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Glycolytic Metabolic Reprogramming and Epigenetic Crosstalk in Pulmonary Fibrosis

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Abstract: *Pulmonary fibrosis is a chronic, progressive, and fatal interstitial lung disease characterized by excessive extracellular matrix deposition and irreversible parenchymal destruction, with idiopathic pulmonary fibrosis (IPF) as its most typical and lethal subtype. IPF confers an extremely poor prognosis, with a median survival of only 2–3 years after diagnosis and no curative therapies available to date. Mounting evidence has validated that the bidirectional crosstalk between glycolytic metabolic reprogramming and epigenetic modifications acts as a core mechanism sustaining the activated phenotype of pulmonary myofibroblasts and reinforcing the pathological progression of pulmonary fibrosis. This review summarizes the signature features of hyperactive glycolysis in pulmonary myofibroblasts, with a focus on the direct regulatory effects of glycolysis-derived metabolites on epigenetic programming: nuclear acetyl-CoA accumulation provides abundant substrates for histone acetylation; an imbalanced NAD^+/NADH ratio suppresses the catalytic activity of Sirtuin family deacetylases; lactate overload induces novel histone lactylation modifications that modulate gene transcription; and α-ketoglutarate depletion and competitive inhibition dampen DNA/histone demethylase activity. Furthermore, we discuss the reverse reinforcing effect of epigenetic remodeling on the persistent expression of glycolysis-related genes, highlighting a reciprocal positive feedback loop between metabolic and epigenetic alterations. This crosstalk network offers a critical theoretical basis and actionable targets for disrupting the pathological homeostasis of fibrosis and developing novel anti-fibrotic interventions.*

Keywords: *pulmonary fibrosis; metabolic reprogramming; glycolysis; epigenetics; myofibroblast activation*

1. Introduction

Pulmonary fibrosis represents a group of chronic, progressive disorders featured by pathological remodeling of the pulmonary interstitium and exaggerated extracellular matrix (ECM) accumulation, with idiopathic pulmonary fibrosis (IPF) as the prototypical form. Clinically, patients develop a relentless decline in lung compliance and irreversible respiratory failure, leading to an extremely dismal prognosis [1–3]. Classical pathogenic mechanisms center on repetitive alveolar epithelial injury, dysregulated repair responses, activation of pro-fibrotic signaling such as transforming growth factor-β (TGF-β), and transition of quiescent fibroblasts into pro-fibrogenic myofibroblasts [1,2,4]. However, the relentless progression and irreversible nature of established fibrosis suggest the existence of a stable regulatory network beyond canonical signaling cascades that perpetuates the pathogenic cellular phenotype.

In recent years, metabolic reprogramming has emerged as a critical hub linking microenvironmental cues to the maintenance of fibrotic phenotypes, among which enhanced aerobic glycolysis (the Warburg effect) represents the most prominent metabolic signature of fibrosis-related cells [5–7]. Elevated glycolysis not only fuels energy supply and biosynthetic demands for cell proliferation, migration, and ECM synthesis but also directly shapes epigenetic landscapes by altering intracellular levels of key metabolites and cofactors [5,8]. Epigenetics refers to heritable changes in gene expression that occur without alterations in the underlying DNA sequence, mainly including DNA methylation, histone post-translational modifications, chromatin remodeling, and non-coding RNA regulation. These modifications construct dynamic chromatin signatures that precisely govern transcriptional activation or silencing.

In this review, we systematically elaborate the mechanistic links between glycolytic metabolic

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reprogramming and pulmonary fibrosis, and dissect the reciprocal interaction patterns between metabolic status and epigenetic modifications. We also highlight the therapeutic potential of targeting this metabolism–epigenetics axis for the treatment of pulmonary fibrosis.

2. Biological Basis of Glycolysis and Metabolic Reprogramming

Metabolic reprogramming refers to the adaptive rewiring of energy metabolism and anabolic pathways triggered by microenvironmental stimuli (e.g., hypoxia, inflammation, mechanical stress) or altered functional demands (e.g., proliferation, differentiation, activation) [6,9]. Major forms of metabolic reprogramming include: rewired glucose metabolism (e.g., Warburg effect, pentose phosphate pathway flux shift), remodeled mitochondrial oxidative metabolism (e.g., tricarboxylic acid [TCA] cycle restructuring, altered oxidative phosphorylation efficiency), rebalanced lipid metabolism (e.g., enhanced fatty acid synthesis or oxidation), and dysregulated amino acid metabolism (e.g., increased glutaminolysis) [6,9,10].

