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STATE OF THE ART REVIEW

Lactate metabolism and lactylation in kidney diseases: insights into mechanisms and therapeutic opportunities

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ABSTRACT

The kidney is essential for lactate metabolism. Under normal conditions, the renal cortex mainly absorbs and metabolizes lactate, with minimal amounts excreted in urine. This process is part of a glucose-lactate recycling system between the cortex and medulla. In conditions such as acute kidney injury (AKI) and diabetic kidney disease (DKD), the kidney's ability to metabolize lactate is impaired, leading to lactate accumulation and exacerbated renal dysfunction. Novel post-translational modifications, such as lactylation, are critical in kidney disease pathophysiology by modulating gene transcription, protein function, and cellular metabolism. Lactylation is involved in inflammatory responses and tumor promotion in AKI, mitochondrial dysfunction in DKD, and tumor progression in clear cell renal cell carcinoma (ccRCC). The lactate-lactylation axis is central to the Warburg effect in ccRCC, where tumor cells preferentially rely on glycolysis rather than oxidative phosphorylation. Understanding the mechanisms of lactate metabolism and lactylation in kidney diseases may offer new therapeutic strategies. This review examines the role of lactate esters, especially lactylation, in kidney diseases, with a focus on their regulatory mechanisms and potential as therapeutic targets.

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1. Introduction

The kidney plays a crucial role in lactate metabolism, serving as the main consumer of lactate after the liver [1,2]. Under normal conditions, the renal cortex primarily absorbs and metabolizes lactate, with urinary excretion representing a minor fraction of total lactate elimination. This metabolic activity is part of a glucose-lactate recycling system between the cortex and medulla. The medulla generates lactate through glycolysis, which is then absorbed by the cortex for oxidation and gluconeogenesis. The cortex's utilization of lactate is closely linked to the glomerular filtration rate, urine flow rate, and sodium reabsorption, highlighting the complex interplay between lactate metabolism and renal function.

In pathological conditions like acute kidney injury (AKI) and diabetic kidney disease (DKD), the kidney's ability to metabolize lactate can be significantly impaired. In AKI, the imbalance between glycolysis and gluconeogenesis leads to lactate accumulation, further impairing renal function [3]. In DKD, elevated urine lactate levels correlate with a rapid decline in kidney function, suggesting lactate's potential as a biomarker for renal dysfunction. Hyperglycemia-induced lactate overproduction is partly mediated by proximal tubular cells, which upregulate glycolytic genes as an adaptation to mitochondrial dysfunction common in DKD. Lactate accumulation may exacerbate mitochondrial dysfunction, creating a feed-forward cycle that worsens renal injury. In clear cell renal cell carcinoma (ccRCC), lactate accumulation in the tumor microenvironment (TME) is linked to metabolic reprogramming and immune suppression, influencing tumor progression and immune evasion, independent of its role in AKI or DKD.

Novel post-translational modifications (PTMs), such as lactylation, are critical in the pathophysiology of kidney diseases by modulating gene transcription, protein function, and cellular metabolism [4]. These PTMs can alter enzyme activity, affect protein stability and interactions, and even modify epigenetic gene regulation. Zhang et al. [5] first discovered a novel modification in histone proteins, termed histone lysine lactylation (Kla). This modification involves adding a lactate derivative to the side chain of lysine residues in histones. In addition to core histones, Kla modification sites have also been observed in other nonhistone proteins within the cell. Lactylation refers to the addition of a lactyl group to histone

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or nonhistone proteins. The lactyl group is thought to attach to proteins *via* lactyl-coenzyme A (lactyl-CoA) or a nonenzymatic mechanism. Previous reviews [6–8] extensively discuss the formation and regulation of lysine lactylation. The discovery of protein lactylation represents a significant advancement in the field of protein PTMs. It opens up new avenues of research for understanding the role of lactate metabolism in various biological contexts, including cancer, lung diseases, liver conditions, brain disorders, heart diseases, and many other fields [6–19].

