Glycolysis in pulmonary fibrosis: From drivers to therapeutic opportunities (Review)

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Abstract. Pulmonary fibrosis (PF) is a chronic and progressive interstitial lung disease with a poor prognosis and limited therapeutic options. Current antifibrotic therapies only slow disease progression, underscoring an urgent need for novel therapeutic strategies. In recent years, metabolic reprogramming, notably the shift towards aerobic glycolysis (the Warburg effect), has emerged as a key driver of PF pathogenesis. This review comprehensively examines the central role of glycolysis in fueling the fibrotic cascade. It summarizes the major risk factors and fundamental pathogenic mechanisms of PF. The review then delves into the molecular mechanisms by which profibrotic signals, such as TGF-β1, remodel cellular metabolism. The upregulation and pathogenic roles of critical glycolytic nodes are detailed-including glucose transporters, hexokinase 2, phosphofructokinase-2/fructose-2,6-bisphosphatase 3, pyruvate kinase M2 and lactate dehydrogenase A-in activated fibroblasts, injured epithelial cells and pro-fibrotic immune cells. Furthermore, the interplay between glycolysis and key signaling pathways (TGF-β1, hypoxia-inducible factor-1α, PI3K/AKT/mTOR, Hippo, AMP-activated protein kinase and sirtuins) that form feed-forward loops to sustain the fibrotic process is discussed. Furthermore, therapeutic strategies targeting glycolytic enzymes and upstream metabolic checkpoints are highlighted, summarizing preclinical evidence for small-molecule inhibitors and non-coding RNAs as emerging regulators of glycolytic reprogramming. By consolidating current knowledge on glycolysis-centric metabolic underpinnings of PF, this review underscores the promise of metabolism-based interventions and discusses challenges for translating these findings into effective therapies.

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Abbreviations: AEC, alveolar epithelial cell; AMPK, AMP-activated protein kinase; AT2, alveolar type 2 cell; EC, endothelial cell; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; FAO, fatty acid oxidation; GLUT, glucose transporter; HIF-1α, hypoxia-inducible factor 1α; HK2, hexokinase 2; IPF, idiopathic pulmonary fibrosis; LDHA, lactate dehydrogenase A; ncRNA, non-coding RNA; PF, pulmonary fibrosis; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PI3K, phosphoinositide 3-kinase; PKM2, pyruvate kinase M2; PPP, pentose phosphate pathway; SIRT, sirtuin; TGF-β1, transforming growth factor-β1; YAP, Yes-associated protein; α-SMA, α-smooth muscle actin

Key words: pulmonary fibrosis, glycolysis, metabolic reprogramming, Warburg effect, myofibroblast, therapeutic target

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1. Introduction

Pulmonary fibrosis (PF) is a chronic, progressive interstitial lung disease characterized primarily by pathologically defined aberrant tissue repair, accumulation of activated fibroblasts and excessive deposition of extracellular matrix (ECM), which collectively lead to irreversible architectural distortion and loss of lung function (1). PF is not a single disease entity but rather a heterogeneous pathological phenotype. As a basket term encompassing a spectrum of fibrotic lung diseases, PF includes idiopathic PF (IPF), of unknown etiology with a usual interstitial pneumonia pattern, as well as secondary forms attributable to known causes, including occupational and environmental exposures, drug toxicities, connective tissue diseases and infections (2). PF represents the final common pathway of multiple interstitial lung diseases (ILDs) and is associated with substantial morbidity and mortality worldwide. Recent global estimates indicate that PF affects ≤0.1%

of the global population, with the global annual incidence of ILD-related PF having more than doubled between 1990 and 2019. Conservative estimates suggest a current incidence of 15-20 cases per 100,000 population (3). PF carries a poor prognosis, with substantial variation in clinical course, disease progression and therapeutic response across its heterogeneous subtypes. In 2014, the Food and Drug Administration (FDA) granted approval for nintedanib and pirfenidone as treatments for IPF (4). Both medications, while effective in slowing the decline in lung function and reducing disease progression, are not curative, and their overall efficacy is limited (5). Nerandomilast is the first new therapy for IPF in over a decade, with its indication expanded in December 2025 to include progressive PF. Despite these advancements, the side effects and restricted efficacy of current antifibrotic agents, coupled with the lack of therapies that can halt or reverse fibrotic lung damage, highlight the pressing need for innovative therapeutic strategies.

The pathogenesis of PF is initiated by various etiological factors, including genetic susceptibility, environmental exposures and lifestyle factors (6). A widely accepted model posits that PF arises from repeated injury to alveolar epithelial cells, which subsequently initiate maladaptive repair mechanisms that fail to restore homeostasis (7). As this injury persists and becomes chronic, unresolved inflammation maintains a pathological microenvironment rich in pro-fibrotic cytokines, such as transforming growth factor (TGF)-β, tumor necrosis factor-α and interleukin (IL)-1β, collectively augmenting fibrogenic signaling and tissue remodeling (8). Within this environment, alveolar epithelial cells may undergo phenotypic transformations, including processes akin to epithelial-mesenchymal transition (EMT), while resident fibroblasts are stimulated to activate and differentiate into myofibroblasts responsible for ECM production (9,10). Concurrently, the accumulation of senescent epithelial cells and fibroblasts amplifies pro-fibrotic signaling via the senescence-associated secretory phenotype, thereby further reinforcing the pro-fibrotic milieu and sustaining aberrant repair pathways (11,12). In summary, inflammation, epithelial dysfunction, fibroblast activation and cellular senescence constitute an interconnected and self-perpetuating network involving multiple effector cells and signaling pathways (13). Importantly, maintaining this persistent profibrotic state requires substantial bioenergetic and biosynthetic support, which is primarily provided by cellular metabolic reprogramming (14).

In recent years, there has been an increasing focus on cellular metabolic reprogramming as a fundamental aspect of pulmonary fibrogenesis. A growing body of evidence correlates metabolic dysregulation, particularly altered glucose metabolism, with the progression of IPF (15). Notably, upregulation of aerobic glycolysis has been recognized as a vital metabolic adaptation in activated fibroblasts, injured alveolar epithelial cells and pro-fibrotic immune cells (16). A notable indicator of this metabolic change is the 'Warburg effect', wherein epithelial cells and macrophages convert glucose into lactate even under oxygen-rich conditions (17). Beyond fulfilling bioenergetic and biosynthetic demands, enhanced glycolysis also functions as a signaling node that actively shapes the profibrotic microenvironment (14,18). Mechanistically, increased glycolytic flux elevates lactate production and contributes to local acidification, which in turn can promote myofibroblast differentiation and reinforce canonical pathways such as TGF-β signaling, thereby establishing feed-forward circuits that sustain fibroblast activation and ECM deposition (19,20). Simultaneously, glycolytic rewiring influences the inflammatory programs of immune cells, further stabilizing a niche conducive to persistent tissue repair and pathological scarring (21,22). Collectively, these mechanisms underscore the crucial role of glycolysis in driving and maintaining PF.

Considering the pivotal role of glycolytic reprogramming in fueling the fibrotic cascade, the present review offers a comprehensive overview of the diverse contributions of glycolysis to PF. First, the major risk factors and fundamental pathogenic mechanisms of PF are summarized. Subsequently, the focus is on how pro-fibrotic signals remodel glycolysis, as well as on the regulatory mechanisms of transcriptional and post-transcriptional networks at key nodes of the glycolytic pathway. Building on this mechanistic understanding, the current study highlights metabolic targets with drug development potential, including glucose transporters (GLUTs), glycolytic rate-limiting enzymes and critical metabolic intermediates. Finally, it summarizes anti-fibrotic intervention strategies targeting the glycolytic pathway and its upstream regulatory factors, along with the latest preclinical evidence. Ultimately, the present study underscores the therapeutic potential of non-coding RNAs (ncRNAs) as modulators of glycolytic pathways and examines the translational challenges and future prospects for metabolism-based interventions in PF.

2. Risk factors of PF

Multiple risk factors can initiate the progression of PF, including genetic factors, aging, smoking, occupational exposure, inhalation from the environment, microbial infection, systemic disease and drug-induced factors. The primary risk factors involved in PF are further illustrated in Fig. 1.

Genetic factors. Genetic factors significantly influence the onset and progression of PF (23). Familial interstitial pneumonia (FIP), also referred to as familial PF, typically exhibits autosomal-dominant inheritance with incomplete penetrance and variable clinical expressivity, thereby emphasizing the contribution of rare, high-impact genetic factors to disease etiology (24). Genome-wide association studies (GWAS) have further confirmed the significant polygenic inheritance effect in PF. Specifically, a previous meta-analysis of GWAS on IPF has identified five new susceptibility signaling loci, with the associated genes primarily involved in biological processes such as the mTOR signaling pathway, spindle assembly and regulation of telomere homeostasis (25). Among these common susceptibility loci, the promoter variant rs35705950 within the mucin 5B, oligomeric mucus/gel-forming gene remains the most consistently replicated and potent genetic risk factor, markedly increasing susceptibility to both sporadic IPF and FIP (26). Additionally, previous research has identified three genes associated with telomeres, which had previously been linked to familial PF. These findings provide evidence supporting the hypothesis that telomere malfunction contributes to the pathogenesis of IPF (27).

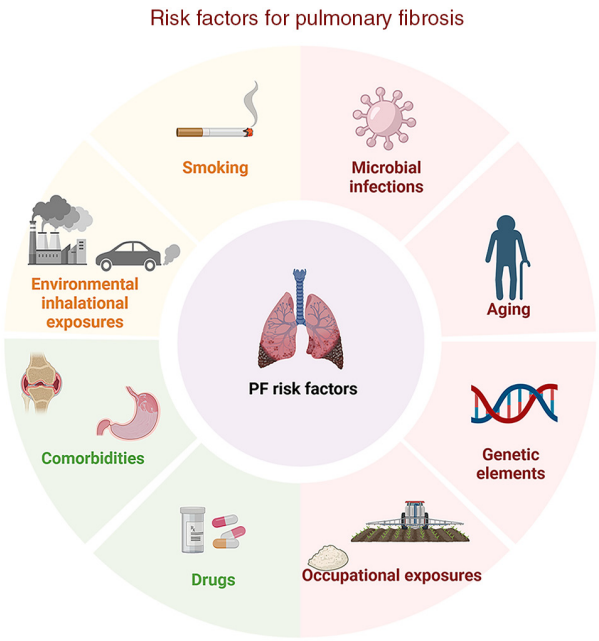

Figure 1. Risk factors for PF. Multiple factors contribute to the development of PF, including smoking, microbial infections, environmental inhalational exposures, aging, comorbidities, genetic elements, drug exposure and occupational exposures. The image was generated utilizing Biorender (https://BioRender.com). PF, pulmonary fibrosis.

Aging. Aging is associated with a progressive decline in tissue homeostasis and regenerative capacity, thereby increasing the likelihood of multiple chronic disorders, notably fibrotic diseases affecting various organs (28). In the pulmonary system, physiological aging correlates with an extensive range of molecular and structural modifications that impair epithelial repair, diminish regenerative responses following injury, and elevate susceptibility to both acute and chronic pulmonary conditions such as chronic obstructive pulmonary disease and interstitial lung fibrosis (29). A total of two cardinal hallmarks of this aging process, namely cellular senescence and telomere attrition, are particularly relevant to IPF. These phenomena significantly contribute to both the onset and advancement of IPF (30). Consistent with this mechanistic link, IPF is predominantly diagnosed in middle-aged and elderly individuals, with age being widely recognized as the most significant risk factor for disease onset and progression (31). Furthermore, epidemiological and experimental evidence further indicates that aged lungs demonstrate a predisposition for disrepair, which may exacerbate abnormal wound-healing responses and facilitate persistent ECM remodeling following injury (32). Mechanistically, aging hallmarks, including cellular senescence and telomere attrition, are increasingly recognized as key contributors to IPF pathogenesis. At the molecular and cellular levels, senescent epithelial cells and fibroblasts acquire a senescence-associated secretory phenotype, sustaining profibrotic signaling, activating fibroblasts and promoting ECM deposition (11,33). In summary, cellular senescence represents a critical risk factor that significantly contributes to the pathogenesis and progression of PF.

