

Glycolysis to lactylation: Unraveling the metabolic and epigenetic landscape in tissue fibrosis (Review)

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Abstract. Tissue fibrosis represents a pathological condition characterized by excessive accumulation of extracellular matrix (ECM) components. Although historically considered a byproduct of glycolysis, lactate has emerged as a key signaling molecule influencing diverse physiological and pathological processes, including fibrosis. Roles have emerged for lactate metabolism and lactylation, a novel post-translational modification, in regulating fibroblast activation, ECM deposition and fibrotic progression. The present review provides a comprehensive analysis of the current understanding of glycolysis, lactate and lactylation in tissue fibrosis, with emphasis on cardiac, liver, renal and pulmonary fibrosis. The present review examines how enhanced glycolysis supports the energetic and biosynthetic requirements of activated fibroblasts, how lactate functions as a signaling molecule promoting fibrogenesis and how lactylation connects metabolic changes to epigenetic regulation of gene expression. Furthermore, the present review explores potential therapeutic approaches targeting metabolic pathways and lactylation to mitigate fibrosis, while highlighting future directions in this rapidly evolving field.

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1. Introduction

Tissue fibrosis is characterized by abnormal accumulation of extracellular matrix (ECM) components, typically following persistent or repeated tissue injury (1,2). Despite its prevalence, effective therapeutic interventions to halt or reverse fibrosis remain limited, highlighting the necessity for a deeper understanding of the mechanisms driving fibrotic progression. Historically, lactate was regarded as a byproduct of glycolysis and considered metabolic waste (3,4); however, previous scientific advances have fundamentally transformed this perspective. The lactate shuttle theory has redefined lactate as a key metabolic intermediary, with its transport between cells, tissues and organs enabled through monocarboxylate transporters (MCTs) (5,6). Metabolic reprogramming, particularly enhanced glycolysis and lactate production, serves a fundamental role in fibroblast activation and ECM deposition, key characteristics of fibrotic diseases (7). Considering the diverse roles of lactate in pathological processes, particularly in tissue fibrosis, the present review provides a comprehensive examination of current knowledge regarding glycolysis, lactate metabolism and lactylation in relation to fibrosis. The present review examines how enhanced glycolysis supports the energetic and biosynthetic requirements of activated fibroblasts, how lactate functions as a signaling molecule affecting fibrogenesis and how lactylation acts as an epigenetic regulator connecting metabolism to gene expression. Through analysis of cardiac, liver, renal and pulmonary fibrosis, the present review aims to elucidate the mechanisms through which metabolic pathways contribute to fibrotic progression and discuss potential therapeutic strategies targeting these pathways.

2. Glycolysis and lactate metabolism

Glycolysis represents a fundamental pathway for cellular energy production (8,9). In its classic understanding, glycolysis involves glucose entering the cell via glucose transporters and undergoing conversion into two pyruvate molecules (4,10). The interconversion between lactate and pyruvate occurs through

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lactate dehydrogenase (LDH) via a reversible redox reaction (10). LDH exists as a tetrameric enzyme comprising two subunit types: M and H. The M subunit, encoded by the LDHA gene, predominantly exists in skeletal muscle, whereas the H subunit, encoded by the LDHB gene, primarily exists in the heart (11). LDHA primarily catalyzes pyruvate conversion to lactate, whereas LDHB promotes the reverse reaction, converting lactate to pyruvate. This structural diversity enables LDH to fulfill distinct functions across different tissues based on cellular metabolic requirements. Beyond the role of LDH, lactate exists in two enantiomeric forms in the human body: L-lactate and D-lactate (10). L-lactate constitutes the primary physiological form, predominantly produced through glycolysis, whereas D-lactate represents a minor fraction, generated through alternative metabolic pathways (12). The primary origins and pathways for L-lactate removal in the cytoplasm are illustrated in Fig. 1.

When oxygen is available, pyruvate generated in the cytoplasm can be transported into the mitochondria through the mitochondrial pyruvate carrier (MPC). Within the mitochondria, pyruvate is converted to acetyl-CoA through the enzymatic action of pyruvate dehydrogenase, which then enters the tricarboxylic acid (TCA) cycle (13,14). Considerable research has demonstrated the presence of aerobic glycolysis, wherein glucose metabolism continues to produce lactate even when oxygen levels are sufficient (15,16). While the LDH and MPC pathways are known to facilitate lactate oxidation, previous studies have highlighted the mitochondrial lactate oxidation complex, located in the inner mitochondrial membrane, as a key component in this process (17,18). In addition to its role in cellular oxidation, lactate functions as a substrate for gluconeogenesis, particularly in hepatic and skeletal muscle tissue (19). During gluconeogenesis, lactate undergoes oxidation to pyruvate before conversion to glucose, thereby maintaining glucose reserves during periods of metabolic demand (20). However, deficiencies in enzymes regulating the irreversible, rate-limiting steps of gluconeogenesis can disrupt this pathway, leading to lactate accumulation in the cytosol (Fig. 1) (21). This buildup impedes effective lactate clearance, highlighting the key role of these enzymes in maintaining metabolic balance. The lactate shuttle theory describes how lactate contributes to metabolic homeostasis through its exchange within the body via MCTs (15). MCTs, first discovered in erythrocytes, serve a key role in facilitating the transmembrane transport of pyruvate and lactate (19). These transporters are present across various cellular and organelle membranes, enabling lactate movement from regions of high to low concentration, thus supporting the lactate shuttle (22). Cells with high glycolytic activity, designated as ‘driver cells’, export lactate through MCTs, while oxidative ‘recipient cells’ import it for oxidation (6). This theory indicates that lactate functions beyond its role as a byproduct of anaerobic metabolism, serving as a notable signaling molecule within the body. This characteristic has led to the term ‘lactormone’, emphasizing the ability of lactate to regulate cellular functions through autocrine, paracrine and endocrine mechanisms (6).

3. Lactylation

Initially documented in 2019, lactylation represents a newly identified post-translational modification that

modifies protein lysine residues using lactate molecules (23). Notably, lactylation demonstrates substantial influence on macrophage phenotypes during inflammatory responses. Research has indicated that lactylation of histone H3 at lysine 18 (H3K18la) in pro-inflammatory M1 macrophages is associated with enhanced expression of M2-like anti-inflammatory genes, indicating the essential role of lactylation in facilitating the transition from pro-inflammatory to anti-inflammatory states (23). The identification of additional proteins undergoing lactylation has increased interest into its role in tumor progression, immunity and metabolic regulation, advancing the understanding of lactate metabolism and its broader implications for cellular function (20–22).