In AKI, lactylation is implicated in inflammatory response activation and tumor promotion, indicating its potential role in disease progression. In DKD, lactate metabolism plays a key role in disease etiology and progression, with hyperglycemia-induced lactate production worsening mitochondrial dysfunction and contributing to renal injury. In ccRCC, lactate supports tumor growth by enhancing oncogene expression and cell proliferation and contributes to immune evasion by modulating the immune response within the TME. The lactate-lactylation pathway is key to the Warburg effect in ccRCC. In these tumor cells, glycolysis is favored over oxidative phosphorylation, resulting in lactate buildup that creates a supportive environment for tumor growth. Our current review explores the role of lactate esters, particularly lactylation, in kidney diseases, focusing on its regulatory mechanisms and potential as a therapeutic target (Table 1).

2. Lactate, lactylation, and AKI

2.1. Lactate metabolism in AKI

AKI is characterized by a rapid decline in renal function, often accompanied by the accumulation of metabolic waste, including lactate. Lactate, traditionally viewed as a byproduct of anaerobic glycolysis, is now recognized as a key metabolite in various physiological and pathological processes. In AKI, lactate metabolism is significantly disrupted [3]. The kidney, a major gluconeogenic organ, typically utilizes lactate under normal conditions. However, during AKI, the balance between glycolysis and gluconeogenesis is disturbed, leading to lactate accumulation. This lactate buildup further exacerbates AKI severity and worsens its prognosis.

During AKI, lactate production increases due to a shift toward aerobic glycolysis, even in the presence of oxygen, known as the Warburg effect. This metabolic reprogramming occurs in tubular epithelial cells, especially in the energy-demanding proximal tubular cells. Impaired mitochondrial function in these cells during AKI contributes to increased lactate production. Additionally, lactate clearance is impaired in AKI due to dysregulation of renal gluconeogenesis. Under normal conditions, the kidneys convert lactate into glucose *via* gluconeogenesis, involving enzymes such as pyruvate carboxylase and phosphoenolpyruvate carboxykinase. However, during AKI, renal function is compromised, leading to decreased expression and/or activity of these key gluconeogenic enzymes. This reduction in enzyme activity impairs lactate conversion to glucose, hindering lactate clearance and contributing to its accumulation in the kidney.

Lactate has immunomodulatory effects in AKI. It influences both innate and adaptive immune responses, affecting the function of immune cells such as macrophages and T lymphocytes. Lactate induces a shift in macrophage polarization toward an M2 phenotype, associated with anti-inflammatory and reparative functions. Lactate also modulates T-cell differentiation, promoting a regulatory phenotype that may contribute to immunosuppression in severe AKI.

2.2. Lactylation modification in AKI

Lactylation involves attaching lactate to histone and nonhistone proteins. This modification regulates gene transcription of metabolic enzymes involved in glycolysis or the Warburg effect. In AKI, Wang et al. [20] show that the glycolytic enzyme PFKFB3 is significantly upregulated in renal proximal tubular cells following ischemia-reperfusion injury and in patients with chronic kidney disease, correlating with the severity of kidney fibrosis. PFKFB3-mediated glycolysis leads to lactate accumulation, promoting histone lactylation, particularly enhancing H4K12la. This histone modification is enriched at the promoters of NF-κB signaling genes, such as Ikbkb, Rela, and Relb, activating their transcription and contributing to inflammation and kidney fibrosis. This study suggests that targeting PFKFB3 to modulate lactate-mediated histone lactylation could offer a novel therapeutic strategy for kidney diseases by reducing renal inflammation and fibrosis through NF-κB signaling inhibition.

Prior research highlights the significant role of lactate metabolism in sepsis-associated acute kidney injury (SA-AKI). Lactate, identified as an independent risk factor, exacerbates SA-AKI through the lactylation of mitochondrial proteins, specifically Fis1 at lysine 20 (Fis1 K20la) [21]. This modification triggers excessive mitochondrial fission, ATP depletion, and reactive oxygen species overproduction, which are hallmarks of cellular damage in SA-AKI. Additionally, lactate levels correlate with the severity of septic shock [22,23], with higher levels correlating with increased incidence of SA-AKI and poor clinical outcomes. Histone H3 lysine 18 lactylation (H3K18la) emerges as a potential biomarker, reflecting critical illness severity and infection presence, and may mediate inflammatory responses in sepsis [24]. These findings highlight the interplay between lactate metabolism and protein lactylation in SA-AKI pathophysiology, suggesting that targeting lactate reduction and lactylation inhibition could offer promising therapeutic approaches.