Metabolic reprogramming supports cellular adaptation and phenotype maintenance by tuning ATP production, NAD(P)H/NAD(P)$^+$ redox balance, and the availability of metabolic substrates and cofactors. Among these, glycolytic reprogramming is a representative metabolic signature in disease states, characterized by markedly increased glycolytic flux. Even under aerobic conditions, cells rely predominantly on glycolysis for energy production while diverting glycolytic intermediates into anabolic pathways [9].

3. Glycolytic Reprogramming in Pulmonary Fibrosis: Features and Upstream Drivers

3.1 Core Features of Glycolytic Reprogramming in Pulmonary Fibrosis

The central pathological event in pulmonary fibrosis is the aberrant activation of pulmonary fibroblasts and their differentiation into myofibroblasts, which serve as the primary effector cells producing massive amounts of collagen, fibronectin, and other ECM components, ultimately leading to destructive parenchymal remodeling. Using integrated transcriptomic and metabolomic profiling, Xie et al. [11] first delineated the metabolic landscape of IPF fibroblasts. Compared with normal fibroblasts, IPF-derived fibroblasts display robust aerobic glycolysis: despite sufficient oxygen tension, cells preferentially generate ATP through glycolysis.

At the molecular level, expression levels of key rate-limiting enzymes involved in glucose uptake and catabolism are significantly upregulated, including glucose transporter1(GLUT1)[12], hexokinase2 (HK2), 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), and lactate dehydrogenase A (LDHA) [11,13]. These changes lead to a pronounced increase in extracellular acidification rate (ECAR) and a relative reduction in oxygen consumption rate (OCR), indicating suppressed mitochondrial respiration. Notably, this metabolic shift is not merely an energy switch but an adaptive response to meet the carbon skeleton demands for rapid proliferation and excessive ECM synthesis. Glycolytic intermediates are shunted into the serine/glycine synthesis pathway and the pentose phosphate pathway, providing building blocks for nucleotide synthesis and maintaining redox balance [6,7,14].

3.2 Upstream Drivers of Glycolytic Reprogramming

3.2.1 Canonical Fibrotic Signaling: TGF-β

TGF-β is a master pro-fibrotic cytokine and a pivotal upstream trigger of glycolytic reprogramming. In addition to the canonical Smad cascade, TGF-β enhances glucose uptake by activating the PI3K/AKT/mTOR axis, stabilizing hypoxia-inducible factor-1α (HIF-1α), and upregulating GLUT1 [12,15]. TGF-β also orchestrates the alanine metabolic axis by upregulating glutamate-pyruvate transaminase 2 (GPT2) and the amino acid transporter SLC38A2 to sustain intracellular alanine pools. Alanine supports collagen synthesis by providing carbon and nitrogen precursors, whereas alanine restriction impairs glycolytic flux and TCA cycle intermediate production [11]. Thus, TGF-β remodels global energy metabolism by integrating glycolysis and amino acid metabolism to support myofibroblast differentiation.

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3.2.2 Key Metabolic Kinase: SIK2

Salt-inducible kinase 2 (SIK2) is specifically overexpressed in activated fibroblasts from IPF patients and animal models. As a direct regulator of glycolysis, SIK2 drives a hyperglycolytic state by enhancing the expression of HK2, PFKFB3, and other rate-limiting enzymes, thereby promoting fibroblast proliferation, migration, and ECM secretion. Genetic ablation or pharmacological inhibition of SIK2 (e.g., YKL06-061, fostamatinib) markedly alleviates bleomycin-induced pulmonary fibrosis in mice, identifying SIK2 as a critical hub linking metabolic reprogramming to the fibrotic phenotype[16-21].