The regulatory mechanisms of histone or non-histone protein lysine lactylation (Kla) demonstrate parallels with those of acetylation. Initially, specialized acyltransferases, designated as ‘writers’, transfer lactyl groups from L-lactyl-coenzyme A (lactyl-CoA) to lysine residues on histone or non-histone proteins, altering their structure and function. Subsequently, ‘erasers’ function as deacylases to remove these lactyl groups, terminating the Kla cycle and preventing persistent protein modifications. Finally, effector proteins, known as ‘readers’, specifically recognize the Kla modification, influencing downstream signaling pathways and initiating various biological processes (Fig. 2). Current evidence has suggested that L-lactate is converted into lactyl-CoA, facilitating the transfer of lactyl groups to lysine residues through CoA-transferases (24–26). Zhang *et al* (23) proposed that the enzyme p300, recognized for its acetyltransferase activity, may catalyze Kla modifications within cells. Subsequent studies have reinforced this hypothesis, demonstrating that decreased p300 expression or inhibition can lead to reduced protein lactylation (27,28). Furthermore, class I histone deacetylases 1–3 and sirtuins (SIRT) 1–3 have been identified as ‘erasers’ of histone Kla, responsible for removing lactylation markers (29,30). The glyoxalase system components also participate in lactylation, functioning as a common non-enzymatic acyl-transfer mechanism (26). During glycolysis, glyceraldehyde-3-phosphate and dihydroxyacetone phosphate are partially converted into methylglyoxal (MGO), which glyoxalase (GLO)1 subsequently transforms into lactoylglutathione (LGSH) in the presence of glutathione (31,32). GLO2 then hydrolyzes LGSH, generating D-lactate and glutathione (31). Research has indicated that MGO and its derivatives influence pathophysiological processes through D-lactylation, particularly via LGSH, which transfers lactyl groups to lysine residues, forming D-LactoylLys modifications that regulate glycolysis (26). Studies have revealed that LGSH-induced D-Kla modifications are associated with enhanced inflammatory responses in macrophages (33,34). Notably, lactate-induced and LGSH-induced lactylation produce distinct outcomes. Lactate-induced lactylation promotes anti-inflammatory macrophage polarization (23), whereas LGSH-induced lactylation is associated with increased pro-inflammatory cytokine production (33). These contrasting effects suggest that the cellular role of lactylation may vary based on the underlying mechanisms. Additional research remains

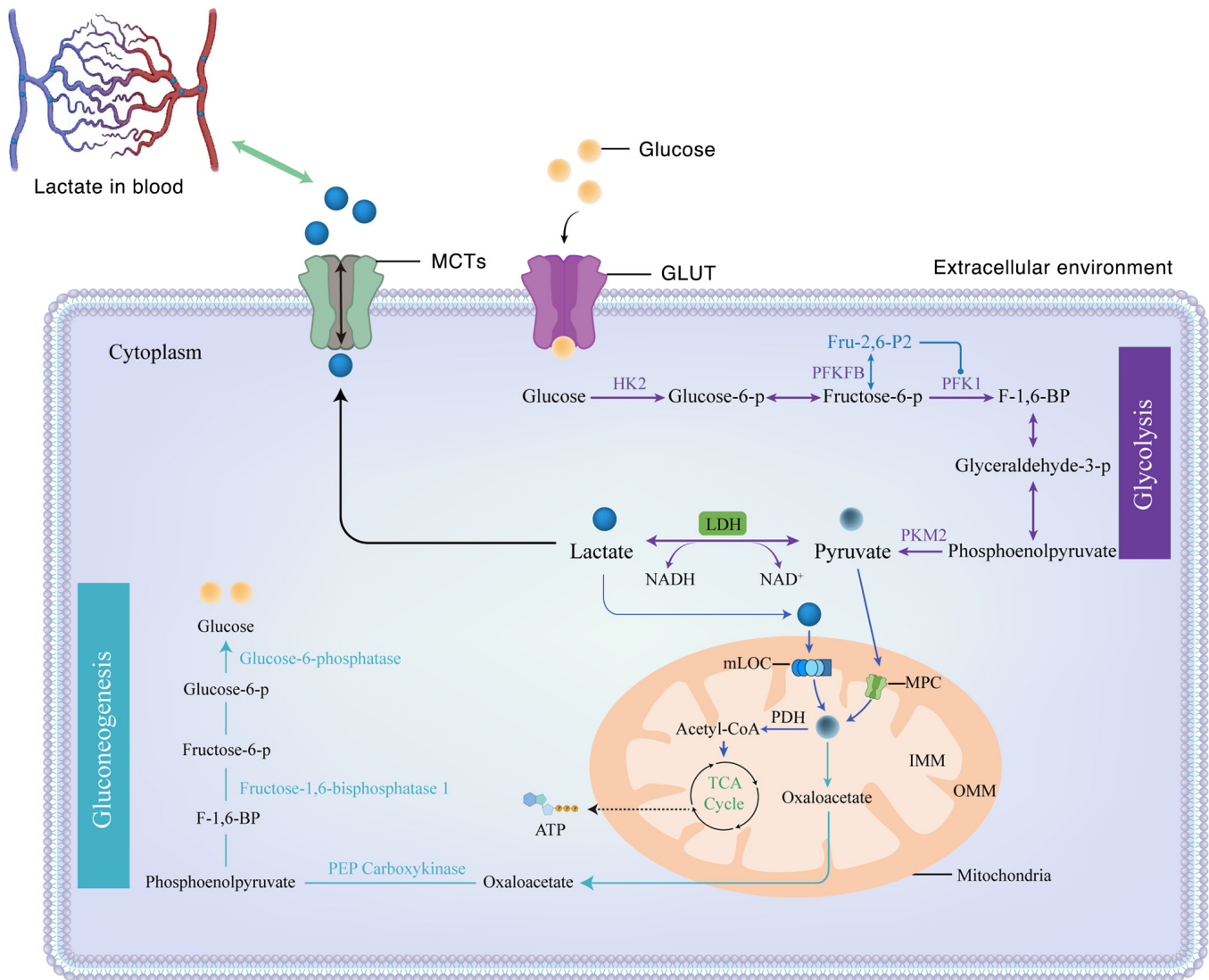


Figure 1. Diagram of lactate metabolism in the cytoplasm. This chart illustrates the glucose metabolism pathways within cells, including uptake, glycolysis, mitochondrial oxidation and gluconeogenesis, reflecting the metabolic equilibrium. Under aerobic conditions, glycolysis produces pyruvate and lactate. Lactate can be oxidized through monocarboxylate transporters or used in the gluconeogenesis process, and it also plays a role in metabolic regulation. ATP, adenosine triphosphate; F-1,6-BP, fructose-1,6-bisphosphate; fructose-6-p, fructose-6-phosphate; GLUT, glucose transporter; glucose-6-p, glucose-6-phosphate; glyceraldehyde-3-p, glyceraldehyde-3-phosphate; HK2, hexokinase 2; IMM, inner mitochondrial membrane; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; mLOC, mitochondrial lactate oxidation complex; MPC, mitochondrial pyruvate carrier; NAD⁺, nicotinamide adenine dinucleotide; OMM, outer mitochondrial membrane; PDH, pyruvate dehydrogenase; PFKFB, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase; PFK1, phosphofructokinase 1; PKM2, pyruvate kinase isoform M2; TCA, tricarboxylic acid cycle.

necessary to fully elucidate the regulatory networks governing lactate- and LGSH-mediated lactylation in cells.