2.3. Research gaps and future directions

Current research highlights the pivotal role of lactate as a metabolic regulator in AKI. However, the precise mechanisms by which lactate metabolism influences renal injury remain unclear. Future studies should focus on elucidating the metabolic pathways that contribute to lactate accumulation in

Table 1. Summary of lactylation mechanisms and implications in renal diseases.

Studies	Diseases	Key Research Contents	Lactylation proteins	Writers	Erasers	Mechanisms	Implications
Wang et al. 2024 [20]	CKD	Explored the role of PFKFB3 in driving kidney fibrosis through promoting histone lactylation and NF-kB activation	H4K12	Not specified	Not specified	PFKFB3-induced lactate accumulation promotes renal inflammation and fibrosis via NF-kB pathway activation	Indicates the potential of targeting PFKFB3 to treat renal fibrosis by modulating histone lactylation and NF-kB signaling
An et al. 2023 [21]	SAKI	PDHA1 hyperacetylation-mediated lactate overproduction promotes sepsis-induced acute kidney injury via Fis1 lactylation	Fis1 K20	PDHA1	SIRT3	Lactate mediates Fis1 lactylation, leading to mitochondrial dysfunction and SAKI	Reducing lactate levels and Fis1 lactylation attenuates SAKI
Qiao et al. 2024 [24]	SAKI	Histone H3K18 and Ezrin lactylation promote renal dysfunction in sepsis-associated acute kidney injury	H3K18 and Ezrin K263	Not specified	Not specified	Lactate-induced lactylation of H3K18 and Ezrin promotes RhoA/ROCK/Ezrin signaling, leading to renal dysfunction	Inhibition of lactate-induced lactylation may improve renal function in SAKI
Chen et al. 2024 [26]	DKD	Lysine lactylation and ACSF2 contribute to mitochondrial dysfunction in diabetic nephropathy	ACSF2 K182	Not specified	Not specified	Lactate accumulation drives lysine lactylation, affecting mitochondrial function	Targeting mitochondrial ACSF2 and lactylation may be a potential strategy for diabetic nephropathy interventions
Zhang et al. 2024 [27]	DKD	Lactate drives epithelial-mesenchymal transition in diabetic kidney disease via the H3K14la/KLF5 pathway	H3K14	Not specified	Not specified	Lactate-induced H3K14la promotes KLF5 expression, driving EMT and DKD progression	Inhibition of KLF5 could be a potential therapeutic strategy for DKD
Liu et al. 2024 [28]	ccRCC	FKBP10 promotes ccRCC progression and regulates sensitivity to HIF2α blockade by facilitating LDHA phosphorylation	Histone lactylation linked to LDHA-Y10 phosphorylation	Not specified	Not specified	FKBP10 binding to LDHA enhances its phosphorylation, promoting glycolysis and ccRCC progression	FKBP10 may be a therapeutic target for ccRCC by enhancing the antitumor effect of HIF2α inhibitors
Liu et al. 2024 [29]	ccRCC	Investigated lactylation modifications in ccRCC using bioinformatics and machine learning	328 lactylation-associated genes; 16 genes correlated with survival (specific sites not detailed)	Not specified	Not specified	Lactylation modifications are linked to patient prognosis and may offer therapeutic opportunities	Identifies lactylation's role in ccRCC prognosis and therapeutic opportunities
Yang et al. 2022 [30]	ccRCC	Identifies a positive feedback loop between inactive VHL and histone lactylation driving ccRCC progression	H3K18 as the main target (other sites not specified)	Not specified	Not specified	Inactive VHL triggers histone lactylation which activates PDGFRβ, forming a positive feedback loop	Suggests targeting histone lactylation and PDGFRβ signaling as a therapeutic strategy for ccRCC

DKD: Diabetic Kidney Disease; SAKI: Sepsis-Induced Acute Kidney Injury; ccRCC: Clear Cell Renal Cell Carcinoma; CKD: Chronic Kidney Disease; EMT: Epithelial-Mesenchymal Transition; ACSF2: Acyl-CoA Synthetase Family Member 2; PDHA1: Pyruvate Dehydrogenase E1 Component Subunit Alpha; SIRT3: Sirtuin 3; Fis1: Mitochondrial Fission 1 Protein; KLF5: Kruppel-Like Factor 5; H4K12: Histone H4 Lysine 12; H3K14: Histone H3 Lysine 14; H3K18: Histone H3 Lysine 18; LDHA: Lactate Dehydrogenase A; PDGFRβ: Platelet-Derived Growth Factor Receptor Beta; VHL: von Hippel-Lindau; HIF: Hypoxia-Inducible Factors; NF-kB: Nuclear Factor kappa B; PFKFB3: 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3.

