lactate↑→H3K14la↑→KLF5↑→EMT↑	[7]
Juan Chen		STZ-induced mice	H3K18	Glis1↓→KAT5↑→H3K18la↑→Renal fibrosis↑	[73]

Notes: This table summarizes representative studies investigating the role of lactylation in DKD, including experimental models, specific lactylation targets, and associated molecular pathways. The findings highlight how site-specific protein lactylation (eg., H3K18la, H3K14la, and non-histone protein lactylation) contributes to key pathological processes, including inflammatory activation, cell death, and renal fibrosis. Arrows (↑/↓) indicate upregulation or downregulation, respectively.

Abbreviations: STZ, streptozotocin; EMT, epithelial–mesenchymal transition; NLRP3, NLR family pyrin domain containing 3; mTORC1, mechanistic target of rapamycin complex 1; ACSF2, acyl-CoA synthetase family member 2; ROS, reactive oxygen species; LARS1, leucyl-tRNA synthetase 1; TRIM65, tripartite motif containing 65; AARS1, alanyl-tRNA synthetase 1; ELOVL5, elongation of very long chain fatty acids protein 5; KAT5, lysine acetyltransferase 5.

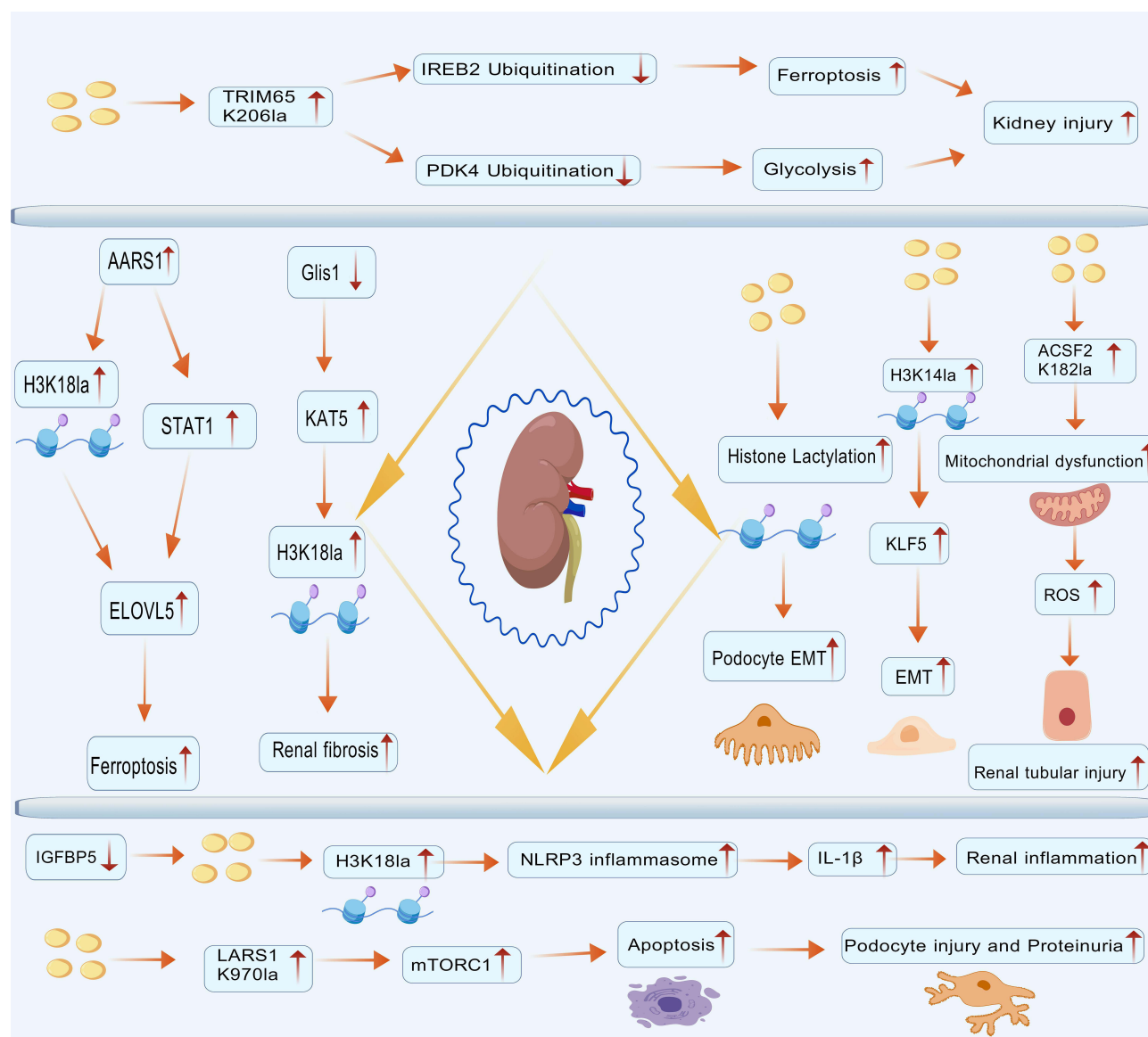


Figure 3 Overview of protein lactylation in diabetic kidney disease. This diagram illustrates reported pathways linking protein lactylation to pathological features of diabetic kidney disease, based on currently available evidence. Protein lactylation has been described in association with inflammatory activation, cell death, and renal fibrosis. Arrows represent reported associations rather than direct causal relationships, and upward arrows indicate relative increases under diabetic conditions. This diagram was independently created by the authors using original graphical elements together with licensed BioGDP components. Created with BioGDP.com.²⁶

a biomarker and the clinical detection of lactylation, and summarizes experimental and clinical studies on targeted therapies for lactate metabolic disturbances, along with their associated adverse effects (Table 3). These observations further support the clinical relevance of lactate metabolism and lactylation in DKD.

Despite these advances, several limitations remain in the current research: First, most current evidence regarding protein lactylation in DKD is derived from experimental studies, including animal models and *in vitro* investigations. Whether the lactylation patterns identified in db/db mouse models accurately reflect those in human DKD remains uncertain, and direct clinical evidence from patients with DKD is still limited. Nevertheless, clinical studies in other diseases provide indirect support for the potential pathological relevance of lactylation. For instance, elevated levels of neutrophil H4K5la have been reported in patients with sepsis and have been proposed as a promising clinical biomarker.¹¹⁷ In ocular melanoma, histone lactylation has been shown to promote tumorigenesis by upregulating the expression of YTHDF2, which recognizes and degrades m6A-modified tumor-suppressor transcripts.¹¹⁸ Similarly, in

Table 3 Pharmacological Interventions Targeting Lactate Metabolism and Lactylation-Related Pathways

Pharmacological Agents	Experiment Type	Intervention	Pathophysiological Outcome	Ref
Loop diuretics	Clinical study	Inhibit sodium reabsorption	Reduce lactate production	[21]
SGLT2	Clinical study	Restore oxidative phosphorylation	Reduce lactate production	[34]