Smoking. Cigarette smoke, a complex mixture of thousands of toxic chemicals and reactive oxidants, induces persistent epithelial injury and chronic pulmonary stress, thereby constituting a significant and modifiable risk factor for IPF and other smoking-related ILDs (34). Mechanistically, cigarette smoke promotes fibrogenesis through convergent pathways involving oxidative stress, persistent inflammatory signaling, disruption of the epithelial barrier, and activation of fibroblasts, thereby lowering the threshold for maladaptive tissue repair (35). At the cellular level, previous experimental evidence indicates that cigarette smoke-mediated inactivation of sirtuin (SIRT)1 induces autophagy-dependent senescence of alveolar epithelial type 2 (AT2) cells, impairing epithelial regeneration and facilitating ECM deposition (36). Concurrently, cigarette smoke may further augment fibrotic remodeling by enhancing mitochondrial oxidative stress and metabolic dysregulation within stromal cells, reinforcing myofibroblast activation and matrix accumulation (37). Emerging data also suggest that smoking-related epigenetic and telomere-associated alterations may exacerbate AT2 cell senescence and accelerate the progression of fibrosis (38). Collectively, these multi-level findings reinforce the understanding of cigarette smoking as a key environmental trigger that drives PF.

Occupational exposure. Occupational exposures are increasingly recognized as significant and potentially preventable determinants of PF (39). A previous comprehensive meta-analysis that synthesized data from numerous international case-control studies found that occupational exposures account for ~16% of the population-attributable risk among the causative factors underlying PF (40). These occupational hazards encompass a diverse range of agents. Epidemiological studies consistently associate IPF with workplace exposures to vapors, gases, dusts and fumes, including metal dust/fumes, wood and agricultural dust and crystalline silica (41). Among these hazards, respirable crystalline silica serves as a quintessential fibrogenic agent; it not only incites classical silicosis, which is characterized by progressive and often irreversible fibrotic remodeling, but may also exacerbate fibrosis through the alteration of lung microbiota composition and associated metabolic pathways (42,43). Another well-established fibrogenic agent is asbestos, whose role warrants further scrutiny; chronic inhalation of its fibers, such as chrysotile and crocidolite, can cause asbestosis, a fibrotic lung disease distinguished by interstitial fibrosis and pleural thickening (44). Additionally, coal workers' pneumoconiosis is a prevalent occupational disease to which coal miners are highly susceptible owing to prolonged exposure to coal dust particles, resulting in PF and impaired immune function (45). Exposures related to metallic substances form another critical category; in industries producing hard metals, inhalation of tungsten carbide-cobalt particulates may provoke epithelial and macrophage injury, accompanied by significant cytokine release, thereby providing mechanistic evidence for subsequent fibrotic remodeling (46). Beyond these traditional occupational hazards, emerging engineered nanomaterials such as carbon nanotubes have been shown to promote fibroblast-to-myofibroblast transition and stromal expansion in experimental models, thus raising concerns regarding their fibrogenic potential (47).

Inhalation from the environment. Environmental inhalational exposures, most notably ambient and indoor air pollution, are increasingly regarded as significant risk factors for IPF.

In urban settings, diesel exhaust is a substantial source of ambient fine particulate matter (PM2.5) and, as a key traffic-related component, a primary contributor to respiratory morbidity (48). Mechanistically, multiple experimental studies have demonstrated that PM2.5 can penetrate deeply into the distal lung and deposit in the alveolar region, triggering a cascade of events, including inflammation, production of reactive oxygen species and damage to alveolar type 2 epithelial (AT2) cells, ultimately lung remodeling and fibrosis (49). In addition to particulate pollution, traffic-related gaseous pollutants such as nitrogen dioxide (NO_2) have been associated with increased mortality and a higher risk of disease progression in IPF, emphasizing the clinical importance of multipollutant exposure burdens (50,51). NO_2 primarily induces PF by initiating sustained oxidative stress in lung tissues, which in turn mediates epithelial cell injury, facilitates inflammatory cell infiltration and ultimately promotes fibroblast activation along with excessive ECM deposition (52). Emerging evidence further indicates that indoor air pollution contributes to adverse IPF outcomes, highlighting the importance of accumulated lifetime inhalational injury that extends beyond outdoor sources (53). Additionally, long-term personal exposure to elevated levels of air pollutants constitutes an independent risk factor for acute exacerbation of IPF. In this regard, it has been hypothesized that this may be associated with air pollution, potentially serving as a repetitive stimulus capable of disrupting telomere shortening and oxidative stress pathways (54).

Microbial infection. An increasing body of evidence indicates that microbial infections, particularly viral infections, may potentially contribute to both the initiation and exacerbation of PF. Viral invasion can cause immediate harm to pulmonary tissues, thereby triggering a cascade of events that lead to persistent lung injury and/or impaired tissue repair mechanisms. This pathophysiological process ultimately results in the progression of PF. Furthermore, viral infections possess the capacity to induce immune-mediated lung pathology. The interaction between viral components and pro-inflammatory and pro-fibrotic mediators, including cytokines and other bioactive factors, contributes to the progression of ongoing and severe pulmonary damage, thereby promoting fibrotic alterations within the lung parenchyma (55). It is noteworthy that fibrotic changes may manifest following the acute phase of viral infections. Specific viruses, including cytomegalovirus, avian influenza virus and coronaviruses such as severe acute respiratory syndrome (SARS)-coronavirus (CoV), Middle East respiratory syndrome-CoV and SARS-CoV-2, are capable of inducing persistent lung damage and facilitating the onset of fibrosis subsequent to the acute infection period (56). Beyond viral pathogens, recent research has clarified the involvement of bacterial infections in the pathogenic mechanisms underlying IPF. Notably, previous research has demonstrated that individuals with IPF possess a higher bacterial load within their bronchoalveolar lavage fluid compared with healthy subjects or patients with chronic obstructive pulmonary disease (57). Building on these epidemiological findings, the colonization and subsequent infection by opportunistic pathogens are posited to potentially facilitate the persistence of a fibrotic microenvironment. This occurs through persistent inflammatory stimulation and aberrant immune responses. A paradigmatic example is *Pseudomonas aeruginosa*, a facultatively anaerobic, Gram-negative bacterium that is one of the principal causative agents of severe infections. It exhibits a notably high prevalence among individuals afflicted with chronic lung conditions, such as cystic fibrosis, thereby underscoring the substantial clinical ramifications associated with its colonization and infection within the setting of chronic pulmonary ailments (58).

Systemic disease. Systemic disorders constitute a significant etiological category for progressive PF, characterized by a convergence of recurrent epithelial injury, dysregulated immunity and impaired inflammatory resolution that sustains a self-perpetuating fibroproliferative response. One such disorder, gastro-esophageal reflux disease (GERD), is commonly observed in IPF and is hypothesized to exacerbate disease progression through chronic microaspiration of gastric contents, thereby sustaining alveolar epithelial injury and promoting profibrotic repair mechanisms (59). Beyond mechanical factors such as GERD, connective tissue disease-associated ILD constitutes another primary category of systemic disorders driving PF. Within this category, systemic sclerosis serves as a prototypical immune-driven fibrotic disorder characterized by vascular damage, immune activation and progressive fibrosis of the skin and internal organs, most notably the lungs (60). Specifically, systemic sclerosis-ILD is a leading cause of morbidity and mortality and often progresses into a fibrosing phenotype marked by declining lung function and increasing radiographic fibrosis (61). Extending beyond systemic sclerosis, rheumatoid arthritis (RA), a systemic inflammatory condition, frequently manifests with pulmonary involvement. RA-ILD represents a major extra-articular cause of morbidity and mortality among affected individuals (62).

Drug-induced PF (DIPF). DIPF, a serious adverse reaction associated with various medication classes, including bleomycin, amiodarone and methotrexate, is driven by a complex cascade involving alveolar epithelial cell (AEC) injury, inflammatory dysregulation, metabolic reprogramming, fibroblast activation and excessive deposition of ECM (63). Chemotherapeutic agents such as bleomycin, a typical fibrogenic agent, lead to an increase in programmed death-ligand 1 expression, initiate EMT and cause fibrosis-like morphological changes in human pulmonary AECs (64). Beyond chemotherapeutics, amiodarone, a first-line antiarrhythmic agent, also induces DIPF through a distinct pathological mechanism characterized by the intracellular accumulation of phospholipid complexes within lung histiocytes and type II pneumocytes, which further exacerbates epithelial injury and pro-fibrotic inflammation (65). In addition, disease-modifying antirheumatic drugs (DMARDs), which constitute the cornerstone of therapy for autoimmune disorders such as RA, systemic lupus erythematosus and psoriatic arthritis, also present a documented risk of DIPF. An analysis of pharmacovigilance data sourced from the FDA Adverse Event Reporting System database indicates that DMARDs are among the drug categories most frequently implicated in reports concerning PF. This finding underscores the critical necessity for vigilant clinical monitoring of medication usage (66). Additionally, nitrofurantoin, a commonly