Collectively, these findings indicate that lactylation functions as a bridge connecting metabolic signals to gene regulation through epigenetic modifications. Beyond protein marking, lactylation, particularly of H3K18la, reprograms transcriptional landscapes in a gene-specific and context-dependent manner. In fibrotic tissues, this regulation activates key pro-fibrotic genes including neuronal regeneration-related protein (NREP) (35) and SOX9 (36). The functional impact of lactylation varies depending on the source and type of lactate (L-lactate vs. LGSH), suggesting a sophisticated regulatory axis with both anti- and pro-inflammatory functions. Additional research is required to systematically map genome-wide lactylation patterns and identify specific reader proteins that interpret lactylation marks in fibrotic disease contexts.

4. Glycolysis, lactate and lactylation in tissue fibrosis

As a common end product of glycolysis, lactate exhibits multiple regulatory roles in various cell types. In this context, the distinct metabolic profiles and functions of fibroblasts, macrophages and epithelial cells during fibrosis have garnered increasing attention (37,38).

In epithelial cells, fibrotic transformation is associated with enhanced glycolysis, activation of the pentose phosphate pathway, lipid metabolic imbalance and reprogrammed amino acid metabolism (39). Mitochondrial dysfunction and accumulation of reactive oxygen species further promote epithelial-mesenchymal transition (EMT) and fibrosis (40). Additionally, epithelial-derived metabolites can activate fibroblasts (38). Fibroblasts undergo substantial metabolic reprogramming, characterized by elevated glycolysis,

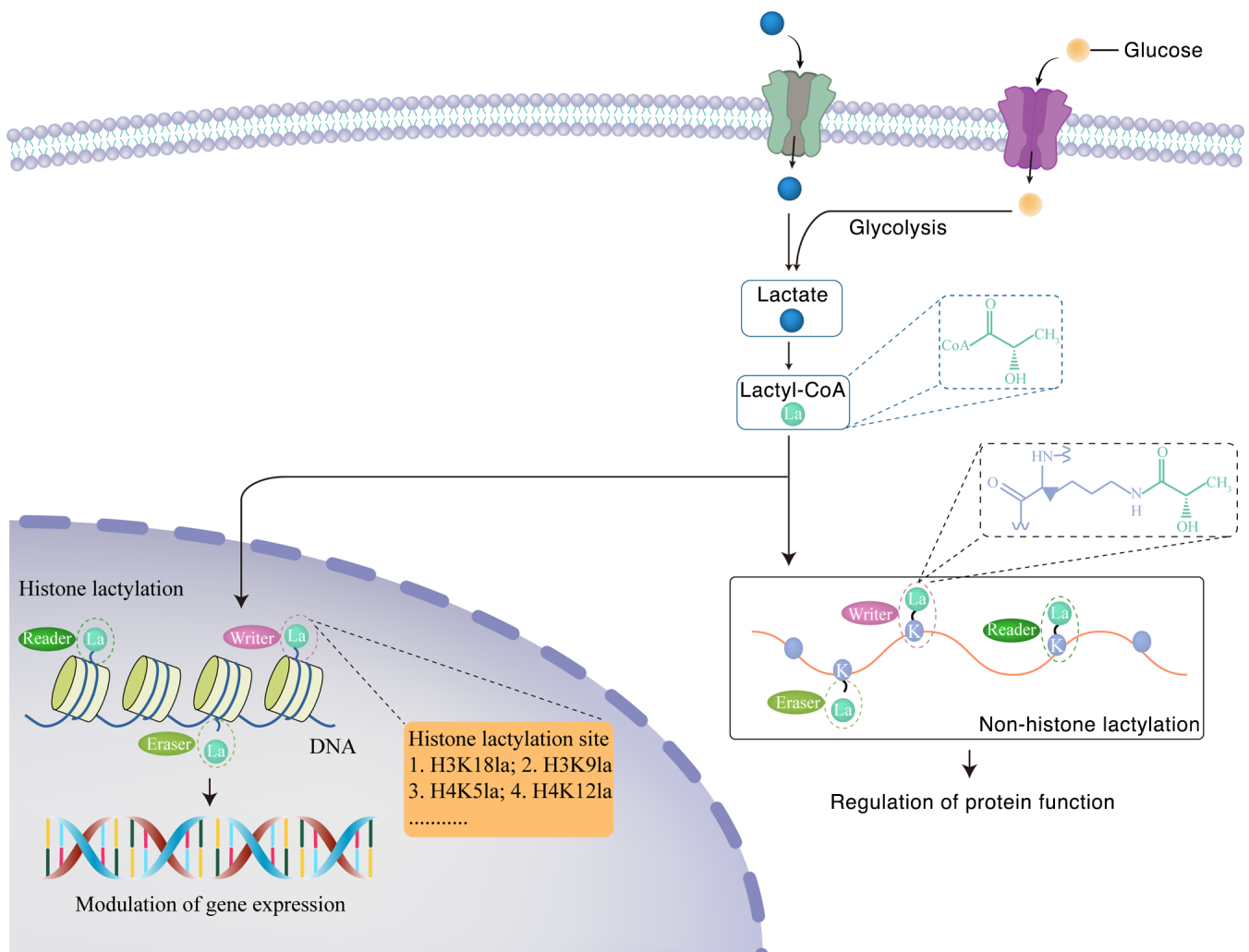


Figure 2. Lactate-induced histone and non-histone lactylation: Forms and dynamics. Lactylation of histones and non-histone proteins is dynamically regulated by writers (adding lactyl groups), erasers (removing lactyl groups) and readers (recognizing modifications), influencing protein function and signaling pathways.

increased lactate production, enhanced glutamine dependence and alterations in lipid and amino acid metabolism. These metabolic shifts support fibroblast activation, proliferation and ECM deposition, while metabolite-mediated signaling amplifies fibrotic progression (41). Activated fibroblasts secrete chemokines such as chemokine (C-C motif) ligand 2 and colony stimulating factor-1, recruiting macrophages to injury sites, where they undergo polarization (42). Classically activated M1 macrophages exhibit enhanced glycolysis and pro-inflammatory responses, potentially contributing to chronic inflammation, whereas alternatively activated M2 macrophages utilize oxidative phosphorylation and fatty acid oxidation to promote tissue repair (43).