AKI and its impact on cellular respiration, the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation. This could involve investigating pyruvate dehydrogenase (PDH) and its regulation by Sirtuin 3 (SIRT3) in renal tubular epithelial cells.

Previous studies indicate that lactylation plays a significant role in AKI pathogenesis [3,21,24]. However, the full extent of lactylation's effects on cellular processes and its potential as a therapeutic target remain unexplored. Future

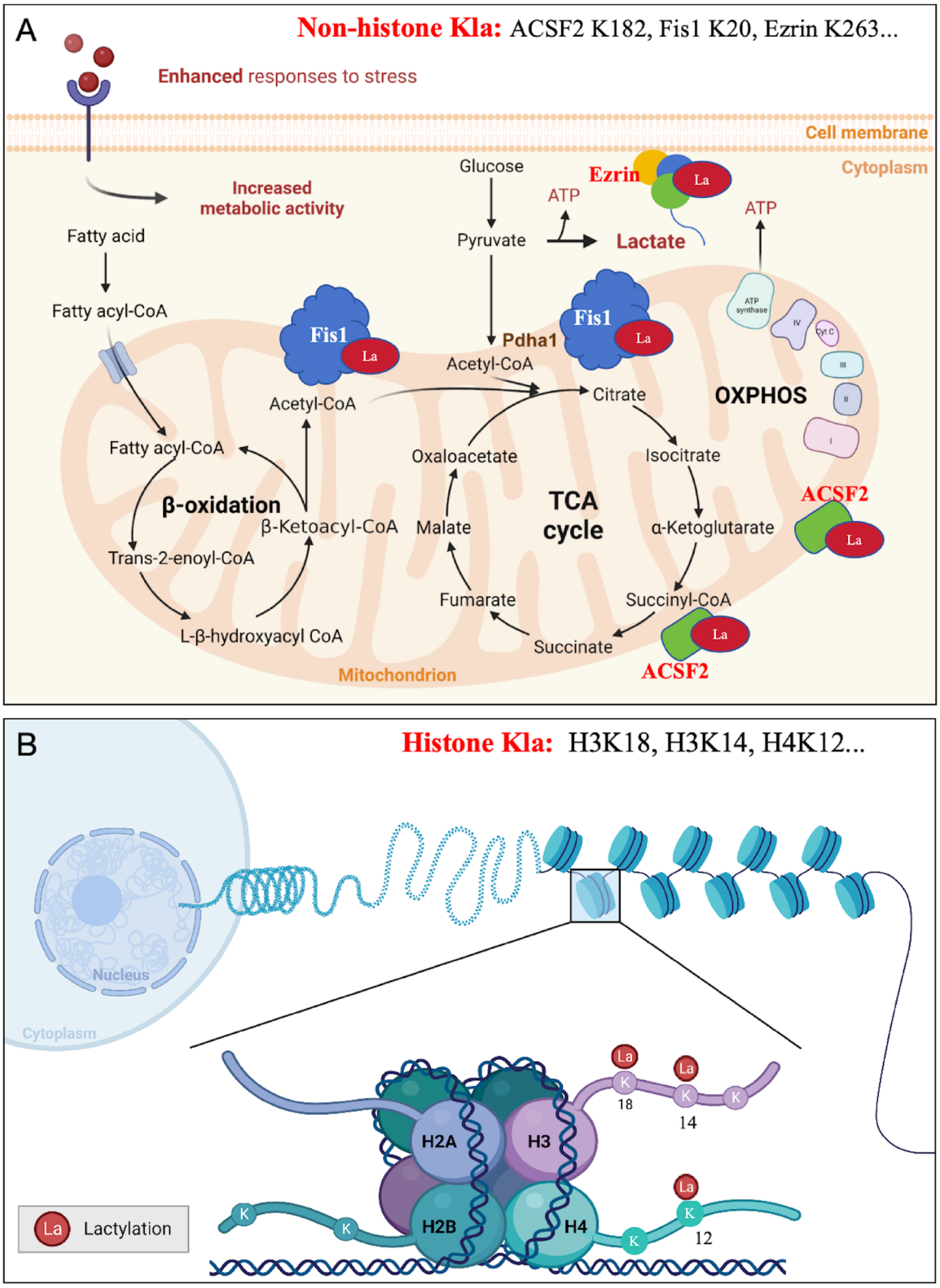

Figure 1. Role of nonhistone (A) and histone (B) lysine lactylation in kidney diseases.
H3K18: Histone H3 Lysine 18; H3K14: Histone H3 Lysine 14; H4K12: Histone H4 Lysine 12; Kla: Lysine Lactylation.

research could focus on identifying additional lactylation targets, especially nonhistone proteins, and understanding how lactylation affects their function in the context of AKI. The role of lactate in epigenetic regulation, especially through histone lactylation, is an emerging research field. Lactate modulates gene expression by altering histone modifications.

Future studies should explore how lactate alters the epigenetic landscape in renal cells and how these changes contribute to AKI development and progression.

Given lactate metabolism's significant role in AKI, interventions targeting lactate production or lactylation pathways offer potential therapeutic strategies. For example, glycolytic inhibitors or activators of PDH have been proposed to reduce lactate levels and alleviate AKI. Moreover, understanding the lactylation process and its impact on gene expression could reveal new targets for modulating the inflammatory response and renal repair mechanisms in AKI. The intricate relationship between lactate metabolism and AKI highlights the importance of considering metabolic pathways in developing therapeutic strategies. Modulating lactate levels and inhibiting detrimental lactylation modifications could provide novel approaches to mitigate AKI severity and improve patient outcomes.