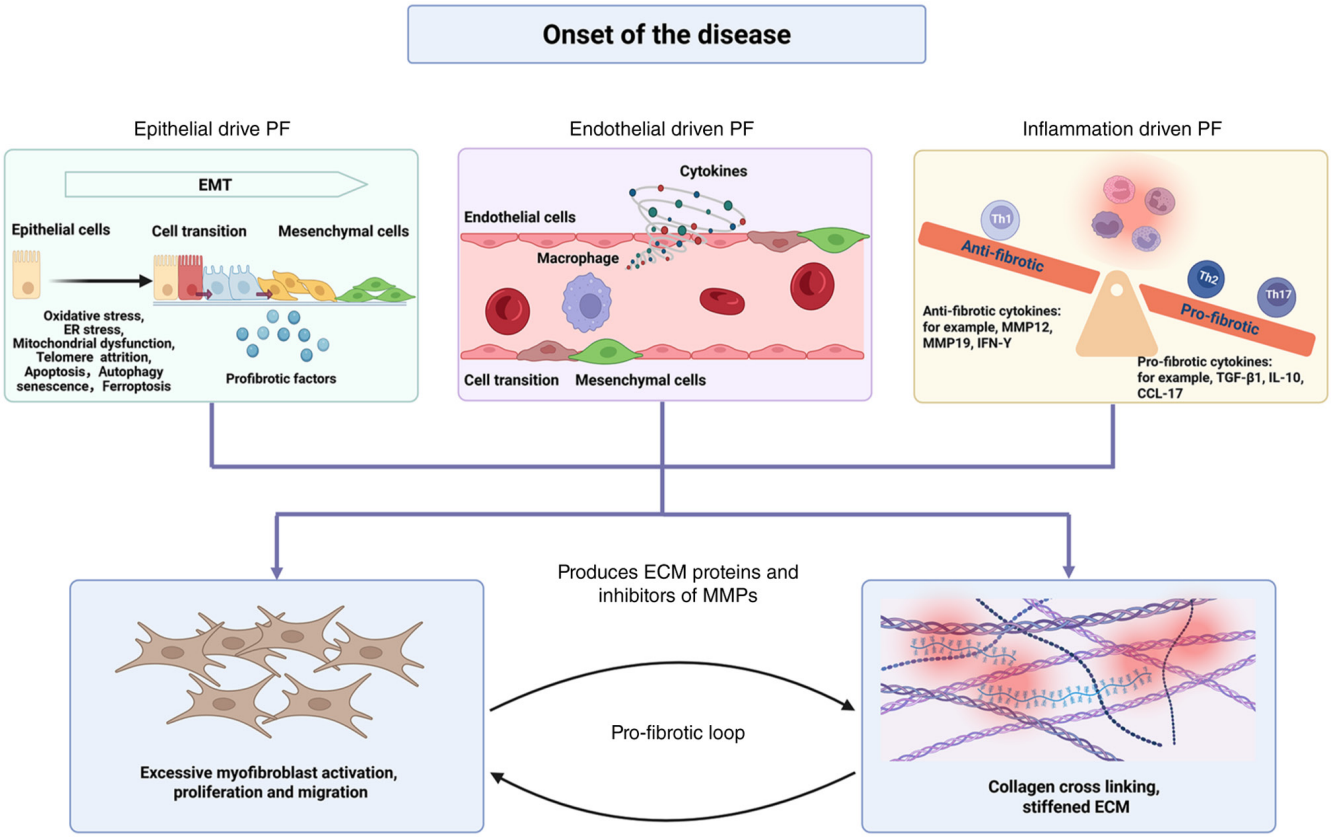

Figure 2. Cellular and molecular mechanisms driving PF. PF involves multiple cell types and interconnected pathways. Epithelial cells contribute via EMT, driven by stressors such as oxidative stress, ER stress, mitochondrial dysfunction, telomere attrition, apoptosis, autophagy, senescence and ferroptosis. Endothelial cells and macrophages are also involved, with macrophages secreting pro-fibrotic and anti-fibrotic cytokines (e.g., TGF-β1, IL-10, CCL-17, MMP12, MMP19, IFN-γ). These pathways converge on excessive myofibroblast activation, proliferation and migration, leading to ECM deposition, collagen cross-linking and ECM stiffening, forming a pro-fibrotic loop that sustains disease progression. The image was generated utilizing Biorender (https://BioRender.com). ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; PF, pulmonary fibrosis.

prescribed antibiotic for urinary tract infections, has been associated with rare but potentially severe pulmonary toxicity. Specifically, its chronic toxicity can induce ILD accompanied by progressive fibrosis, which may result in substantial and occasionally irreversible pulmonary impairment (67).

3. Cellular and molecular mechanisms of PF

The pathogenesis of PF involves multiple cell types, including AECs, fibroblasts, macrophages and ECs. This section elaborates on the respective roles of these cells in PF, as illustrated in Fig. 2.

AECs. Alveolar epithelial integrity is fundamental to lung homeostasis, and its injury is widely recognized as a critical initiating and driving event in the pathogenesis of IPF (68). In the healthy alveolus, squamous type 1 alveolar epithelial AT1 cells form the primary gas-exchange surface in close apposition to ECs, whereas cuboidal AT2 cells produce phospholipid-rich surfactant and serve as facultative progenitors that replenish the epithelium by generating AT1 cells after injury (69). In striking contrast, in IPF, repetitive micro-injuries and a failure of normal repair mechanisms lead to a profound dysfunction of this regenerative program. Consequently, this results in AT2-cell dysfunction and impaired differentiation into AT1 cells, while also promoting aberrant epithelial-mesenchymal interactions-a constellation of defects that collectively propel the lung into a state of persistent, maladaptive wound healing (69-71). Within this deleterious microenvironment, AT2 cells demonstrate increased sensitivity to disturbances in intracellular homeostasis, encompassing oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction and telomere attrition, which collectively compromise epithelial cell viability and regenerative potential (72,73). As a result, AT2 cells undergo various injury and death pathways, such as apoptosis, autophagy-related damage, cellular senescence and ferroptosis, further limiting their ability to proliferate and restore the epithelial barrier. Furthermore, epithelial cells exhibit increased plasticity, undergoing EMT-like transitions that enable them to directly produce ECM components and secrete pro-fibrotic mediators, thereby actively fueling interstitial remodeling (74). Beyond these well-established cellular outcomes, epithelial injury in fibrotic conditions is also associated with organelle and metabolic stress. For instance, abnormal mitochondrial iron accumulation has been observed in AT2 cells within bleomycin-induced fibrosis models and in epithelial cells exposed to bleomycin. This indicates that dysregulation of mitochondrial iron may be a pivotal factor in the damage and depletion of AT2 cells, consequently accelerating fibrotic remodeling (75). In summary, dysfunction of AECs is intricately associated with PF pathogenesis, operating through a multifaceted network of cellular stress, cell fate dysregulation and metabolic dysfunction.

Fibroblasts. In PF, lung fibroblasts secrete substantial quantities of collagen, which is integral to the progression of the disease. Within the activated fibroblast population, myofibroblasts-differentiated cells characterized by smooth muscle-like contractile properties and α-smooth muscle actin (SMA) expression-are regarded as the primary effector cells responsible for fibrotic remodeling (76). The master driver of this transition is TGF-β1, which is largely secreted by injured AECs and other cellular sources within the fibrotic microenvironment (77). Through this transformation, fibroblasts directly fuel the excessive deposition of ECM, the pathological hallmark and critical endpoint in the progression of PF (78). Meanwhile, the buildup of myofibroblasts in fibroblastic foci causes lung tissue contraction and thickening of the alveolar-capillary membrane. These structural alterations, in turn, result in a lasting reduction in pulmonary diffusing capacity, restrictive ventilatory failure and PF (79). Previous research on mouse models indicate that periostin (Postn) functions as a reliable and specific biomarker for pulmonary myofibroblasts. Furthermore, the removal of Postn-positive myofibroblasts following injury has been demonstrated to mitigate lung fibrosis, implying that targeting these cells could represent a promising strategy for future therapeutic interventions in PF (80).

Macrophages. In the context of fibrotic progression, the immune microenvironment serves as a crucial factor that significantly amplifies the entire cascade of fibrotic events. In the context of healthy lungs, macrophages represent the predominant immune cell population and can be categorized into two principal subsets: Alveolar macrophages (AMs) and interstitial macrophages. Among these, AMs serve as the primary innate immune cells residing in the lungs, playing a pivotal role in maintaining tissue homeostasis (81). Based on the distinct local microenvironments they encounter, macrophages have the capacity to undergo polarization, adopting either a classically activated (M1) or an alternatively activated (M2) phenotype. Typically, M1 macrophages are primarily involved in the initial phases of wound repair subsequent to alveolar epithelial damage, whereas M2 macrophages are mainly tasked with facilitating the resolution of wound healing or promoting fibrosis (82). Macrophages of both M1 and M2 phenotypes are implicated in the onset of lung injury and its subsequent progression towards PF. An overabundance of M1 macrophages can induce epithelial cell apoptosis and hinder the repair process, whereas an excessive presence of M2 macrophages results in aberrant and poorly regulated repair mechanisms, which are hallmarks of progressive fibrotic conditions (83). M2 macrophages secrete profibrotic mediators such as TGF-β1, IL-10 and C-C motif chemokine ligand 17 (CCL17), which enhance fibroblast proliferation, myofibroblast differentiation and ECM deposition, thereby amplifying fibrogenesis (84). Furthermore, macrophage polarization is tightly shaped by T helper (Th)-cell cytokines: Th1-derived IFN-γ tends to restrain profibrotic macrophage programs, whereas Th2 cytokines (IL-4/IL-13) promote M2-like polarization and reinforce TGF-β-driven matrix accumulation. Th17 responses further sustain macrophage inflammatory circuits and tissue injury, while Th22/IL-22 primarily supports epithelial integrity and indirectly dampens macrophage-driven profibrotic remodeling (85,86). Previous research findings indicate that anti-fibrotic therapy employing pirfenidone interferes with both the polarization process and mechanical activation of macrophages that promote fibrosis, thereby suppressing fibrotic progression (87).

ECs. In addition to the contributions of epithelial, stromal and immune cells, the vascular system undergoes notable structural and functional alterations that play a profound role in the progression of fibrosis. ECs constitute the innermost lining of the vasculature and are essential for maintaining pulmonary homeostasis through the regulation of vascular tone, permeability and leukocyte trafficking (88). In PF, however, this homeostatic function is disrupted. Increasing evidence suggests that PF is associated with persistent EC activation and dysfunction of the vascular barrier, as evidenced by abnormal vascular endothelial cadherin/CD31 signaling, increased adhesion between ECs and immune cells and an overall reduction in barrier integrity (89). These functional alterations, in turn, can amplify fibro-inflammatory signaling and facilitate ECM remodeling (90). Importantly, aging further predisposes the lung to fibrosis by inducing EC dysfunction, which compromises vascular repair capacity after injury and facilitates the persistence of fibrotic remodeling (91). A central mechanism linking these vascular changes to fibrosis is endothelial-to-mesenchymal transition (EndMT), a process during which ECs undergo transcription factor-driven reprogramming, losing their characteristic cobblestone morphology and endothelial identity, and acquiring spindle-shaped, mesenchymal or myofibroblastic features (92). This transition is promoted by profibrotic pathways, including TGF-β/mothers against decapentaplegic homolog (Smad) and Wnt/β-catenin signaling cascades, and can be further exacerbated by cigarette smoke exposure and pro-inflammatory cytokines, thereby aggravating endothelial dysfunction and vascular remodeling in fibrotic lungs (74). Consistent with this, mediators derived from ECs have been demonstrated to actively direct the process of fibrosis. For instance, matrix metalloproteinase (MMP)19 facilitates PF by inducing EndMT and promoting monocyte infiltration (93). Conversely, macrophage-derived MMP12 sustains endothelial injury, thereby reinforcing a positive feedback loop between vascular damage and fibrogenesis (94). In cases of silica-associated fibrosis, senescent EC-derived galectin-3 further accelerates disease progression through crosstalk between ECs, fibroblasts and macrophages (95). Reinforcing these observations at the molecular level, recent single-cell and genetic studies further substantiate an active vasculofibrotic interaction, demonstrating that EC-intrinsic programs, such as forkhead box F1 (FOXF1)/related RAS viral oncogene homolog signaling, serve to inhibit fibroblast activation, whereas the loss of endothelial FOXF1 amplifies inflammation and collagen deposition (96). To summarize, a series of interconnected processes, encompassing endothelial damage, impairment of barrier function and EndMT, are intricately linked with epithelial injury, immune-mediated inflammation and remodeling of the interstitial tissue. These processes collectively contribute to the formation and perpetuation of the intricate pathological network that underlies the progression of PF.