In summary, fibroblasts, macrophages and epithelial cells each demonstrate distinct metabolic changes during fibrosis, which are intricately interconnected. A comprehensive understanding of these cell-specific metabolic pathways may reveal novel therapeutic approaches for treating fibrotic diseases.

Glycolysis, lactate and lactylation in cardiac fibrosis. Cardiac fibrosis, characterized by scar formation in the heart, is a prevalent feature of various cardiac diseases (44,45). An imbalance

in ECM dynamics drives fibrosis, marked by excessive accumulation of type I and III collagens (46). During fibrosis, cardiac fibroblasts (CFs) undergo activation, transforming into myofibroblasts, which increases matrix stiffness and impairs cardiac function, ultimately leading to heart failure with reduced ejection fraction (47,48). While the primary cell types within the cardiovascular system exhibit distinct metabolic characteristics in their normal state, alterations in glycolysis within fibroblasts are associated with phenotypic changes during pathological conditions (49).

Chen *et al* (50) used 2-deoxy-D-glucose (2-DG), a glycolysis inhibitor, to intervene in a myocardial infarction (MI)-induced fibrosis mouse model and observed a substantial reduction in collagen and α -smooth muscle actin expression levels. Additionally, clinical myocardial fibrosis samples revealed pronounced upregulation of key rate-limiting enzymes of glycolysis, including hexokinase 2 (HK2), 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) and pyruvate kinase isoform M2 (PKM2). These findings suggest that glycolysis may have a key role in post-infarction fibrosis progression. Moreover, TGF- β 1-stimulated CFs, a marked elevation in extracellular acidification rate and

increased lactate levels were detected (51). This indicates that CFs undergo a metabolic shift towards enhanced glycolytic activity. PFKFB3, a bifunctional isoenzyme of PFKFB with considerably increased kinase activity, serves a key role in glycolysis by synthesizing fructose-2,6-bisphosphate. A recent study demonstrated that adeno-associated virus 9-mediated gene silencing of PFKFB3 markedly suppressed fibrosis induced by MI in a mouse model (51). Another study revealed that PFKFB3 exhibits similar functions in endothelial cells by altering metabolic patterns and disrupting mitochondrial respiration, thereby promoting myocardial fibrosis (52). Based on these findings, researchers have developed a pharmacological inhibitor targeting PFKFB3, salvianolic acid C, a phenolic compound derived from *Salvia miltiorrhiza*. By specifically inhibiting PFKFB3-driven glycolysis, it effectively blocks endothelial-to-mesenchymal transition (EndoMT) and fibrosis progression to treat isoprenaline-induced cardiac fibrosis in a mouse model (52). Notably, previous studies have revealed that transgenic overexpression of 6-PFKFB3 in mice results in notable cardiac damage, characterized by changes in heart weight-to-body weight ratio, cardiomyocyte length and increased cardiac fibrosis (51,53). To date, several small-molecule inhibitors targeting glycolysis in myocardial fibrosis have been identified. For instance, salvianolic acid A, a phenolic compound derived from *Salvia miltiorrhiza*, reduces LDHA-driven glycolysis, thereby decreasing collagen-related protein (Collagen I, Collagen III) expression and ameliorating myocardial fibrosis (54). Hspa12a inhibits the activation and fibrosis of CF. It is highly expressed in resting CF and decreases after activation. Hspa12a inhibits glycolysis by stabilizing p53, blocks the transformation of CF into myofibroblasts and alleviates fibrosis after myocardial infarction. New therapeutic strategies can be developed targeting Hspa12a (55).

Beyond key glycolytic enzymes participating in myocardial fibrosis, research has demonstrated the involvement of regulators that modulate glycolysis and subsequently affect fibrosis. Chen *et al* (56) identified Linc00092, a long non-coding RNA involved in glycolysis, through differential screening. Further mechanistic investigations revealed that Linc00092 may regulate glycolysis-induced fibrosis in an ERK-dependent manner (56). Liu *et al* (57), using single-cell sequencing, identified a notable elevation in aerobic glycolysis levels in cardiac fibrosis of patients with MI. The study also revealed that the antifibrotic mechanism of IL-22 operates by regulating PKM2 via the JNK pathway (57). Another study demonstrated that the knockout of Serpina3c, a homolog of human kallistatin, exacerbates the progression of myocardial fibrosis (58). Further investigation revealed that Serpina3c interacts with Nr4a1, regulating its acetylation and promoting its degradation. This, in turn, affects enolase 1 (ENO1)-mediated glycolysis, ultimately contributing to the development of myocardial fibrosis (58).

Current research on lactate-induced lactylation in myocardial fibrosis remains limited, warranting additional investigation to increase understanding of this process. A recent study by Yao *et al* (59) demonstrated that elevated lactate levels can markedly accelerate cardiac fibrosis and exacerbate cardiac dysfunction by inducing endothelial-to-mesenchymal transition in the myocardium following MI.

Glycolysis, lactate and lactylation in liver fibrosis. Liver fibrosis represents a reparative response to chronic liver damage (59). As fibrosis advances, liver function deteriorates, potentially progressing to cirrhosis (60,61). At present, liver transplantation remains the sole definitive treatment for liver fibrosis (62). The fibrotic process is primarily driven by the activation of hepatic stellate cells (HSCs), which transform into myofibroblasts, generating excessive ECM components (63). Previous studies have emphasized the importance of metabolic alterations, particularly aerobic glycolysis, in facilitating HSC activation (64-66). Through glycolysis inhibition, this activation can be suppressed, as lactate serves a fundamental role in regulating gene expression levels following HSC activation. Chen *et al* (66) initially demonstrated that during the transformation of quiescent HSCs into myofibroblasts, glycolysis increases substantially, evidenced by enhanced expression of key glycolytic enzymes. This transformation coincides with increased intracellular lactate accumulation. The inhibition of glycolysis using 2DG or blocking lactate production with FX11 (an LDHA inhibitor) effectively regulates HSC fate, emphasizing the key role of metabolic pathways. The increased expression of these enzymes demonstrates their importance in regulating HSC activation and liver fibrosis progression (66). Subsequently, Mejias *et al* (64) substantiated the essential role of glycolysis in liver fibrosis progression through knockdown studies and the application of 3PO, a small molecule antagonist targeting the glycolytic rate-limiting enzyme PFKFB3. This finding received further validation in subsequent research, including studies utilizing the PKM2 antagonist shikonin and its allosteric activator TEPP-46 (67), which provided additional support for the role of glycolysis in HSC activation and liver fibrosis (68). Beyond direct involvement in HSC activation, glycolysis has been demonstrated to enhance macrophage-driven inflammatory responses, thereby intensifying fibrosis (68). These investigations provide valuable insights into the metabolic mechanisms underlying liver fibrosis and potential therapeutic targets. Given the fundamental role of glycolysis in liver fibrosis, substantial research continues to explore regulatory mechanisms and develop small molecule inhibitors targeting glycolysis.