While previous studies propose several therapeutic strategies targeting lactate metabolism, such as PDH activators and lactate dehydrogenase inhibitors, their feasibility and efficacy in clinical settings are yet to be established. Future research should focus on translating these findings into clinical trials to evaluate the safety and effectiveness of such interventions for treating AKI.

3. Lactate, lactylation, and DKD

3.1. Lactate metabolism in DKD

In DKD, glycolytic lactate is a critical factor in disease progression. Studies show that urine lactate levels are elevated in patients with type 2 diabetes and kidney disease compared to healthy controls [25]. Elevated urine lactate levels correlate with a more rapid decline in estimated glomerular filtration rate, suggesting a potential role in renal function deterioration [25].

In hyperglycemia, glucose-stimulated lactate production likely originates, in part, from proximal tubular cells. This is evidenced by reduced lactate production with sodium-glucose cotransporter-2 (SGLT2) inhibition in kidney sections and SGLT2-deficient mice. The upregulation of glycolytic genes in diabetic human proximal tubules suggests an enhanced glycolytic shift, potentially compensating for reduced mitochondrial function. Notably, lactate levels above 2.5 mM inhibit mitochondrial oxidative phosphorylation in human proximal tubule cells [25]. This suggests that increased lactate production in diabetic conditions contributes to mitochondrial dysfunction, potentially driving a feed-forward mechanism in DKD pathogenesis.

These findings suggest that lactate, derived from altered glycolysis due to mitochondrial dysfunction, plays a significant role in DKD progression. Targeting this metabolic pathway could provide novel therapeutic strategies for treating DKD. These studies highlight the critical role of lactate metabolism in DKD pathogenesis. Elevated urine and plasma lactate levels in DKD patients indicate mitochondrial dysfunction. SGLT2 inhibition reduces lactate production, suggesting a potential therapeutic target. Increased glycolytic gene expression and the inhibition of mitochondrial oxidative phosphorylation by high lactate levels emphasize lactate's detrimental impact on renal cells in diabetes. These findings suggest that lactate not only acts as a metabolic by-product but also disrupts mitochondrial function, contributing to DKD progression.