4. Glycolysis-related factors and PF

Aerobic glycolysis, traditionally known as the Warburg effect, describes the metabolic tendency of cells to convert glucose into

lactate despite the presence of sufficient oxygen, a phenomenon initially identified in cancer cells. The biological importance of this mechanism of reprogramming extends beyond merely providing a swift energy source; it is of even greater importance in preserving the pool of glycolytic intermediates. This preservation of glycolytic intermediates plays a pivotal role by channeling a portion of the carbon flux towards the pentose phosphate pathway (PPP), as well as anabolic routes including lipid, amino acid and nucleotide biosynthesis. Consequently, this orchestrated shunting of carbon flux underpins the accumulation of biomass that is essential for cellular proliferation and ECM synthesis (97,98). Specifically, glucose-6-phosphate (G-6-P) enters the PPP to support nucleotide synthesis, while dihydroxyacetone phosphate and 3-phosphoglycerate act as precursors for lipid and amino acid biosynthesis, respectively. At the molecular level, this metabolic shift is regulated through the coordinated upregulation and activation of rate-limiting glycolytic enzymes and transporters, including hexokinase (HKs), phosphofructokinase (PFK)-1 and pyruvate kinases (PKs), as well as GLUTs such as GLUT1. In PF, activated fibroblasts, damaged AECs and inflammatory cells exhibit increased glycolytic activity, driven by the upregulation of HK2, PFK1, PKM2 and GLUT1, to fulfill their heightened bioenergetic and biosynthetic demands.

Glucose transport. Glucose transport across the plasma membrane is mediated by facilitative GLUTs, a family of integral membrane proteins that regulate cellular glucose uptake and thereby maintain metabolic homeostasis (99). Once transported into the cytoplasm by GLUTs, glucose is channeled into glycolysis, a cytosolic pathway consisting of 10 enzyme-catalyzed reactions that ultimately convert glucose to pyruvate, with concomitant production of adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (reduced) (NADH) (100). This GLUT family encompasses a total of 14 distinct members. Each GLUT variant exhibits unique transporter kinetics and tissue-specific distribution patterns, thereby conferring individual characteristics to every member within this family. Among them, GLUT1 is the most ubiquitously expressed isoform and is frequently upregulated under stress conditions. Increased GLUT1 expression enhances glucose influx, augments glycolytic flux and elevates lactate production, thereby favoring glucose-dependent metabolic programs (101). Consistent with this role, GLUT1-driven aerobic glycolysis provides both ATP and anabolic intermediates required for tumor cell proliferation and metastatic dissemination (102). In contrast to GLUT1's high-affinity and proliferation-supporting role, GLUT2 functions as a low-affinity, high-capacity transporter, which is highly expressed in the liver, intestine and kidney, as well as in pancreatic β-cells, where it contributes to hepatic glucose export, intestinal and renal glucose handling and glucose-sensing-dependent insulin secretion (103). GLUT3, which exhibits a particularly high affinity for glucose, supports basal glucose uptake in tissues with high metabolic demand (104). GLUT4 is a GLUT responsive to insulin and exercise, which translocates to the plasma membrane in skeletal muscle and adipose tissue, thereby enhancing glucose uptake for glycolysis and ATP synthesis (105). Considering their key role in supporting glycolysis, GLUTs are promising therapeutic targets, with numerous GLUT-focused strategies currently being explored in the context of oncology.

HKs. HKs are the initial rate-limiting enzymes in the glycolytic pathway, catalyzing the irreversible phosphorylation of glucose to G-6-P immediately following its entry into the cell via GLUTs (106). Previous studies have identified four distinct HK isozymes (HK1, HK2, HK3 and HK4), each exhibiting unique tissue-specific expression profiles and enzymatic kinetic characteristics (107,108). Among these, HK2 has garnered particular attention for its crucial role in mediating aerobic glycolysis, a metabolic hallmark widely observed in cancer cells, and its upregulation is closely linked to tumor growth and progression (109). Functionally, HK2 can channel G-6-P into glycogen synthesis and the PPP within the cytoplasm. However, when associated with mitochondria, HK2 preferentially supports glycolytic flux and oxidative phosphorylation processes (110). Emerging evidence suggests that this HK2-centered metabolic switch is also active in PF. In fibroblasts derived from patients with IPF and in bleomycin-induced PF models, TGF-β1 signaling drives HK2 accumulation (via the MYC proto-oncogene) to enhance aerobic glycolysis, promote myofibroblast differentiation and increase collagen synthesis. Genetic silencing of HK2 or pharmacological inhibition with lonidamine reduces fibrogenic gene expression and alleviates bleomycin-induced lung fibrosis *in vivo* (111). Further underscoring the pathogenic relevance of HK2, vitamin D alleviates silica-induced PF partly by inhibiting signal transducer and activator of transcription (STAT)3/HK2-mediated glycolysis in fibroblasts (112). Consistently, in TGF-β1-stimulated human lung fibroblasts *in vitro*, strategies that suppress HK2 expression-such as alamandine/Mas-related G protein-coupled receptor D (MrgD) signaling-disrupt the lactate-HK2 feed-forward loop, restrain fibroblast activation and produce anti-fibrotic effects (113). Collectively, these findings highlight HK2 as a promising metabolic target for the development of therapies against PF.

PFK-1. PFK-1 functions as the second primary rate-limiting enzyme in glycolysis, catalyzing the irreversible conversion of fructose-6-phosphate to fructose-1,6-bisphosphate and thereby committing glucose to glycolytic degradation (114). Although PFK-1 is encoded by three distinct genes (PFKL, PFKM and PFKP), its enzymatic activity is further regulated by the PFKFB family of bifunctional enzymes (namely PFKFB1-PFKFB4), which produce fructose-2,6-bisphosphate, a potent allosteric activator of PFK-1. Among the PFKFB isozymes, PFKFB3 is the most extensively studied and is frequently overexpressed in various cancer types, where it enhances glycolytic flux and facilitates the Warburg effect, thereby supporting tumor cell proliferation and survival (115). Beyond its established role in cancer, emerging evidence indicates that the pathogenic role of PFKFB3-driven glycolysis extends to fibrotic diseases. For instance, in IPF, PFKFB3-mediated glycolysis has been mechanistically linked to fibroblast activation, and pharmacological inhibition of PFKFB3 reduces bleomycin-induced and lipopolysaccharide (LPS)-induced PF in animal models (116,117). In silica-induced fibrosis, activation of glucagon-like peptide-1 receptor disrupts the interaction between the NLR family pyrin domain containing 3 inflammasome and PFKFB3-driven glycolysis, leading to decreased lactate production and histone lactylation, thereby inhibiting fibroblast activation (118). Furthermore, the natural compound peimine, extracted from

Fritillaria, has been demonstrated to inhibit fibroblast activation and alleviate bleomycin-induced PF by suppressing glycolysis via the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/PFKFB3 signaling pathway (119).

PK. PK serves as a pivotal regulatory enzyme at the terminal stage of the glycolytic pathway, where it assumes a critical function in sustaining the rate of glycolytic flux and facilitating energy generation (120). Specifically, PK catalyzes the conversion of phosphoenolpyruvate and ADP into pyruvate and ATP, thereby functioning as a critical metabolic checkpoint that links glycolytic flux to cellular energy demands (121). In mammals, two genes encode four major isoforms (PKL/PKR and PKM1/PKM2). Among these, PKM2 stands out for its pronounced conformational plasticity, switching between a low-activity dimer and a high-activity tetramer to direct glucose carbon toward either ATP production or anabolic biosynthesis (122). During fibrotic remodeling in IPF and related PF models, PKM2 is increasingly recognized as a pathogenic metabolic hub: Myofibroblast differentiation prompts the upregulation of PKM2 and favors its dimeric form, which reroutes glycolytic intermediates toward *de novo* glycine synthesis, thereby supporting collagen biosynthesis and the maintenance of activated myofibroblasts (123). Consistent with this pathogenic role, genetic deletion of PKM2 significantly attenuates bleomycin-induced PF and suppresses myofibroblast activation by dampening TGF-β1 signaling (124). Beyond its metabolic functions, PKM2 can perform non-canonical signaling roles, including stress-induced nuclear translocation in myeloid cells, potentially amplifying inflammatory responses relevant to fibrotic progression (125). Together, these observations position PKM2 as a tractable glycolytic regulator linking metabolic rewiring to matrix accumulation in PF.

Lactate dehydrogenase (LDH). LDH, predominantly the A isoform (LDHA), catalyzes the terminal reaction of glycolysis by reducing pyruvate to lactate while oxidizing NADH to nicotinamide adenine dinucleotide (oxidized) (NAD^+), thereby maintaining cytosolic redox balance and sustaining glycolytic flux when mitochondrial oxidation is constrained or biosynthetic demand is high (126). Under physiological conditions, high LDH activity maintains the pyruvate-lactate equilibrium and supports lactate as a diffusible metabolite within tissues, consistent with its role as a physiological end product of glycolysis (127). By contrast, under pathological conditions such as IPF, lactate is enriched in diseased lungs and functions as an active profibrotic signal rather than a passive by-product (20). Mechanistically, elevated lactate promotes extracellular acidification, which can activate latent TGF-β1 in a pH-dependent manner and induce fibroblast-to-myofibroblast differentiation, thereby creating a feed-forward loop of matrix accumulation (19). Furthermore, lactate derived from myofibroblasts can induce histone lactylation in macrophages and amplify profibrotic transcriptional programs, thereby further supporting fibro-inflammatory remodeling (21). Accordingly, pharmacological inhibition of LDHA decreases lactate production and mitigates bleomycin-induced PF, thereby highlighting the LDH-lactate axis as a potential therapeutic target in PF (128).

5. Glycolysis-related signaling pathways and PF

Multiple signaling pathways are involved in the pathogenesis of PF, including TGF-β1, hypoxia-inducible factor (HIF)-1α, PI3K/Akt/mTOR, Hippo, AMP-activated protein kinase (AMPK) and SIRT. This section will elaborate on the respective roles of these pathways in PF, as illustrated in Fig. 3.

TGF-β. TGF-β is a pleiotropic cytokine that orchestrates tissue repair and immune homeostasis; however, when persistently activated, it is widely regarded as a master profibrotic program in fibrosis, driving fibroblast-to-myofibroblast differentiation, epithelial plasticity and excessive ECM deposition (129,130). In mammals, TGF-β exists in three subtypes: TGF-β1, TGF-β2 and TGF-β3, with TGF-β1 playing a dominant role in PF, as demonstrated in IPF lung tissues, bleomycin-induced PF models and silicosis models, through its integration with glycolysis (131). In human IPF lung tissues and in bleomycin- and silica-induced PF models, TGF-β1 serves as a crucial profibrotic signal generated by damaged epithelial and immune cells, including macrophages. Through canonical Smad2/3 signaling, it facilitates the transition of fibroblasts to myofibroblasts and promotes ECM accumulation (132). At the molecular level, TGF-β1 interacts with its receptors, TGF-β receptor I and II, consequently inducing the phosphorylation and activation of Smad2 and Smad3. Notably, Smad7 serves as an inhibitory regulatory element, providing negative feedback in this pathway. Upon activation, phosphorylated Smad2 and Smad3 form complexes with Smad4 and translocate to the nucleus, where they play a critical role in regulating the expression of essential target genes (1). Beyond this canonical signaling cascade, recent research highlights that TGF-β signaling is tightly coupled to glycolytic reprogramming during myofibroblast differentiation, enabling fibroblasts to meet the increased bioenergetic and biosynthetic demands of collagen production (133). Specifically, TGF-β enhances glucose uptake and glycolytic flux by upregulating pivotal glycolytic nodes such as GLUT1, HK2 and PFKFB3, which leads to increased lactate production and fosters a profibrotic metabolic milieu (20,111,133). This lactate, in turn, is not merely a metabolic by-product; it contributes to the acidification of the extracellular space and may induce the activation of latent TGF-β1 through pH alterations. Thus, a feed-forward mechanism involving 'TGF-β-glycolysis-lactate' is established, which maintains myofibroblast viability and perpetuates ECM remodeling (19).