Several key pathways and molecules have been identified: Hedgehog signaling, through transcription factor GLI family zinc finger 2, promotes glycolysis by activating hypoxia inducible factor (HIF)-1 α , which controls glycolysis-related enzyme expression levels (66). Embryonic liver fordin facilitates glycolysis and ECM production in HSCs via the PI3K/Akt pathway (69). Cytoplasmic polyadenylation element binding protein 4 enhances PFKFB3 expression by binding to its untranslated mRNA region, thereby promoting glycolysis and exacerbating liver fibrosis (64). TGF- β 1 triggers liver fibrosis by activating the Smad, p38 MAPK and PI3K/Akt pathways, which upregulate glucose transporter 1 (GLUT1) and increase aerobic glycolysis in HSCs (70). Wnt/ β -catenin signaling activates glycolysis and HSCs by transactivating and translocating LDHA to the nucleus, where it stabilizes HIF-1 α , offering a therapeutic target for fibrosis (71).

Suv39h1, a lysine methyltransferase, promotes glycolysis in HSCs by enhancing the recruitment of HIF-1 α and upregulating HK2 transcription, contributing to liver fibrosis in non-alcoholic fatty liver disease (72). Focal adhesion kinase-related

non-kinase inhibits aerobic glycolysis in HSCs by blocking the focal adhesion kinase/Ras/c-myc/ENO1 pathway, reducing liver fibrosis and presenting a potential therapeutic target (73). Brain and muscle arnt-like protein-1 regulates glycolysis in HSCs through the isocitrate dehydrogenase 1/ α -ketoglutarate pathway, influencing liver fibrosis progression (74). Activated HSCs have been demonstrated to transfer GLUT1 and PKM2 to quiescent HSCs, Kupffer cells and liver sinusoidal endothelial cells via exosomes, further exacerbating liver fibrosis (75). Glycolysis amplifies liver fibrosis by promoting the release of fibrogenic extracellular vesicles (EVs) from HSCs, particularly in the hepatic pericentral zone, highlighting glycolysis as a therapeutic target (76). Additionally, several natural compounds have demonstrated potential in targeting glycolysis and mitigating fibrosis: Curcumin has been shown to alleviate liver fibrosis by modulating Hedgehog signaling activation and adenosine monophosphate-activated protein kinase (AMPK), thereby influencing glycolysis (77,78). The natural compound oroxylin A has been demonstrated to inhibit both the expression and activity of LDHA in HSCs, suggesting its potential as a therapeutic agent in reducing glycolysis and mitigating liver fibrosis (79). Costunolide has been reported to target HK2, thereby disrupting the glycolytic process, inhibiting the activation of HSCs and slowing the progression of liver fibrosis (80). Furthermore, various other small molecules that regulate glycolysis have been discovered, highlighting glycolysis as a potential therapeutic target for liver fibrosis (81-86).

Recent research has revealed that lactylation, driven by glycolysis-produced lactate, may be a key factor in HSC activation (87). Studies have demonstrated that lactate generated by HK2 in HSCs promotes histone lactylation, including modifications such as H3K18la, H3K9la, H3K14la, H4K8la and H4K12la (87,88). These lactylation modifications influence gene expression, thereby contributing to HSC activation and liver fibrosis progression (87). Furthermore, insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2), an m6A-binding protein, has been identified as promoting liver fibrosis through regulation of glycolysis and aldolase A (ALDOA) expression levels, resulting in histone lactylation and HSC activation, suggesting its potential as a therapeutic target (89). Notably, H3K18la enhances SOX9 transcription, a key fibrosis factor, indicating that this pathway may present novel therapeutic opportunities for hepatic fibrosis treatment (90). Rho *et al* (87) established that HK2-driven lactate production in HSCs modulates gene expression levels through histone lactylation. Their research revealed that HSC activation-related gene promoters demonstrate H3K18la enrichment and increased glycolysis results in widespread lactylation of lysine residues on both histone H3 and H4 and non-histone proteins. Additionally, IGF2BP2, an m6A reader protein that enhances mRNA stability, has been revealed to be notably upregulated in liver fibrosis, whereas IGF2BP2 suppression can attenuate fibrotic progression. The mechanism involves IGF2BP2 enhancing the m6A modification and stability of ALDOA mRNA, leading to increased ALDOA expression levels and lactate production, which subsequently promotes H3K18la and accelerates liver fibrosis (91). Wu *et al* (90) revealed that during liver fibrosis, the lactation level of H3K18 increases, and when LDHA is reduced, H3K18 lactation decreases, inhibiting the activation and fibrotic process of

HSC. Further experiments demonstrated that H3K18 lactation promotes liver fibrosis by enhancing SOX9 gene expression, and overexpression of SOX9 can reverse the anti-fibrotic effect of reduced LDHA, indicating that H3K18 lactation promotes liver fibrosis development by regulating SOX9 (90).

Chen *et al* (92) revealed that lactate-driven H3K18la upregulates interferon regulatory factor 4 transcription, promotes the differentiation of CD4 T cells into T helper 17 cells and leads to an increase in IL-17A secretion, thereby accelerating the activation of HSCs and exacerbating arsenite-induced liver fibrosis. Zhou *et al* (89) revealed that in a mouse model of carbon tetrachloride-induced liver fibrosis, the overall lactation level increased, and in TGF- β 1-treated LX-2 cells with liver fibrosis, both the overall lactation and H3K18la levels increased. By contrast, correcting abnormal lactation or supplementing lactic acid may alter the activated phenotype of LX-2 cells, while interfering with lactic acid production reduces H3K18la levels and inactivates HSCs (89). Moreover, as H3K18la is enriched in activated HSCs, these findings suggest that H3K18la is associated with liver fibrosis (89). However, the current understanding of lactylation modifications in liver fibrosis remains incomplete, necessitating further research to fully understand their roles in fibrogenesis.