3.2.3 Environmental Stress and Oxidative Stress

Environmental pollutants such as $PM_{2.5}$ induce excessive reactive oxygen species (ROS) generation in the lung, triggering mitochondrial damage, mitophagy, and dysfunction. Cells are forced to switch from oxidative phosphorylation to glycolysis to maintain survival. ROS also stabilize HIF-1α in a hypoxia-independent manner (pseudo-hypoxia) and cooperate with the NF-κB pathway to promote epithelial-mesenchymal transition (EMT) and inflammation, jointly upregulating glycolytic genes including PKM and LDHA. Antioxidant agents (e.g., trans-stilbene glycoside) can reverse this process, positioning the ROS–HIF-1α–NF-κB axis as a key metabolic switch in environment-induced fibrosis.

3.2.4 Transcriptional Network: HIF-1α and NF-κB

HIF-1α functions as a master regulator of glycolysis, directly binding to promoters of HK2, PFKFB3, LDHA, and other glycolytic genes to initiate the glycolytic program. HIF-1α activity is negatively modulated by Sirtuin deacetylases (e.g., SIRT1); however, the reduced NAD^+/NADH ratio in fibrotic cells blunts SIRT1 activity, leading to hyperacetylation and stabilization of HIF-1α and amplified transcriptional output [22,24]. Concurrently, persistent NF-κB activation promotes inflammatory mediator release and forms a positive feedback loop with HIF-1α, collectively maintaining the hyperglycolytic and pro-fibrotic state of fibroblasts.

4. Glycolysis-Mediated Epigenetic Regulation in Pulmonary Fibrosis

4.1 Acetyl-CoA Flux Couples with Histone Acetylation

Acetyl-CoA is a central TCA cycle intermediate and the exclusive acetyl donor for histone acetyltransferases (HATs). In quiescent cells, acetyl-CoA is mainly produced in the mitochondrial matrix and cannot easily cross the inner mitochondrial membrane. In fibrotic cells with enhanced glycolysis, excess citrate is exported to the cytoplasm and nucleus, where ATP-citrate lyase (ACLY) cleaves citrate into acetyl-CoA and oxaloacetate [21]. Nuclear ACLY activity and local acetyl-CoA concentration directly determine histone acetylation levels.

Elevated nuclear acetyl-CoA promotes HAT-mediated acetylation of histone H3 and H4 lysine residues (e.g., H3K9, H3K14, H3K27, H4K16). Acetylation neutralizes the positive charge of histones, weakening electrostatic interactions with negatively charged DNA and relaxing chromatin structure from condensed heterochromatin to accessible euchromatin. In pulmonary fibrosis, glycolysis-driven H3K27ac enrichment increases chromatin accessibility at promoters of pro-fibrotic genes including COL1A1, FN1, and ACTA2, facilitating transcription factor binding and perpetuating the activated phenotype [11].

4.2 NAD^+/NADH Imbalance Inhibits Sirtuin Deacetylases

Nicotinamide adenine dinucleotide (NAD^+) is an essential cofactor for class III histone deacetylases (HDACs) known as the Sirtuin family (SIRT1–7). Unlike class I/II HDACs, Sirtuin activity is strictly dependent on the NAD^+/NADH ratio, making these enzymes bona fide metabolic sensors [21]. In fibrotic fibroblasts, although LDHA-mediated pyruvate-to-lactate conversion regenerates partial NAD^+, mitochondrial dysfunction and excessive anabolism lead to NADH accumulation and a markedly reduced NAD^+/NADH ratio [9,23].

NADH competes with NAD^+ for Sirtuin catalytic sites, directly inhibiting deacetylase activity. Inactivated Sirtuins lead to two pathological outcomes: (1) sustained histone hyperacetylation (e.g., H3K9ac, H4K16ac) that disables transcriptional repression; (2) impaired deacetylation of non-histone substrates including HIF-1α and Smad3, enhancing their stability and transcriptional activity and further amplifying pro-fibrotic signaling [24].

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4.3 Lactate Accumulation Induces Histone Lactylation

Lactate, once considered a waste product, can modulate gene expression via histone lactylation. Massive intracellular lactate generated by hyperactive glycolysis is converted into lactyl-CoA, which is then transferred to histone lysine residues (e.g., H3K18lac) by HATs. Similar to acetylation, histone lactylation relaxes chromatin and promotes gene transcription. In pulmonary fibrosis, myofibroblast-derived lactate promotes inflammatory cytokine expression in macrophages, in which histone lactylation serves as a key regulatory mechanism [25–28].