HIF. HIF serves as a transcriptional activator that is frequently triggered under hypoxic conditions (134). Structurally, HIF is a heterodimeric transcription factor composed of α and β subunits. The α subunits include HIF-1α, HIF-2α and HIF-3α, while the β subunits comprise aryl hydrocarbon receptor nuclear translocator (ARNT1) (also known as HIF-1β) and ARNT2 (135). Under normoxic conditions, HIF-1α undergoes hydroxylation facilitated by prolyl hydroxylase domain enzymes (PHDs), which are recognized by the von Hippel-Lindau E3 ligase complex, leading to ubiquitination and subsequent degradation. Conversely, hypoxic conditions inhibit PHD activity, resulting in the rapid stabilization and nuclear accumulation of HIF-1α, which heterodimerizes with

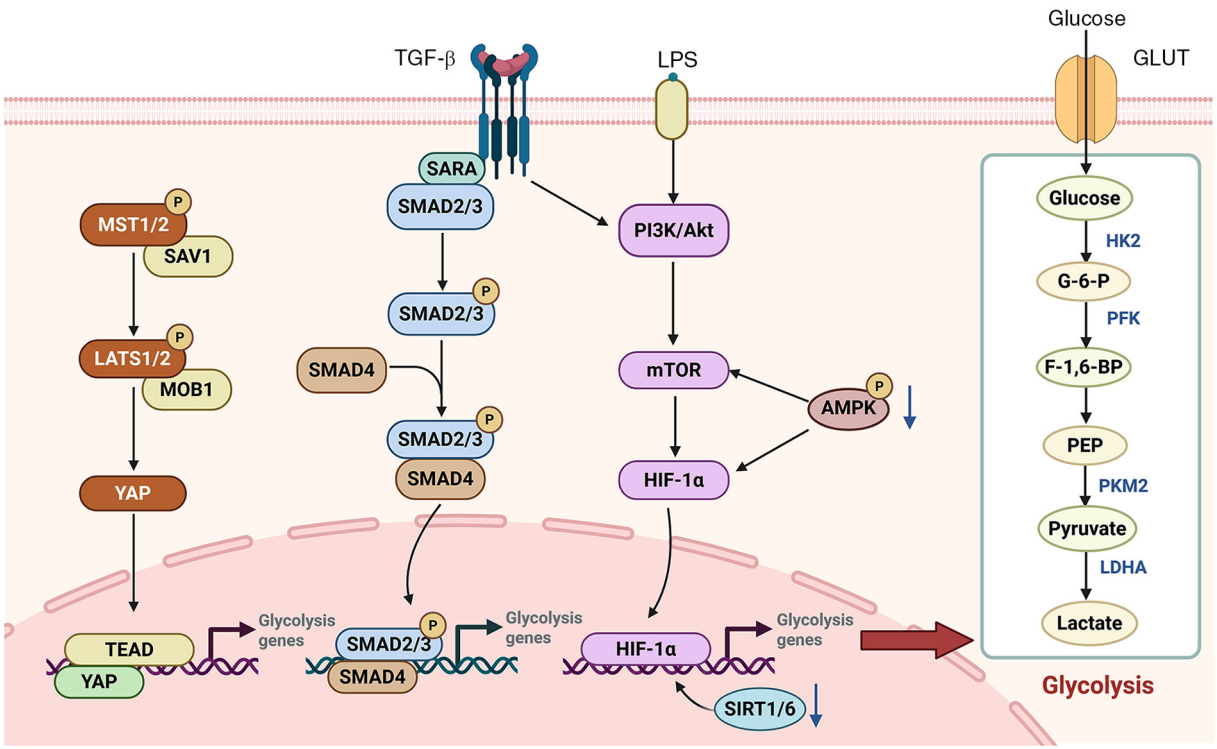

Figure 3. Signaling pathways regulating glycolysis in PF. Multiple signaling cascades converge to modulate glycolytic metabolism in the context of PF. The Hippo pathway (MST1/2-LATS1/2-YAP/TEAD), TGF-β/SMAD signaling (SMAD2/3-SMAD4) and LPS-induced PI3K/Akt-mTOR-HIF-1α axis collectively drive the transcription of glycolysis-related genes (e.g., *HK2*, *PFK*, *PKM2*, *LDHA*), thereby enhancing glucose uptake and conversion to lactate. AMPK and SIRT1/6 act as negative regulators, inhibiting mTOR and HIF-1α activity, respectively, to counteract glycolytic flux. This coordinated signaling network highlights the central role of augmented glycolysis in the pathogenesis of PF, positioning it as a potential therapeutic target. The image was generated utilizing Biorender (https://BioRender.com). PF, pulmonary fibrosis; HIF, hypoxia-inducible factor; HK2, hexokinase 2; LPS, lipopolysaccharide; LATS1/2, large tumor suppressor kinase 1/2; LDHA: Lactate dehydrogenase A ; YAP, Yes-associated protein; TEAD, TEA domain transcription factor; TGF-β, transforming growth factor-β; MST1/2, mammalian sterile 20-like kinase 1/2; SAV1, Salvador family WW domain-containing protein 1; MOB1, Mps one binder kinase activator protein 1; SARA, SMAD anchor for receptor activation; SMAD2/3, sons of mothers against decapentaplegic 2/3; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; AMPK, AMP-activated protein kinase; SIRT1/6, silent information regulator 1/6; GLUT, glucose transporter; G-6-P, glucose-6-phosphate; PFK, phosphofructokinase; F-1,6-BP, fructose-1,6-bisphosphate; PEP, phosphoenolpyruvate; PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase A; P, phosphorylation.

HIF-1β and binds to hypoxia-responsive elements to initiate the transcription of downstream genes (136). Beyond its involvement in angiogenesis and ECM remodeling, HIF-1α is a critical factor in metabolic reprogramming from oxidative phosphorylation toward glycolysis. At the metabolic level, HIF-1α enhances glucose uptake by inducing the GLUT family and broadly upregulates the transcription of glycolytic enzymes, thereby augmenting glycolytic flux. Key glycolytic enzymes upregulated by HIF-1α include HK2, PFK and PFKFB3, which collectively facilitate increased glucose utilization and lactate production (136). In addition, HIF-1α promotes the diversion of pyruvate away from mitochondrial oxidation by inducing pyruvate dehydrogenase kinase 1 (PDK1), which inhibits the pyruvate dehydrogenase complex and further reinforces the glycolytic phenotype (137). Thus, enhanced glycolysis and lactate accumulation serve as functional readouts of HIF-1α-dependent transcriptional activation, providing a direct link between this transcription factor and the metabolic phenotype of fibrotic tissues.

Consistent with the aforementioned link, accumulating evidence supports a close association between aberrant HIF-1α activation and PF pathogenesis (138). Within IPF lung tissues, HIF-1α-mediated metabolic dysfunction in AECs results in elevated lactate production. This lactate, in turn, triggers the activation of interstitial fibroblasts, ultimately expediting the progression of PF (139). Elevated HIF-1α expression has been observed in AECs in bleomycin-induced models and in human fibrotic lung tissues, indicating its critical role in disease progression (140). Consistently, targeting the HIF-1α-glycolysis axis, particularly the HIF-1α/PDK1 metabolic switch and lactate-associated signaling, has emerged as a promising strategy to mitigate PF by disrupting profibrotic metabolic reprogramming.

PI3K/Akt/mTOR. The PI3K/Akt signaling cascade constitutes a crucial intracellular pathway that plays a central role in the regulation of the cell cycle. To date, extensive investigations have been undertaken to elucidate the structural attributes and functional mechanisms of PI3Ks, including class I, class II and class III PI3Ks. Upon activation, PI3K generates PIP3, which subsequently activates Akt and stimulates mTOR signaling, thereby driving profibrotic cellular programs (141). Notably, the PI3K/Akt/mTOR pathway also facilitates metabolic reprogramming towards glycolysis. One critical mechanism linking this pathway to glycolysis is its regulation of HIF-1α. HIF-1α is stabilized and activated by growth factors and cytokines via PI3K/Akt/mTOR signaling. Specifically, by activating mTOR complex (mTORC)1, this pathway enhances protein translation

and stabilizes HIF-1α, leading to the transcriptional activation of glycolytic genes such as GLUT1, HK2 and PFKFB3. Previous research findings indicate that the activation of the PI3K-Akt-mTOR signaling axis plays a role in modulating cellular aerobic glycolysis. For instance, in the lung, LPS may induce aerobic glycolysis in pulmonary fibroblasts by activating the PI3K-Akt-mTOR/PFKFB3 pathway, thereby contributing to the pathogenesis of LPS-induced PF (117). Beyond fibroblasts, the PI3K/Akt/mTOR axis also mediates metabolic crosstalk between immune and stromal cells: In neodymium oxide-induced PF, glycolytic reprogramming in macrophages leads to lactate-mediated histone lactylation, which activates the PI3K/Akt/mTOR pathway and promotes TGF-β1 secretion, thereby facilitating macrophage-fibroblast crosstalk and fibrotic progression (142). Providing a more detailed mechanistic view in PF, in bleomycin-induced models, hyperactivated PI3K/Akt/HIF-1α signaling modulates aberrant cell proliferation and apoptosis through oxidative stress mechanisms (143). Recent comprehensive reviews have further consolidated the central role of PI3K/Akt, mTOR and HIF-1α in the network-based regulation of glycolysis in PF (144).

Hippo pathway. The Hippo pathway is a conserved kinase cascade that governs tissue growth and regeneration. Its core regulatory module comprises mammalian STE20-like kinase 1/2 (MST1/2), Salvador homolog 1, large tumor suppressor kinase 1/2 (LATS1/2) and the transcriptional co-activators Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) (145). In the canonical setting, MST1/2 activates LATS1/2, which phosphorylates YAP/TAZ, promoting their cytoplasmic retention and proteasomal degradation, thereby suppressing YAP/TAZ-dependent transcriptional programs. Conversely, when Hippo signaling is inhibited, dephosphorylated YAP/TAZ accumulate in the nucleus and preferentially cooperate with TEA domain transcription factor (TEAD) to induce pro-proliferative and pro-remodeling genes, including connective tissue growth factor and cysteine-rich angiogenic inducer 61, positioning YAP/TAZ as central effectors of Hippo output (146,147). In IPF, aberrant activation and nuclear localization of YAP/TAZ represent a major profibrotic driver across multiple cell types (148). In fibroblasts, mechanical cues such as ECM stiffening can sustain YAP/TAZ nuclear activity, reinforcing fibroblast contractility and ECM synthesis and thereby promoting progressive scarring (149). In macrophages, YAP/TAZ activation is markedly enriched in lung macrophages during bleomycin-induced injury, where it shapes macrophage heterogeneity and profibrotic functions that facilitate fibrosis progression (150). In AECs, Hippo/YAP signaling is implicated in alveolar epithelial regeneration, particularly in AT2 self-renewal and differentiation into AT1 cells, underscoring its context-dependent roles in repair vs. fibrotic remodeling (151).