Glycolysis, lactate and lactylation in renal fibrosis. Chronic kidney disease (CKD) represents a notable public health challenge (93). Renal fibrosis, characterized by excessive ECM accumulation in the interstitial space of the kidneys, is a defining feature of CKD (94,95). Emerging evidence has increasingly demonstrated the relationship between glycolysis and renal fibrosis. The importance of glycolysis in renal fibrosis was initially demonstrated by Ding *et al* (96); this previous study revealed that aerobic glycolysis inhibitors, such as 2-DG, or PKM gene silencing with its inhibitor shikonin, effectively reduced fibrosis in a mouse model of unilateral ureteral obstruction and TGF- β -induced fibroblast activation. These observations have been supported by studies demonstrating that PKM2 overexpression in rat renal fibroblasts can directly trigger fibroblast activation and enhance glycolytic activity (97,98). PKM2, a key glycolytic enzyme, exists in multiple forms, monomers, dimers and tetramers, each serving distinct pathophysiological functions (99). Liu *et al* (100) demonstrated that TEPP-46, a small-molecule activator that stabilizes PKM2 tetramer formation and enhances PK activity, inhibited both renal fibrosis and glycolysis in kidney cells (101,102). Further research by Wei *et al* (103) and Yu *et al* (104) revealed that glycolysis inhibition using dichloroacetate (DCA) (103) or 3-bromopyruvate (104) could reduce renal fibrosis. Notably, the study by Wei *et al* (103) indicated that glycolysis may have varying effects in different cell types, while glycolysis inhibition can reduce fibrosis in fibroblasts, it may promote fibrosis in renal tubular epithelial cells.

Transgenic models have further validated the essential role of glycolysis in renal fibrosis. Lee *et al* (105) demonstrated that PFKFB2 isoform phosphorylation in the kidney markedly influences fibrosis progression. Mutations inactivating Ser468 and Ser485 of PFKFB2 (PFKFB2 knock-in mice) have been shown to intensify renal fibrosis (105), whereas specific PFKFB2 knockout in renal fibroblasts (106), myeloid

cells (107) and kidney proximal tubular cells (108) can reduce fibrosis progression.

The regulatory mechanisms underlying glycolysis in renal fibrosis have emerged as a central focus of research, particularly in developing small-molecule inhibitors targeting this metabolic process. Srivastava *et al* (109) demonstrated that SIRT3 deficiency contributes to diabetes-associated kidney fibrosis through mechanisms involving HIF-1 α accumulation and PKM2 dimer formation. Research has also indicated that Honokiol-induced activation of SIRT3 mitigates fibrosis, potentially through deacetylation of pyruvate dehydrogenase E1 α , an enzyme connecting glycolysis to the TCA cycle (110). Furthermore, aldehyde dehydrogenase 2 has been identified as a notable factor in glycolysis-induced renal fibrosis (111,112). Tuberous sclerosis complex 1 (Tsc1)-mediated target of rapamycin complex 1 activation contributes to the glycolytic process in renal tubular cells, thereby intensifying fibrosis (113). Various other molecules have been demonstrated to be involved in glycolysis-mediated fibrosis, including Tsc1 (113), COUP-TFII (NR2F2) (114), GPR87 (115), YY1 (116), platelet isoform of PFK (117) and forkhead box protein K1 (118). Additionally, signaling pathways such as the cGAS-STING pathway increase PFKFB3 expression levels, contributing to hypoxia-induced renal fibrosis (119). HIF-1 α has a key role in glycolysis regulation. Both Sanqi oral solution (120) and sodium-glucose cotransporter 2 (SGLT2) inhibitors (121) demonstrate effectiveness in modulating HIF-1 α expression levels, thereby reducing glycolysis and its fibrogenic effects. Traditional Chinese medicine formulations, including Huangqi-Danshen decoction (122) and Shen Shuai II Recipe (123), have also been demonstrated to exhibit efficacy in regulating glycolysis and diminishing fibrosis progression.

Recent studies have revealed that lactylation, driven by lactate produced through glycolysis, may constitute a key factor in the progression of renal fibrosis (108,115). Wang *et al* (108) demonstrated that persistent glycolysis in kidney tubular epithelial cells promotes histone H4 lysine 12 lactylation, activating NF- κ B-related gene transcription, thus establishing a connection between metabolism and inflammation-mediated fibrosis in renal fibrosis. Despite these advances, the study of lactylation modifications in renal fibrosis requires additional research to elucidate their specific contributions to fibrogenesis.

Glycolysis, lactate and lactylation in idiopathic pulmonary fibrosis (IPF). IPF is characterized by excessive accumulation of ECM proteins, resulting in progressive lung tissue scarring and compromised respiratory function. Research has emphasized the fundamental role of metabolic reprogramming, particularly enhanced glycolysis, in IPF pathogenesis. Xie *et al* (124) identified glycolytic reprogramming as an essential early event in myofibroblast differentiation. Their research demonstrated elevated levels of enzymes including PFK1, HK2 and PFKFB3 in fibrotic lungs, leading to increased glycolysis. Supporting these findings, Kang *et al* (125) utilized metabolic profiling to reveal elevated levels of glycolysis-related metabolites in IPF lung tissues, indicating a shift toward aerobic glycolysis. Zhao *et al* (126) revealed altered glycolytic intermediates in IPF lungs, characterized by reduced levels of key glycolytic enzymes and increased lactic acid, suggesting disrupted glycolysis and a shift toward anaerobic metabolism. Notably,

GLUT1 demonstrates considerable importance in this metabolic shift. Cho *et al* (127) revealed elevated GLUT1-dependent glycolysis in age-associated lung fibrosis. By contrast, GLUT1 inhibition using phloretin reduced fibrotic markers and improved lung function in mice, highlighting GLUT1 as a potential therapeutic target (127).