Oxa	Animal study	Inhibit LDHA activity	Reduce lactate production	[71]
ARB	Animal study	Inhibit LDHA activity	Reduce lactate production	[87]
Syrosingopine	Animal study	Inhibit MCT	Inhibit lactate transport	[91]
AZD3965	Clinical study	Inhibit MCT	Inhibit lactate transport	[92]
A-485	Animal study	Inhibit P300	Suppress histone modifications	[96]
HKL	Clinical study	Activate SIRT3	Inhibit lactylation	[98]

Notes: This table summarizes representative pharmacological agents that modulate lactate production, transport, and lactylation-associated epigenetic regulation. The type of experiment (clinical or animal studies), intervention (eg., inhibition of LDHA activity, lactate transport, or p300-mediated histone modification, and activation of SIRT3), and corresponding pathophysiological outcomes are presented. These interventions highlight potential therapeutic strategies for regulating metabolic–epigenetic pathways in DKD.

Abbreviations: SGLT2, sodium–glucose cotransporter 2; LDHA, lactate dehydrogenase A; ARB, angiotensin II receptor blocker; MCT, monocarboxylate transporter; p300, E1A-binding protein p300; SIRT3, sirtuin 3; HKL, honokiol.

hepatocellular carcinoma, H3K14la promotes chemoresistance by increasing NEDD4 expression, leading to PTEN ubiquitination and activation of the PI3K/Akt/mTOR signaling pathway.¹¹⁹ Furthermore, a clinical study titled “The mechanism of lactylation involved in the development of diabetes-related complications” (ChiCTR2500109301) is currently underway.¹²⁰ Collectively, these findings highlight the potential mechanistic and clinical relevance of lactylation in human diseases and suggest that similar mechanisms may also exist in DKD. Therefore, large-scale studies involving human cohorts are urgently needed to determine whether the lactylation patterns observed in experimental models truly reflect the progression of DKD in patients. Secondly, current assessment of lactylation in clinical settings largely relies on lactate measurement, which serves only as an indirect and insufficient surrogate for actual lactylation levels. Although lactylation directed antibodies are available, they are primarily used in research settings and are limited by cost as well as suboptimal sensitivity and specificity. Furthermore, the limited availability of highly specific and well validated lactylation antibodies, together with the lack of high sensitivity mass spectrometry platforms, continues to hinder the clinical translation of lactylation as a reliable biomarker for diagnosis and prognosis. Finally, currently, no specific therapeutic agents directly targeting protein lactylation are available in clinical practice. Existing intervention strategies primarily focus on modulating lactate production and transport, as well as enzymes involved in lactate metabolism and lactylation. These include SGLT2 inhibitors, MCT inhibitors, LDHA inhibitors, and modulators of enzymes involved in lactylation and delactylation. Such approaches may indirectly influence lactylation levels by reducing intracellular lactate concentrations or by modulating enzymes associated with lactylation, thereby potentially attenuating the progression of kidney injury. However, these interventions may disrupt cellular energy homeostasis and lead to off-target metabolic effects, raising potential safety concerns.