Beyond its cell-type-specific roles in fibrosis, Hippo/YAP/TAZ signaling is intricately associated with cellular metabolism and aerobic glycolysis. Mechanistically, under conditions of glucose deprivation or energy stress, AMPK and kinases linked to the Hippo pathway phosphorylate and inhibit the activity of YAP (145,152), whereas YAP activation sustains glycolytic metabolism and glucose homeostasis, partly through the regulation of glucose transport mechanisms (153). Conversely, glycolytic activity can directly enhance the transcriptional activity of YAP/TAZ. For example, during aerobic glycolysis, PFK1 interacts with TEAD1 and stabilizes the YAP/TAZ-TEAD transcriptional complex, thereby augmenting the expression of genes related to glycolysis; conversely, inhibition of glucose metabolism diminishes YAP/TAZ-driven transcription (154). This bidirectional regulation is further modulated by lactate, a glycolytic end-product enriched in fibrotic lungs, which can facilitate the activation of YAP/TAZ and the subsequent expression of profibrotic genes (20). In conclusion, persistent YAP/TAZ activation fosters a glycolysis-boosting environment, providing vital resources for fibroblast activation, ECM buildup and immune tissue remodeling, thus advancing PF.

AMPK. AMPK traditionally serves as a crucial cellular energy sensor. It is triggered into activation when the cellular energy level declines. Upon activation, AMPK functions to re-establish energy balance within cells. It achieves this by facilitating catabolic pathways that generate ATP and, concurrently, suppressing processes that consume energy (155). Through phosphorylation of various downstream substrates, AMPK orchestrates lipid catabolism, glucose uptake, glycolytic flux, autophagy and insulin sensitivity, thereby maintaining cellular energy homeostasis (156). Previous research has shown that the phosphorylation of AMPK can initiate the activation of the mTORC2-AKT signaling cascade, leading to phosphorylation of cytosolic glycolytic enzymes and increased HIF-1α expression, which collectively promote the transcription of glycolysis-related genes and enhance aerobic glycolysis (157). However, in the context of fibrotic stress, AMPK predominantly acts as an anti-fibrotic metabolic checkpoint, restraining pathological glycolytic reprogramming and limiting profibrotic signaling.

For example, in sepsis-associated PF, LPS stimulation promotes fibroblast activation, which is accompanied by AMPK inactivation, HIF-1α induction and increased aerobic glycolysis. Conversely, AMPK activation or HIF-1α inhibition suppresses glycolysis and fibroblast activation, attenuating fibrosis *in vivo* (158). Supporting this anti-fibrotic role, AMPK activation has been shown to mitigate pulmonary inflammation and fibrosis by antagonizing TGF-β1 signaling and promoting autophagy via the AMPK-mTOR axis (159). Clinical observations further reveal that fibrotic regions within IPF lungs, such as fibroblastic foci, show reduced AMPK activation, and impaired AMPK signaling may exacerbate mitochondrial dysfunction and metabolic reprogramming, thereby supporting the transition of fibroblasts to myofibroblasts and excessive ECM production (160). Beyond stromal remodeling, AMPK also exerts disease-relevant metabolic control in the alveolar epithelium. Furthermore, impaired regulation of AT2 cell metabolism by AMPK has been directly associated with PF in both murine models and human IPF samples, a condition in which deficient AMPK signaling correlates with increased glycolysis, decreased mitochondrial biogenesis, disrupted fatty acid oxidation (FAO), accumulation of dysfunctional mitochondria and loss of AT2 progenitor capacity. Pharmacological modulation of AMPK activity restores metabolic health and reduces fibrosis *in vivo* (161). Finally, in the context of

aging-associated lung fibrosis, increased GLUT1-dependent glycolysis is observed. Both genetic and pharmacological inhibition of GLUT1 suppress fibroblast activation markers (such as α-SMA) and alleviate bleomycin-induced PF, further emphasizing glycolysis as a key driver of fibrogenesis (101).

SIRTs. SIRTs constitute a highly conserved family of seven NAD^+-dependent deacetylases and deacylases (SIRT1-SIRT7), each with distinct subcellular localization: SIRT1, SIRT6 and SIRT7 are predominantly nuclear, while SIRT2 is primarily cytosolic, and SIRT3, SIRT4 and SIRT5 are mainly mitochondrial (162). These proteins are involved in the regulation of cellular metabolism and participate in various biological processes, including cell viability, DNA repair, cellular aging and response to oxidative stress. Therefore, SIRTs may be implicated in the pathogenesis of fibrotic diseases (163-165). Notably, SIRT signaling intersects with glycolytic regulation, particularly through the modulation of the HIF-1α axis. For instance, SIRT1 directly deacetylates HIF-1α, restraining its transcriptional activity and consequently suppressing HIF-1α-dependent glycolytic gene expression under hypoxic conditions (166). Similarly, SIRT6 functions as a corepressor of HIF-1α by deacetylating histone H3K9 at promoters of glycolytic genes. Loss of SIRT6 enhances glucose uptake and glycolytic flux while diminishing mitochondrial respiration, underscoring its role as a critical regulator of the glycolysis-mitochondrial function balance (167,168). Collectively, these mechanisms suggest that SIRTs can influence fibrogenesis through the modulation of pathological glycolytic remodeling and metabolic stress signaling.

Building on this metabolic connection, it is well established that SIRT1, SIRT3, SIRT6 and SIRT7 play protective roles in preventing the onset and progression of IPF. However, the regulatory functions of the remaining members of the SIRT family in this pathological process necessitate further investigation (169). SIRT1 and SIRT3 serve as crucial modulators in the context of lung fibrosis, given their capacity to mitigate the profibrotic actions triggered by TGF-β, as evidenced by both *in vitro* and *in vivo* experimental studies (163). By contrast, SIRT2 appears to exert pro-fibrotic effects: Gong *et al* (170) demonstrated that SIRT2 is upregulated in TGF-β1-stimulated human lung fibroblasts and in bleomycin-treated mouse lungs, and pharmacological inhibition of SIRT2 alleviates fibroblast activation and PF, at least in part via suppression of Smad2/3 signaling. Specifically, a deficiency of mitochondrial SIRT3 has been identified in AECs in cases of IPF, and genetic ablation of SIRT3 aggravates experimental lung fibrosis, concomitant with mitochondrial DNA damage in AECs and activation of intrinsic apoptotic pathways, thereby indicating that impaired mitochondrial quality control may heighten epithelial susceptibility and promote remodeling (171). Additionally, SIRT6 confers epithelial protection and reduces bleomycin-induced PF by facilitating lipid catabolism, augmenting cellular energy supplies and decreasing lipid peroxidation-related injury (172). Finally, in fibroblasts, a broad reduction in SIRT expression has been observed in PF, with SIRT7 showing the most marked decrease. Accordingly, overexpression of SIRT7 inhibits TGF-β-induced collagen synthesis and α-SMA expression, suggesting that SIRT7 functions as a negative regulator of fibroblast activation (173). In essence, SIRTs exert either protective or pathogenic roles in various aspects of PF, including epithelial damage, interstitial activation and immune-metabolic remodeling, by integrating energy sensing, epigenetic regulation and metabolic pathways.

6. Interaction between glycolysis and other metabolic pathways

Glycolysis-FAO metabolic switch. FAO constitutes a principal mitochondrial catabolic mechanism that transforms fatty acids into acetyl-CoA via β-oxidation, thereby providing energy for the tricarboxylic acid cycle and oxidative ATP synthesis (174). In cigarette smoke-induced PF, emerging evidence indicates an association with lipid metabolic dysregulation and a maladaptive shift in substrate utilization. For instance, cigarette smoke induces mitochondrial oxidative stress and disrupts autophagy flux, suppressing peroxisome proliferator-activated receptor α/carnitine palmitoyltransferase 1a-mediated FAO and lipid droplet autophagy. Consequently, this enhances lipid accumulation and fibroblast activation in the lungs, suggesting that abnormal lipid metabolism along with mitochondrial dysfunction jointly promote fibrotic remodeling (37).

Beyond these environmental triggers, a key feature of fibrotic metabolic remodeling is the reciprocal association between enhanced glycolysis and suppressed FAO, which appears to couple energy metabolism to ECM homeostasis. Supporting this reciprocal association, in fibroblasts, inhibition of HIF-1α blunts the TGF-β1-driven glycolytic program and is accompanied by restoration of FAO, suggesting that the TGF-β/HIF-1α axis participates in coordinating the glycolysis-FAO switch during fibroblast activation (175). Consistent with the functional importance of FAO, impaired FAO in aging AT2 cells compromises injury-induced alveolar regeneration and promotes the accumulation of intermediate epithelial states with aberrant basaloid/secretory features, which are associated with increased fibrotic susceptibility (176). Other previous research findings suggest that fibroblast-intrinsic metabolic rewiring may also be driven by metabolite signaling. For example, enhanced glycolysis together with reduced FAO has been linked to succinate accumulation, and targeting succinate dehydrogenase (SDH) in fibroblasts attenuates bleomycin-induced lung fibrosis, highlighting the succinate-SDH axis as a potential therapeutic entry point to counteract pro-fibrotic metabolic programming (177).

Effects of energy homeostasis imbalance. Mitochondria are indispensable to cellular energy metabolism, as they generate the majority of intracellular ATP. This ATP production maintains a high ATP-to-ADP ratio, which is vital for cellular homeostasis and function (178,179). Conversely, disruptions in mitochondrial dynamics lead to loss of mitochondrial homeostasis and subsequently impair mitochondrial functionality. For example, dysregulation of mitochondrial fusion and fission destabilizes mitochondrial networks, diminishes respiratory capacity and amplifies stress responses, collectively contributing to the pathogenesis of pulmonary diseases, including fibrosis (180). Within this framework, mitochondrial dysfunction has been widely recognized as a principal pathogenic contributor to various pulmonary disorders, exhibiting a strong correlation with both the initiation and progression

of IPF (181). At the cellular level, mitochondrial dynamics and bioenergetic capacity are closely linked to myofibroblast differentiation (182). Furthermore, mitochondria offer an additional layer of quality control, with the phosphatase and tensin homolog-induced kinase 1/Parkin pathway serving as a key mediator of mitophagy. Deficiency in this pathway results in inefficient clearance of damaged mitochondria, thereby exacerbating oxidative stress and pro-fibrotic signaling. Conversely, enhanced mitophagy, such as through the upregulation of acyl-CoA synthetase long-chain family member 1, may serve to alleviate fibrosis (183). These findings highlight mitochondrial quality control as a promising target for intervention to restore energy homeostasis and mitigate fibrotic progression.

7. Therapeutic strategies and challenges of targeting glycolysis in PF

Throughout this section, interventions that directly inhibit defined glycolytic enzymes or transporters are distinguished from those that indirectly modulate glycolytic flux through upstream signaling. Genetic evidence, including knockdown, knockout and rescue-of-function experiments, provides higher-confidence target-dependency validation compared with pharmacological treatment alone, given that numerous small-molecule compounds exert pleiotropic off-target effects.

Direct inhibitors of glycolytic enzymes and transporters. Inhibition of glycolytic enzymes has become a mechanism-based adjunct to antifibrotic therapy, as restricting glucose flux can limit the bioenergetic and biosynthetic inputs that support myofibroblast differentiation and ECM deposition (116). A range of natural and synthetic small-molecule agents has been developed as potential inhibitors targeting distinct stages of glycolysis, including glucose uptake, its rate-limiting step, and lactate generation. Numerous glycolytic nodes have been validated as legitimate therapeutic targets through complementary genetic and pharmacological methods (Table I).