Key glycolytic enzymes serve a notable role in fibroblast activation in IPF. Kim *et al* (128) demonstrated that HK2 connects glycolysis to the profibrotic effects of TGF- β (129), and HK2 inhibition can decrease collagen production and myofibroblast differentiation (129). Hu *et al* (130) established that the PI3K-Akt-mTOR/PFKFB3 pathway controls glycolysis and collagen production in lung fibroblasts during lipopolysaccharide-induced pulmonary fibrosis. Notably, PFKFB3 inhibition can reduce glycolytic flux and collagen deposition (130). Research has also indicated that metformin, a common antidiabetic drug, inhibits PFKFB3-mediated glycolysis and decreases collagen production in lung fibroblasts through modulation of the AMPK/mTOR pathway (131). Similarly, Chen *et al* (132) determined that anlotinib suppresses PFKFB3-driven glycolysis in myofibroblasts, reversing pulmonary fibrosis in bleomycin-induced mouse models. The mTORC1 pathway also influences metabolic reprogramming in IPF. O'Leary *et al* (133) revealed that TGF- β drives metabolic reprogramming in lung fibroblasts by triggering activating transcription factor 4 through an mTORC1-dependent mechanism, enhancing serine and glycine synthesis essential for collagen production. HIF-1 α serves as another key regulator of glycolysis in IPF. Xu *et al* (134) established that high mobility group box protein 1 promotes fibroblast proliferation and ECM production through activating HIF1 α -regulated aerobic glycolysis. Goodwin *et al* (135) revealed that targeting the HIF1 α /3-phosphoinositide-dependent protein kinase 1 (PDK1) axis with DCA inhibits bleomycin-induced pulmonary fibrosis by suppressing glycolysis. Additionally, the Akt2-PDK1 signaling pathway contributes to lactate accumulation and fibrosis. Sun *et al* (136) demonstrated that lactate buildup, driven by Akt2-PDK1 signaling, promotes pulmonary fibrosis through increased glycolysis. By contrast, Schruf *et al* (137) theorized that the fibroblast-to-myofibroblast transformation does not result from an LDH5-dependent metabolic shift towards aerobic glycolysis, indicating that glycolysis might not be the sole driver of fibrosis. In mechanical ventilation-induced pulmonary fibrosis, Mei *et al* (138) revealed that the integrin β 3-PKM2 pathway mediates aerobic glycolysis, contributing to fibrosis. In addition, it has been demonstrated that fenbendazole attenuates fibrosis by inhibiting glycolysis and fibroblast activation (139). Furthermore, the alamandine/MrgD axis prevents TGF- β 1-mediated fibroblast activation by regulating aerobic glycolysis and promoting mitophagy (140). Dishevelled-binding antagonist of β -catenin 2 protects against pulmonary fibrosis by suppressing glycolysis in lung myofibroblasts (141).

Lactate has emerged as a key signaling molecule in IPF. Cui *et al* (28) revealed that lung myofibroblasts enhance macrophage profibrotic activity through lactate-induced histone lactylation. Histone lactylation represents a novel epigenetic modification connecting cellular metabolism to gene expression. Wang *et al* (35) demonstrated that H3K18la promotes the progression of arsenite-related IPF via the YTH

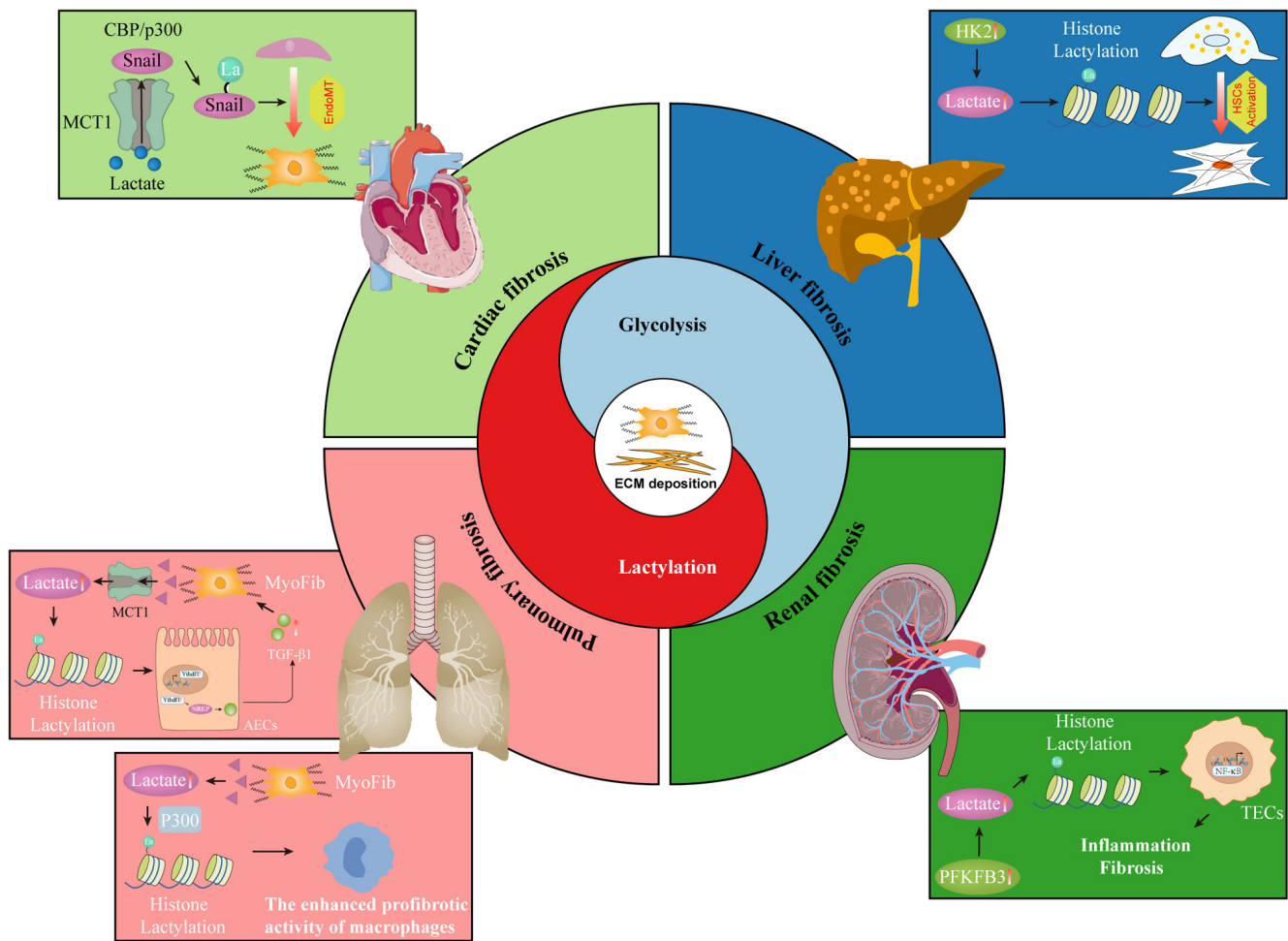


Figure 3. Role of glycolysis-regulated lactylation in tissue fibrosis. This schematic illustrates how the glycolysis-lactylation metabolic axis drives fibrotic processes in heart, liver, kidney and lungs through lactate transport and histone lactylation mechanisms, elucidating the crucial role of metabolic reprogramming in multi-organ fibrosis. MCT, monocarboxylate transporter; EndoMT, endothelial-to-mesenchymal transition; HK2, hexokinase 2; HSCs, hepatic stellate cells; MyoFib, myofibroblast; TECs, tubular epithelial cells; AECs, alveolar epithelial cells; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; ECM, extracellular matrix.