3.2. Lactylation modification in DKD

Lysine lactylation plays a key role in the progression of diabetic nephropathy. Chen et al. [26] show that lactate levels are increased in the kidneys and serum of db/db mice, a diabetic nephropathy model, and in individuals with diabetic nephropathy. Global lactylome profiling revealed increased lactylation sites on proteins, particularly those in the mitochondria, linked to mitochondrial dysfunction. Lactylation of acyl-CoA synthetase family member 2 (ACSF2), especially at K182 (K182la), is linked to mitochondrial dysfunction in renal tubular epithelial cells. The study suggests that lactylation exacerbates reactive oxygen species accumulation in mitochondria, leading to cellular damage and contributing to diabetic nephropathy progression. Mechanistically, ACSF2 lactylation may affect its enzymatic activity or interactions with other proteins, influencing mitochondrial function and potentially promoting ferroptosis, a form of regulated cell death linked to lipid peroxidation. These findings link lactate-driven lysine lactylation (especially ACSF2 lactylation) to mitochondrial dysfunction, suggesting that targeting this lactylation event could offer a novel therapeutic strategy for diabetic nephropathy.

Lactate-induced histone lactylation also plays a key role in the epigenetic regulation of epithelial-mesenchymal transition (EMT) in DKD. Elevated lactate levels in diabetes increase histone H3 lysine 14 lactylation (H3K14la), promoting the transcription of Krüppel-like factor 5 (KLF5) [27]. KLF5 binds to the E-cadherin promoter and inhibits its transcription, facilitating EMT and renal fibrosis. Both genetic knockdown and pharmacological inhibition of KLF5 reduce EMT and renal fibrosis, suggesting that targeting the lactate-driven H3K14la/KLF5 pathway could be a novel therapeutic strategy for DKD by disrupting the metabolic-epigenetic mechanisms contributing to renal fibrosis and dysfunction [27]. These findings highlight lactate's role as a signaling molecule that drives epigenetic modifications, regulating gene expression and processes like EMT.

3.3. Research gaps and future directions

Recent studies have highlighted the importance of lactate metabolism and lactylation in DKD, but several research gaps remain. Current research has mainly focused on the correlation between elevated lactate levels and renal function deterioration. However, the exact mechanisms by which lactate contributes to DKD pathogenesis remain unclear. For example, it is unclear whether elevated lactate levels cause or

result from mitochondrial dysfunction in renal cells. Moreover, the specific cellular pathways and molecular targets affected by lactate and lactylation in DKD are not well understood.

Lactylation is an emerging area of interest, but its role in DKD remains largely unexplored. Some studies suggest that lactylation could disrupt normal cellular functions, but the specific proteins and pathways affected by this modification in DKD remain unidentified. Comprehensive proteomic analyses are needed to map lactylation sites and understand how these modifications affect protein function and cellular processes in diabetic kidneys. Furthermore, the temporal dynamics of lactylation during DKD progression have not been studied, creating a gap in understanding how these modifications evolve and contribute to disease progression.

Understanding the mechanisms of lactate metabolism and lactylation in DKD may lead to novel therapeutic strategies. Potential interventions could include targeting glycolytic pathways to reduce lactate production or developing inhibitors that specifically block harmful lactylation modifications. Investigating the effects of existing treatments, such as SGLT2 inhibitors, on lactate metabolism and lactylation could provide valuable insights into their therapeutic potential in DKD. Addressing these research gaps could lead to the development of more effective treatments that improve renal outcomes for patients with diabetes.

4. Lactate, lactylation, and ccRCC

4.1. Lactate metabolism in ccRCC

Lactate metabolism plays a critical role in ccRCC progression through the Warburg effect, where cancer cells preferentially rely on aerobic glycolysis, resulting in lactate accumulation even in the presence of oxygen. This metabolic reprogramming supports rapid cell proliferation by supplying energy and metabolic intermediates required for biosynthesis. The high lactate levels are not just metabolic byproducts; they actively modulate the tumor microenvironment (TME) and influence various cellular processes. Lactate can inhibit the function of immune cells, such as T cells and natural killer cells, promoting immune evasion and creating an immunosuppressive environment that supports tumor growth.

Lactate also serves as a signaling molecule that activates oncogenic pathways and promotes angiogenesis, further driving tumor progression. Proteins such as lactate dehydrogenase A (LDHA) are frequently upregulated in ccRCC, facilitating the conversion of pyruvate to lactate and maintaining high glycolytic flux. This metabolic shift is closely linked to the stabilization of hypoxia-inducible factors, particularly in the context of von Hippel-Lindau (VHL) mutations, which are prevalent in ccRCC [28]. The stabilization of hypoxia-inducible factors induces the transcription of genes involved in glycolysis, angiogenesis, and cell survival, thereby reinforcing the Warburg effect and promoting the aggressive nature of ccRCC. Understanding these mechanisms underscores the potential of targeting lactate metabolism as a therapeutic strategy to disrupt the metabolic and signaling pathways that sustain ccRCC growth and progression.