With the continued advancement of research methodologies and deeper mechanistic investigations, studies on lactate-mediated protein lactylation are expected to further elucidate the pathogenesis of DKD and facilitate the development of novel therapeutic strategies.

Conclusion

In summary, lactate-mediated protein lactylation represents a novel link between metabolic reprogramming and epigenetic regulation in the pathogenesis of DKD. Although dysregulated lactate metabolism and enhanced lactylation have been associated with key pathological processes such as inflammation, cell death, and fibrosis, the exact mechanisms underlying these associations remain poorly understood and warrant further investigation. Future studies should focus on elucidating the interactions between lactylation and various pathogenic pathways in DKD, including inflammation, oxidative stress, metabolic dysregulation, and epigenetic modifications, to establish a more definitive link between lactylation and the progression of DKD. These insights highlight lactylation as a potential integrative mechanism linking metabolic and epigenetic dysregulation in DKD. Additionally, while clinical research on lactylation in diseases beyond

diabetes and clinical trials exploring lactylation in diabetic complications have been initiated, most current evidence remains largely derived from preclinical studies, and the clinical application of lactylation as a biomarker in DKD is still limited due to challenges in detection methods. Therapeutic strategies targeting lactylation primarily focus on regulating lactate metabolism, transport, and enzymes involved in lactylation and delactylation to mitigate kidney damage caused by lactylation. However, these strategies may carry potential clinical side effects, and there is a lack of specific pharmacological agents targeting lactylation in DKD. Therefore, future efforts should prioritize clinical validation, the development of biomarkers, and the creation of specific drugs that target lactylation, which could ultimately translate these findings into novel diagnostic and therapeutic strategies for DKD.

Abbreviations

DKD, Diabetic kidney disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; MRAs, mineralocorticoid receptor antagonists; GLP-1R, glucagon-like peptide-1 receptor; PTM, post-translational modification; EMT, epithelial-mesenchymal transition; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase; MCTs, monocarboxylate transporters; LDHA, lactate dehydrogenase A; LDHB, lactate dehydrogenase B; SPHK1, sphingosine kinase 1; SIRT1, sirtuin 1; AARS1, alanyl-tRNA synthetase 1; HDAC1–3, deacetylases 1–3; SIRT1–3, sirtuins 1–3; PDHE1 α , pyruvate dehydrogenase E1 α ; HAT, histone acetyltransferase; PKR, protein kinase R; H3K18la, H3 lysine 18 lactylation; PCT, prolactin; IGFBP5, insulin-like growth factor binding protein 5; EndoMT, endothelial-mesenchymal transition; AMPK, AMP-activated protein kinase; ROS, reactive oxygen species; IREB2, iron response element-binding protein 2; PDK4, pyruvate dehydrogenase kinase 4; ELOVL5, elongase-5; TGF- β 1, transforming growth factor- β 1; PKM2, pyruvate kinase M2; LGALS3, galectin-3; FGFR4, fibroblast growth factor receptor 4; eGFR, estimated glomerular filtration rate; ACR, albumin/creatinine ratio; ChIP-seq, chromatin immunoprecipitation sequencing; SGLT2, sodium-glucose cotransporter 2; Oxa, oxalate; ARB, angiotensin-receptor blocker; IRI, ischemia-reperfusion injury; NAD⁺, nicotinamide adenine dinucleotide; HKL, honokiol; CCNE2, cyclin E2.

Data Sharing Statement

No data was created or analysed in this study.

Author Contributions

Lele Sun: Conceptualization, Data curation, Writing – original draft, Visualization, Funding acquisition. Yuanyuan Yang: Conceptualization, Writing – original draft, Visualization, Writing – review and editing. Wenyi Pan: Data curation, Writing – original draft, Writing – review and editing. Chenghua Zhang: Supervision, Conceptualization, Writing – original draft, Funding acquisition, Writing – review and editing. Jiawei Lu: Data curation, Writing – review and editing, Supervision. Shaowen Guo: Supervision, Funding acquisition, Data curation, Writing – review and editing. Ying Zhu: Writing – original draft, Conceptualization, Writing – review and editing, Supervision. Meifeng Zhu: Conceptualization, Supervision, Funding acquisition, Writing – review and editing. Lele Sun, Yuanyuan Yang, and Wenyi Pan contributed equally to this work as co-first authors. All authors contributed to the article, gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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