domain-containing family protein 1/m6A/NREP pathway. Arsenite exposure increases lactate production, resulting in enhanced histone lactylation and activation of profibrotic signaling pathways (35). Li *et al* (142) revealed that airborne PM2.5 induces pulmonary fibrosis by activating glycolysis and triggering histone lactylation in macrophages. The produced lactate enhances EMT in epithelial cells, promoting fibrosis (142). Feng *et al* (143) revealed that lipopolysaccharide-induced inhibition of monocarboxylate transporter 1 (MCT1) leads to lactate accumulation, initiating EMT and pulmonary fibrosis. Enhancement of lactate transport through MCT1 reduces lactate levels and mitigates fibrosis (143). Additionally, lactate serves a role in intercellular communication in the fibrotic microenvironment. Wang *et al* (135) revealed that microRNA-21 in EVs from pulmonary epithelial cells promotes myofibroblast differentiation via glycolysis in arsenic-induced pulmonary fibrosis. Lactate accumulation increases glycolytic activity in fibroblasts, driving their activation, thereby creating a feed-forward loop that exacerbates fibrosis.

In summary, enhanced glycolysis in lung fibroblasts serves a key role in the pathogenesis of IPF by providing

energy and biosynthetic precursors essential for fibroblast activation and ECM production. Key glycolytic enzymes and pathways, including GLUT1, HK2, PFKFB3, and the mTORC1 and HIF-1 α pathways, demonstrate upregulation in IPF and present potential therapeutic targets (114,117-119,122). Lactate, the end product of glycolysis, functions not merely as a metabolic byproduct but as a signaling molecule that promotes fibrosis through histone lactylation and modulation of gene expression (28,35). Lactate-induced histone lactylation in macrophages and epithelial cells augments the expression of profibrotic genes and facilitates processes such as EMT, contributing to fibrosis progression. Targeting metabolic pathways involved in glycolysis and lactate metabolism presents promising therapeutic strategies for IPF. Interventions including glycolysis inhibitors, lactate transport modulators and agents that disrupt lactate signaling demonstrate efficacy in preclinical models (131,132,134,135,141,143). Understanding the complex relationship between cellular metabolism and fibrotic signaling pathways remains essential for developing novel treatments for IPF. Future research should emphasize on translating these findings into clinical therapies that can halt or reverse fibrosis by targeting metabolic dysregulation.

5. Future perspective

The emerging understanding of glycolysis, lactate metabolism and lactylation in tissue fibrosis reveals new avenues for research and therapeutic intervention (Fig. 3). Despite considerable progress, several key questions remain unanswered. Firstly, while the role of enhanced glycolysis in fibroblast activation is well-documented, the precise regulatory mechanisms governing this metabolic shift require further investigation. Examining the upstream signals that initiate metabolic reprogramming in fibroblasts and other cell types within the fibrotic microenvironment could identify novel targets for intervention. Additionally, understanding how different cell types interact metabolically during fibrosis might reveal important intercellular communication pathways mediated by metabolites such as lactate. Secondly, the importance of lactate as a signaling molecule and its role in histone lactylation warrant deeper exploration. Future studies should aim to map the complete spectrum of proteins subject to lactylation in fibrotic tissues, determine the functional consequences of these modifications, and identify the enzymes involved in writing, reading and erasing lactylation markers. Glycolysis inhibitors, lactate transport modulators and agents affecting lactylation enzymes present potential strategies. HIF-1 α , a glycolytic master transcriptional regulator that transactivates several glycolytic genes, is upregulated in IPF and represents a potential target for fibrosis treatment (144,145). Hu *et al* (120) demonstrated that Sanqi oral solution can inhibit the HIF-1 α /PKM2/glycolytic-fibroblast activation axis and delay renal fibrosis progression. LDHA primarily functions to convert pyruvate into lactic acid. Salvianolic acid A has demonstrated inhibition of LDHA-driven glycolysis, thereby reducing fibrosis severity (54). HSC activation represents a target for hepatic fibrosis, with aerobic glycolysis as one of its metabolic characteristics; therefore, blocking glycolysis presents a new therapeutic direction for hepatic fibrosis (146). Ban *et al* (80) revealed that costunolide can inhibit HK2, reduce HSC glycolysis and thus inhibit the activation of HSCs. However, given the essential roles of these metabolic processes in normal physiology, specificity and minimizing off-target effects remain key. The development of targeted delivery systems or prodrugs that preferentially accumulate in fibrotic tissues may enhance therapeutic efficacy while reducing systemic toxicity.

Emerging technologies such as single-cell RNA sequencing, metabolomics and advanced imaging techniques could prove instrumental in dissecting the complex metabolic networks in fibrosis. Integration of these data could facilitate the identification of metabolic signatures predictive of disease progression or therapeutic response, establishing foundations for personalized medicine approaches in fibrosis management.

6. Conclusion

In conclusion, the complex interplay between glycolysis, lactate metabolism and lactylation substantially contributes to the pathogenesis of tissue fibrosis. Enhanced glycolysis provides the essential energy and biosynthetic precursors for activated fibroblasts, while lactate functions as a signaling molecule influencing fibroblast activation, macrophage

polarization and EMT. The discovery of lactylation as a novel epigenetic modification emphasizes the profound impact of metabolic changes on gene expression regulation during fibrosis. Understanding these metabolic and epigenetic mechanisms provides new insights into fibrotic disease progression and highlights potential therapeutic targets. Interventions aimed at modulating glycolysis, lactate production and lactylation demonstrate promise in preclinical models, suggesting metabolic reprogramming as a viable strategy for treating fibrosis.

Future research should focus on elucidating the detailed molecular mechanisms, exploring the specificity of potential therapeutic agents and translating these findings into clinical applications. Through continued investigation of the metabolic and epigenetic landscape of fibrosis, progress continues toward developing effective therapies that can improve outcomes for patients affected by these conditions.

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Availability of data and materials

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Authors' contributions

LZ collected the literature and wrote the manuscript. QL and YD contributed to literature collection, and analysis and interpretation of the results. LZ, YZ, LW and JL revised the manuscript. All authors reviewed the final draft of the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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