4.2. Lactylation modification in ccRCC

Lactylation has emerged as a key player in the progression of ccRCC. This modification serves as a critical link between cellular metabolism and gene expression, translating the cell's metabolic state into stable gene expression patterns that drive tumorigenesis. In ccRCC, lactylation influences various oncogenic pathways, promoting tumor growth and progression [29].

A key mechanism by which lactylation exerts its effects in ccRCC is through the modulation of gene expression. For example, studies show that inactive VHL protein, a common mutation in ccRCC, triggers histone lactylation. This modification activates the transcription of genes like platelet-derived growth factor receptor β (PDGFRβ), creating a positive feedback loop that accelerates tumor progression [30]. This highlights the oncogenic potential of lactylation in ccRCC by directly influencing the expression of genes involved in cell proliferation and survival.

Lactylation also interacts with other epigenetic modifications, such as N6-methyladenosine (m6A) RNA methylation, further influencing cancer progression. Current studies have shown that lactylation can drive m6A modifications [31–33], which are known to regulate RNA stability and translation. The crosstalk between lactylation and m6A modifications underscores a complex network of epigenetic regulation that drives ccRCC development and resistance to therapies. By modulating both DNA and RNA, lactylation provides a robust and multifaceted approach to promoting tumor growth.

The immunosuppressive effects of lactate and lactylation in the TME are also critical in facilitating tumor immune escape and progression. High levels of lactate in the TME can inhibit T cell function and promote the polarization of macrophages toward an immunosuppressive phenotype. This creates an environment that promotes tumor growth and resistance to immune checkpoint inhibitors. Proteins such as FKBP10 [28], which enhance lactate production and histone lactylation, further contribute to the immunosuppressive milieu, highlighting the role of lactylation in shaping the TME to support tumor survival.

In summary, lactylation plays a key role in ccRCC by modulating gene expression, interacting with other epigenetic modifications, and shaping the immunosuppressive TME. These processes collectively drive tumor progression and resistance to conventional therapies. Understanding these mechanisms offers valuable insights into potential therapeutic targets, such as inhibiting key enzymes involved in lactate production or lactylation, to improve treatment outcomes for ccRCC patients. Future research should focus on developing inhibitors that specifically target these pathways and assess their efficacy in clinical trials.

4.3. Immunosuppressive effects of lactate and lactylation in the TME

Lactate and lactylation in the TME are crucial for tumor immune evasion by inhibiting T-cell function and promoting macrophage polarization toward an immunosuppressive

phenotype. Liu et al. [28] demonstrated that FKBP10, a protein involved in regulating LDHA phosphorylation, enhances lactate production and histone lactylation, contributing to the aggressive behavior of ccRCC. The immunosuppressive environment created by lactate and lactylation modifications supports tumor growth and resistance to immune checkpoint inhibitors, making it a critical target for cancer therapy.

4.4. Research gaps and future directions

Despite significant progress in understanding the role of lactate metabolism and lactylation in ccRCC, several research gaps persist. One major limitation is the reliance on *in vitro* studies and animal models, which may not fully reflect the complexity of human ccRCC. While studies have demonstrated the oncogenic potential of lactylation and its interaction with other epigenetic modifications, these findings need validation in clinical samples from diverse patient populations. Furthermore, the exact molecular mechanisms through which lactylation influences gene expression and tumor progression remain unclear. These studies often focus on a limited set of genes and pathways, potentially overlooking other critical factors in the lactylation landscape.

Future research should aim to provide a more comprehensive understanding of the molecular mechanisms underlying lactylation in ccRCC. This includes identifying all potential substrates of lactylation and understanding how these modifications affect their function. Advanced techniques, such as mass spectrometry-based proteomics, could be employed to comprehensively map the lactylation landscape. Furthermore, integrating multi-omics approaches, including genomics, transcriptomics, proteomics, and metabolomics, could provide a holistic view of how lactylation interacts with other cellular processes. This approach would help identify novel therapeutic targets and elucidate the broader implications of lactylation in cancer biology.