The pathogenic role of HK2 in PF has been firmly established through both genetic and pharmacological approaches. In models of TGF-β1-stimulated human lung fibroblasts and bleomycin-induced PF, TGF-β1 signaling drives the accumulation of HK2 in a MYC-dependent manner, enhancing aerobic glycolysis, promoting myofibroblast differentiation and increasing collagen synthesis. Notably, genetic silencing of HK2 or pharmacological inhibition with lonidamine significantly reduces fibrogenic gene expression and alleviates bleomycin-induced lung fibrosis *in vivo* (111). Furthermore, evidence indicates that vitamin D mitigates silica-induced PF, in part by inhibiting STAT3/HK2-mediated glycolysis in fibroblasts (112). Additionally, alamandine/MrgD signaling disrupts the lactate-HK2 feedback loop, thereby restraining fibroblast activation (113). Collectively, these studies provide compelling genetic evidence that HK2 acts as a causal mediator rather than merely a correlate of fibrotic glycolysis. In glycolysis, PFKFB3 boosts glycolytic flux by upregulating PFK1 activity via fructose-2,6-bisphosphate production. Multiple studies indicate its pathogenic role in PF remodeling and fibroblast activation. In PF models, multiple PFKFB3 inhibitors have demonstrated efficacy. The PFKFB3 inhibitor 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO) reduces glycolysis and mitigates fibrotic phenotypes. For instance, in LPS-induced PF, the PI3K-Akt-mTOR/PFKFB3 pathway drives fibroblast aerobic glycolysis and collagen synthesis, effects that are mitigated by 3PO (117). In pulmonary myofibroblasts, 2-deoxy-D-glucose (2-DG) blocks HK-initiated glycolysis, while 3PO inhibits PFKFB3 to reduce PFK-1 activity. Both interventions suppress myofibroblast proliferation, contractility and collagen accumulation, which are key fibrotic features. In mice with bleomycin-induced PF, 3PO also reduces fibrosis (116). Anlotinib has emerged as a novel candidate for PF treatment, inhibiting PFKFB3-driven glycolysis in myofibroblasts (184). Peimine suppresses fibroblast activation and ameliorates bleomycin-induced PF by inhibiting glycolysis through the PI3K/Akt/PFKFB3 signaling pathway (119). PKM2 is a core glycolytic checkpoint that shapes metabolic reprogramming in profibrotic lung cells (124). Compound 3k is a PKM2-targeted small-molecule inhibitor that directly disrupts PKM2 tetramer assembly. Pharmacological or genetic suppression of PKM2 curbs aerobic glycolysis, lowers the supply of biosynthetic precursors and attenuates PF in bleomycin-challenged mice (124,185). Of note, tetramer-disrupting compound 3k also indirectly dampens profibrotic TGF-β-dependent signaling as a secondary downstream consequence of altered PKM2 protein conformation, though this is not its primary mechanism of action. Genetic knockdown of PKM2 recapitulates the antifibrotic effects, further confirming the pathogenic contribution of PKM2-driven glycolysis. These findings collectively establish PKM2 as a therapeutic target with strong genetic validation.

As the terminal glycolytic enzyme, LDHA catalyzes pyruvate-to-lactate conversion to regenerate cytosolic NAD^+, sustaining high glycolytic flux in profibrotic lung cells. Pharmacological inhibition of LDHA interrupts this late-stage glycolytic step and curtails lactate overproduction. The LDHA inhibitor gossypol dampens aerobic glycolysis and lactate accumulation in primary human lung fibroblasts, which in turn limits pH-dependent latent TGF-β activation and myofibroblast differentiation (128). *In vivo*, gossypol reduces collagen deposition in both bleomycin- and radiation-induced PF, and retains efficacy even when intervention is delayed (128,186). Pre-administration of the selective LDHA inhibitor GNE-140 effectively mitigated PM2.5-provoked pulmonary inflammation and fibrosis in a murine model via suppression of glycolysis and downstream histone lactylation (187). While genetic studies specifically targeting *LDHA* in PF models are limited, the consistent efficacy of structurally distinct LDHA inhibitors and the well-defined role of lactate in activating latent TGF-β1 and promoting histone lactylation provide strong pharmacological validation for this axis (19). In the context of glycolytic substrate provision, the transmembrane movement of glucose predominantly relies on the GLUT protein family. Consequently, therapeutic approaches aimed at modulating GLUT activity possess a clearly delineated mechanistic rationale. A diverse array of GLUT inhibitors has been identified, encompassing both naturally occurring substances from plants or microorganisms and synthetic small molecules (188). For example, quercetin inhibits GLUT1 by binding at an exofacial site, demonstrating the feasibility of pharmacologically targeting GLUT-mediated glucose uptake (189). In addition, in

Table I. Therapeutic targeting of glycolysis in PF with small-molecule compounds: Targets, models, mechanisms and translational outlook.

Metabolic target	Targeting mode	Compound	Relevant cell type(s)	Major mechanism	PF model	Evidence level	Clinical development status	Key limitations	(Refs.)
HK2	Direct	Lonidamine	Lung fibroblasts	Inhibits HK2; reduces glycolysis, suppresses myofibroblast differentiation and collagen synthesis	TGF-β1-stimulated human lung fibroblasts; BLM-induced mouse PF	*In vitro*; animal	Preclinical (oncology history; not in PF trials)	Non-selective HK inhibitor; may affect other HK isoforms; hepatotoxicity reported	(111)
HK2	Direct	2-DG	Lung myofibroblasts; alveolar macrophages in silica model	Glucose analog; competitively inhibits HK and blocks the initial step of glycolysis; suppresses myofibroblast proliferation, contractility and collagen accumulation; inhibits HIF-1α in alveolar macrophages in silicosis	BLM-induced PF; silica-induced PF; other preclinical PF models	*In vitro*; animal	Preclinical (various diseases; not in PF trials)	Broad metabolic inhibitor; low oral bioavailability; short half-life; off-target effects	(116,204, 205)
PFKFB3	Direct	3PO	Lung fibroblasts/ myofibroblasts	Inhibits PFKFB3; reduces F2,6BP production and PFK-1 activity, thereby suppressing glycolytic flux and collagen synthesis	LPS- and BLM-induced PF	Animal	Preclinical	Poor water solubility; rapid clearance; high or frequent dosing needed	(116,117)
PFKFB3	Direct	Anlotinib	Lung fibroblasts	Multi-target TKI; downregulates PCBP3 and inhibits PFKFB3 translation, reducing glycolysis and reversing PF	BLM-induced PF; TGF-β1-stimulated cells	*In vitro*; animal	Approved for cancer; preclinical for PF	Approved for cancer, but PF use is off-label; antifibrotic mechanism still needs verification	(184)
PFKFB3	Direct (via PI3K/ AKT/ PFKFB3)	Peimine	Lung fibroblasts	Natural isosteroidal alkaloid; inhibits the PI3K/Akt/PFKFB3 pathway, reducing glycolysis and fibroblast activation	BLM-induced PF; TGF-β1-stimulated cells	*In vitro*; animal	Preclinical	Natural product; possible multi-target effects; selectivity and *in vivo* PK data limited	(119)

Table I. Continued.

Metabolic target	Targeting mode	Compound	Relevant cell type(s)	Major mechanism	PF model	Evidence level	Clinical development status	Key limitations	(Refs.)
PKM2	Direct	Compound 3k	Lung fibroblasts	Directly targets glycolytic enzyme PKM2 and disrupts PKM2 tetramer formation; suppresses PKM2-driven aerobic glycolysis and reduces biosynthetic precursor supply in lung fibroblasts	BLM-induced PF	Animal	Preclinical	Target selectivity against PKM isoforms requires further validation; off-target effects cannot be fully excluded; only validated in bleomycin-induced PF model, no human data available	(124,185)
LDHA	Direct	Gossypol	Primary human lung fibroblasts	Directly inhibits glycolytic terminal enzyme LDHA, curtails glycolytic flux and lactate overproduction; reduced lactate limits pH-dependent latent TGF-β activation and myofibroblast differentiation	BLM-induced PF; radiation-induced PF	Animal	Preclinical (oncology history; not in PF trials)	Not LDHA-specific; multiple off-target cytotoxic effects; only preclinical, no human data	(128,186)
LDHA	Direct	GNE-140	Macrophages	Selective LDHA inhibitor; reduces lactate production and histone lactylation, suppressing profibrotic macrophage phenotypes	PM2.5-induced PF	Animal	Preclinical	Limited *in vivo* PF model data; lung-targeting delivery challenge	(187)
GLUT1	Direct	BAY876	Lung fibroblasts	Selective GLUT1 inhibition; reduces glucose uptake and suppresses TGF-β-induced fibroblast-to-myofibroblast differentiation and ECM production	TGF-β1-stimulated human lung fibroblasts	*In vitro*; animal	Preclinical	No *in vivo* PF data; target selectivity and lung delivery remain to be evaluated	(190,191)

Table I. Continued.

Metabolic target	Targeting mode	Compound	Relevant cell type(s)	Major mechanism	PF model	Evidence level	Clinical development status	Key limitations	(Refs.)
GLUT1/ other	Direct (GLUT1/ pleio-tropic)	Quercetin	Multiple cell types	Natural flavonoid; binds an exofacial site on GLUT1 and inhibits glucose transport	Not reported in the cited PF context	*In vitro* (mecha-nistic)	Preclinical	Multi-target effects; GLUT1 specificity questionable; low oral bioavailability	(189)
TGF-β/ Smad	Indirect	Albenda-zole	Lung fibroblasts	Suppresses upstream TGF-β1/Smad profibrotic signaling; reduces ECAR and lactate production and down-regulates PFKFB3 to dampen TGF-β-driven aerobic glycolysis	TGF-β1-stimulated human lung fibroblasts; bleomycin-induced mouse PF	*In vitro*; animal	Preclinical	Broad-spectrum antiparasitic agent with multiple off-target bioactivities; exact primary molecular target in fibrotic contexts remains incomple-tely defined; no dedicated clinical trials for PF	(192)
YAP/ TEAD	Indirect	Verteporfin	Alveolar epithelial cells	Inhibits YAP-TEAD protein-protein inter-action. Based on established transcriptional regulation of glycolytic genes by YAP-TEAD, glycolysis suppression is theoretically predicted as an indirect downstream consequence; direct glycolysis-related experi-mental evidence in PF is lacking	BLM-induced PF	Animal	Preclinical (off-label; preclinical for PF)	Targets YAP-TEAD transcriptional complex rather than glycolytic machinery; predicted glycolysis-modulating effect lacks direct experi-mental data in PF models; broad cellular off-target effects	(213)
AMPK	Indirect	Metformin	Alveolar epithelial cells, fibroblasts	AMPK activator; inhibits HIF-1α-induced aerobic glycolysis, antagonizes TGF-β1 signaling, promotes autophagy and attenuates fibrosis	Sepsis-associated PF; silica-induced PF	Animal	Approved for T2DM; early-phase/repurposing exploration for PF	Non-specific AMPK activation; broad metabolic effects; gastrointestinal effects	(158,159)

Table I. Continued.