4.4 α-Ketoglutarate Depletion Impairs Demethylase Function

α-ketoglutarate (α-KG) is a critical TCA cycle intermediate and an essential cofactor for TET DNA demethylases and JmjC-domain histone demethylases. These dioxygenases regulate DNA and histone methylation to maintain chromatin plasticity and gene expression balance. In fibroblasts with glycolytic reprogramming, TCA cycle flux redistribution and mitochondrial dysfunction reduce α-KG production. Meanwhile, succinate and fumarate accumulation competitively inhibit α-KG-dependent enzymes, suppressing demethylase activity. The resulting hypermethylation of DNA and histones silences anti-fibrotic genes and stabilizes the pro-fibrotic phenotype [29-31].

4.5 RNA Epigenetics: m⁶A Modification as a Novel Regulatory Layer

Beyond DNA and histone modifications, RNA N⁶-methyladenosine (m⁶A) modification constitutes a critical post-transcriptional regulatory layer. m⁶A deposition is controlled by writers (METTL3/14), erasers (FTO, ALKBH5), and readers (YTHDF1–3). The efficiency of m⁶A modification depends on S-adenosylmethionine (SAM), whose synthesis is linked to glycolytic flux via the pentose phosphate pathway.

In pulmonary fibrosis, METTL3 is upregulated in IPF lung tissues and TGF-β1-stimulated fibroblasts, increasing m⁶A levels in the 3′-UTR of COL1A1 and ACTA2 mRNAs. YTHDF1 binding enhances translation efficiency rather than degradation, specifically amplifying collagen and α-SMA protein production. Inhibiting METTL3 or overexpressing FTO reduces myofibroblast activation and ECM deposition, establishing a metabolism–RNA modification–protein output axis that represents a novel intervention target [36-38].

5. Epigenetic Reinforcement of Glycolytic Reprogramming

5.1 Chromatin Remodeling Stabilizes Glycolytic Gene Expression

Promoters of glycolytic rate-limiting enzyme genes (e.g., PFKFB3, HK2) in activated pulmonary fibroblasts show robust enrichment of activating histone marks (H3K27ac, H3K9ac) [11]. These marks relax chromatin and recruit metabolic transcription factors (HIF-1α, c-Myc) to sustain high glycolytic gene expression. Importantly, this process establishes epigenetic memory: hyperacetylated histones recruit BRD4, which further recruits P-TEFb and phosphorylates RNA polymerase II, ensuring continuous transcription of glycolytic genes. This mechanism explains why fibroblasts maintain hyperglycolysis and activation long after TGF-β1 withdrawal, representing a core barrier to fibrosis reversal [32,33]. Targeting BRD4 effectively attenuates pulmonary fibrosis, offering a new strategy to disrupt the glycolysis–epigenetics axis [33].

5.2 Non-Coding RNAs Fine-Tune Glycolytic Programs

Long non-coding RNA H19 is overexpressed in fibrotic lung tissues and acts as a competing endogenous RNA (ceRNA) to sponge miR-140, de-repressing glycolytic genes and amplifying metabolic reprogramming [34]. MiR-21 also modulates cellular metabolic activation by targeting upstream signaling molecules [35].

6. Conclusion and Perspectives

This review demonstrates that bidirectional crosstalk between glycolytic reprogramming and epigenetic modifications functions as a core driver of sustained myofibroblast activation and

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pathological progression in pulmonary fibrosis. Mechanistically, glycolysis-derived metabolites serve as substrates or cofactors for epigenetic modifications to reshape chromatin landscapes and activate pro-fibrotic gene programs; in turn, epigenetic alterations lock in the hyperglycolytic phenotype by stably upregulating metabolic enzymes, forming a self-sustaining pathological feedback loop.

Despite substantial progress, clinical translation remains challenging. Future studies should integrate single-cell multi-omics, spatial transcriptomics, and metabolic flux analysis to delineate the spatiotemporal dynamics of this network across fibrosis stages. On this basis, highly specific intervention targets with minimal off-target effects should be identified and validated in clinical cohorts as diagnostic biomarkers and therapeutic candidates. A deeper understanding of glycolysis–epigenetics crosstalk will open new avenues for the precise prevention and treatment of pulmonary fibrosis.

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