Another critical area for future research is the clinical validation of preclinical findings. This involves conducting large-scale studies using clinical samples to confirm lactylation's role in ccRCC progression and patient outcomes. Additionally, there is a need to develop and test specific inhibitors of lactylation-related enzymes, such as LDHA and PDGFRβ, in clinical trials. These inhibitors could disrupt the metabolic and epigenetic support for tumor growth, offering new therapeutic avenues. Furthermore, exploring combination therapies that target lactylation alongside other established treatments, such as immune checkpoint inhibitors, could enhance treatment efficacy and overcome resistance mechanisms.

The interaction between lactylation and the TME represents another promising area for future research. High lactate levels in the TME create an immunosuppressive environment that facilitates tumor immune escape. However, the specific mechanisms through which lactylation influences immune cell function and the TME remain unclear. Future studies should investigate how lactylation affects various immune cell types, such as T cells and macrophages, and their roles in tumor progression. Additionally, understanding how lactylation interacts with other metabolic pathways in the TME could offer insights into developing more effective immunotherapies. This could involve studying lactylation's effects on immune checkpoint molecules and exploring potential synergies with existing immunotherapies.

5. Writers and erasers of protein lactylation

Most acylation reactions in cells, especially those involved in gene regulation, are tightly controlled by specific epigenetic enzymes called writers and erasers [34]. These enzymes act as molecular switches, attaching or removing acyl groups—such as acetyl, methyl, phospho, or lactyl groups—from lysine residues on histone proteins. These modifications alter chromatin structure, directly impacting gene expression.

Writers are enzymes that modify histones with specific acyl groups, thereby determining the transcriptional activity of associated genes. For instance, lactylation significantly influences gene expression in various contexts. Current research has identified several lactylation writers, including alanyl-tRNA synthetase (AARS1), AARS2, HBO1, KAT8, α-tubulin acetyltransferase 1 (ATAT1), CBP/p300, and GCN5 [35–44]. These writers play crucial roles in regulating gene expression by modifying histones and altering chromatin accessibility.

Conversely, erasers are enzymes that remove these acyl groups, enabling dynamic regulation of gene expression patterns. This tight regulation by epigenetic enzymes creates a complex system that governs histone acylation reactions, including lactylation, contributing to the fine tuning of gene expression in cellular processes. Currently identified erasers of histone lactylation include HDAC1-3 and SIRT1-3 [43,45–50]. These erasers ensure histone modifications are reversible, enabling cells to respond to changing environmental and metabolic conditions.

The interplay between lactylation and its regulatory enzymes highlights the precision of epigenetic control mechanisms in kidney diseases. However, whether specific lactylation writers and erasers are present in the kidneys remains unclear. Further research is needed to elucidate the roles of these enzymes in renal tissues and their impact on kidney function and disease. Understanding specific epigenetic modifications and their regulatory mechanisms in the kidneys could provide new insights into kidney disease pathogenesis and reveal novel therapeutic targets.

6. Conclusion

Lactate metabolism and its post-translational modifications, particularly lactylation, play critical roles in the pathophysiology of various kidney diseases, including AKI, DKD, and ccRCC (Figure 1). The kidney's ability to metabolize lactate is crucial for maintaining renal function under normal conditions. However, in pathological states, impaired lactate metabolism leads to its accumulation, exacerbating renal dysfunction and disease progression. For more details on lactate metabolism and kidney diseases, refer to previous reviews [2,3,25].

Lactylation influences gene transcription, protein function, and cellular metabolism, contributing to inflammatory responses, mitochondrial dysfunction, and tumor progression.

Understanding the mechanisms of lactate metabolism and lactylation in kidney diseases opens new avenues for therapeutic interventions. Targeting these metabolic pathways could mitigate renal injury and improve patient outcomes. Future research should focus on elucidating the specific pathways and molecular targets affected by lactate and lactylation and developing inhibitors to modulate these processes. Clinical trials are necessary to validate the efficacy and safety of these therapies. Overall, the lactate-lactylation axis is a promising target for novel therapeutic strategies aimed at treating kidney diseases and improving renal health.

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Author contributions

Yuhua Cheng and Linjuan Guo finished all aspects of the work.

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