Metabolic target	Targeting mode	Compound	Relevant cell type(s)	Major mechanism	PF model	Evidence level	Clinical development status	Key limitations	(Refs.)
AMPK	Indirect	Fenbendazole	Lung fibroblasts	Activates AMPK signaling; reduces glucose consumption and ECAR to dampen aerobic glycolysis	TGF-β1-stimulated lung fibroblasts; bleomycin-induced mouse PF	*In vitro*; animal	Preclinical	Veterinary-use anthelmintic; off-target bioactivities cannot be fully excluded; no dedicated human clinical trials for PF	(193)
SIRT3	Indirect	Baicalein	Lung fibroblasts; macrophages	Restores mitochondrial SIRT3 signaling and inhibits TGF-β1/Smad activation; suppresses aerobic glycolysis in both fibroblasts and macrophages	TGF-β1-stimulated lung fibroblasts; bleomycin-induced mouse PF	*In vitro*; animal	Preclinical	Broad biological activities; multiple off-target pathways; no dedicated clinical trials for PF	(195)

2-DG, 2-deoxy-D-glucose; 3PO, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one; BLM, bleomycin; AMPK, AMP-activated protein kinase; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; F2,6BP, fructose-2,6-bisphosphate; GLUT, glucose transporter; HIF-1α, hypoxia-inducible factor 1α; HK2, hexokinase 2; IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis; PFK1, phosphofructokinase-1; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PI3K, phosphoinositide 3-kinase; PKM2, pyruvate kinase M2; SIRT, Sirtuin; TGF-β1, transforming growth factor-β1; YAP, Yes-associated protein; SIRT1/6, silent information regulator 1/6.

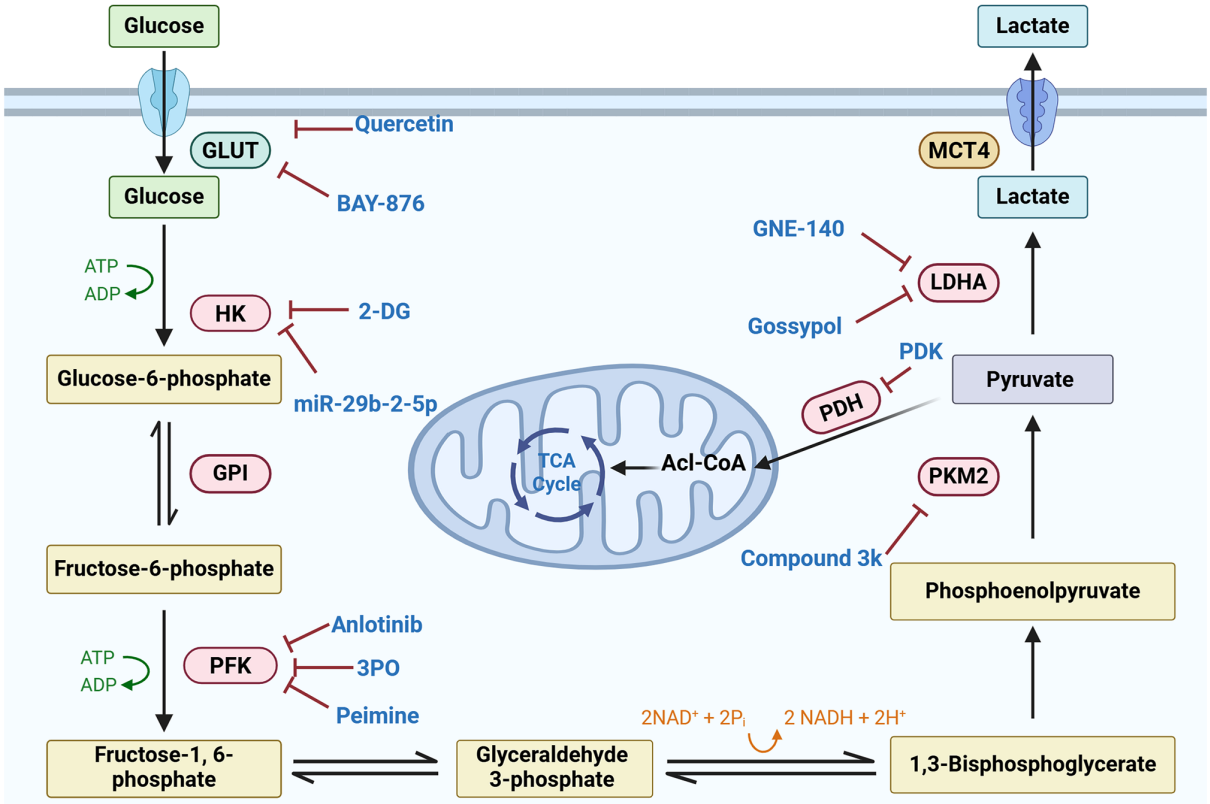

Figure 4. Therapeutic targets in PF. This schematic illustrates key glycolytic pathways involved in PF and highlights various pharmacological inhibitors targeting these metabolic nodes, including glucose and lactate transporters (e.g., BAY-876, GNE-140) and glycolytic enzymes (e.g., 2-DG, gossypol, shikonin, Compound 3k, 3PO), as well as natural compounds such as quercetin and curcumin. The image was generated utilizing Biorender (https://BioRender.com). PF, pulmonary fibrosis, 2-DG, 2-deoxy-D-glucose; 3PO, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one.

TGF-β-stimulated human lung fibroblasts *in vitro*, treatment with the selective GLUT1 inhibitor BAY876 markedly attenuates TGF-β-triggered profibrotic responses in lung fibroblasts, as evidenced by suppressed myofibroblast differentiation and reduced expression levels of the signature profibrotic proteins α-SMA, collagen and fibronectin (190,191) (Fig. 4).

It should be noted, however, that quercetin and curcumin are broad-spectrum natural compounds with multiple reported targets; their antifibrotic effects are accompanied by alterations in glycolytic signaling but have not been confirmed by target-dependency experiments (such as genetic knockdown/knockout or rescue studies), and therefore, glycolysis should not yet be regarded as their primary causal therapeutic target.

Indirect modulators of glycolysis via upstream signaling pathways. A large number of interventions that exhibit reported anti-fibrotic effects and associated alterations in glycolysis do not function by directly inhibiting glycolytic enzymes. Instead, they modulate upstream signaling pathways that regulate the expression of glycolytic genes. In these instances, the observed changes in glycolytic flux may result from more extensive effects on cell proliferation, differentiation or survival, and should not be interpreted as evidence that glycolysis is the primary therapeutic target (Table I).

One such upstream target is the TGF-β pathway. Albendazole is a small-molecule compound that suppresses upstream TGF-β1/Smad profibrotic signaling in human lung fibroblasts. Both *in-vitro* fibroblast experiments and bleomycin-challenged mouse PF models demonstrate that albendazole dampens TGF-β-triggered aerobic glycolysis. It reduces the extracellular acidification rate (ECAR) and lactate production, accompanied by downregulation of the key glycolytic effector PFKFB3. Since albendazole primarily targets the upstream TGF-β/Smad cascade rather than glycolytic enzymes, glycolysis suppression represents an indirect downstream biological consequence of TGF-β pathway inhibition (192). In mice with bleomycin-induced PF, inhibition of epithelial YAP-TEAD/lysyl oxidase signaling, including pharmacological blockade of YAP-TEAD with verteporfin, reduces ECM crosslinking and remodeling, thereby attenuating fibrosis. Biochemical studies have established that YAP-TEAD transcriptional activity drives the expression of multiple glycolytic genes (154). Therefore, verteporfin treatment is theoretically expected to indirectly dampen glycolytic reprogramming by disrupting YAP-TEAD-dependent transcription. Nevertheless, direct experimental evidence demonstrating that verteporfin alters glycolytic flux or glycolytic-enzyme abundance in PF cellular or animal models remains absent. In PF, AMPK activation has emerged as a promising anti-glycolytic strategy. Metformin, an AMPK activator, suppresses HIF-1α expression and alleviates sepsis-associated PF by inhibiting HIF-1α-induced aerobic glycolysis (158). Another AMPK-activating compound is fenbendazole. *In vitro* experiments in TGF-β1-stimulated lung fibroblasts and bleomycin-challenged mouse PF models demonstrate that fenbendazole activates AMPK signaling,

reduces glucose consumption and ECAR and dampens aerobic glycolysis. Since fenbendazole primarily triggers AMPK activation rather than directly targeting glycolytic enzymes, glycolysis suppression represents an indirect downstream metabolic consequence of AMPK-mediated signaling reprogramming (193). Similarly, AMPK-mediated suppression of HIF-1α represents an indirect mechanism of glycolytic downregulation. SIRTs, NAD^+-dependent deacylases, integrate the metabolic state with stress responses and transcriptional regulation (194). For example, restoring mitochondrial SIRT3 signaling with baicalein intervention inhibits TGF-β1/Smad activation and fibroblast-macrophage metabolic crosstalk, thus diminishing PF. Baicalein suppresses aerobic glycolysis in both lung fibroblasts and macrophages in bleomycin-induced PF models (195). Since baicalein primarily targets upstream SIRT3/TGF-β1/Smad signaling rather than glycolytic enzymes, glycolysis inhibition represents an indirect downstream metabolic outcome. SIRT7 levels are decreased in PF and can suppress the fibrotic phenotype of lung fibroblasts by downregulating Smad3-dependent profibrotic outputs, supporting SIRTs as viable targets beyond canonical glycolytic enzymes (196). SIRTs play a crucial role in the regulation of glycolysis, exerting their influence indirectly through deacetylation of HIF-1α, modifications of histones and activation of metabolic sensor pathways (166,167). Consequently, it is important to note that the observed anti-fibrotic effects of SIRT modulators cannot be solely ascribed to the inhibition of glycolytic processes.

Therapeutic potential of ncRNAs. ncRNAs, including microRNAs (miRNAs or miRs), long ncRNAs (lncRNAs) and circular RNAs (circRNAs), have emerged as critical regulators of glycolytic reprogramming in PF. Notably, several ncRNAs have been validated through genetic approaches that provide strong evidence for target dependency. By modulating the expression of key glycolytic enzymes, upstream transcription factors and metabolic sensors, ncRNAs influence core fibrotic processes such as myofibroblast activation, excessive ECM deposition and inflammatory amplification. This pivotal regulatory role emphasizes their translational potential as innovative therapeutic targets. Among ncRNAs, miRNAs function as short, post-transcriptional repressors that directly target glycolytic regulators. For example, genetic knockout of miR-21 abolishes arsenate-induced Akt activation and glycolytic upregulation, thereby inhibiting myofibroblast differentiation *in vivo* (197). Similarly, in a Dahuang Zhechong pill-treated rodent model of PF, miR-29b-2-5p suppressed glycolysis and fibroblast activation by targeting HK2, contributing to attenuated fibrosis (198). Another key miRNA, miR-30a-3p, in mice with silica-induced PF, acts as a glycolytic brake by directly targeting the transcriptional activator FOXK2. Overexpression of miR-30a-3p reduces glycolytic flux in fibroblasts and mitigates PF, further supporting its therapeutic potential (199). In contrast to miRNAs, circRNAs and lncRNAs primarily exert their effects through competing endogenous RNA (ceRNA) networks, where they sequester miRNAs to modulate downstream signaling pathways. For instance, circ0066187, which is upregulated in fibrotic models, promotes STAT3-mediated glycolytic signaling. Silencing circ0066187 disrupts this pathway and inhibits fibroblast-to-myofibroblast transition (200). Similarly, circHIPK3 enhances FOXK2 expression and fibroblast glycolysis by sponging miR-30a-3p. *In vivo*, adeno-associated virus-mediated silencing of circHIPK3 alleviates silica-induced PF (199). Regarding lncRNAs, in the same pathological context, lncRNA PVT1 is transcriptionally activated by FOXM1 and promotes fibroblast proliferation by acting as a ceRNA for miR-497-5p. Inhibition of the FOXM1/PVT1 axis reduces fibrosis, further underscoring lncRNAs as promising targets for disrupting pro-fibrotic metabolic reprogramming (201). Collectively, these findings illustrate a multi-layered ncRNA network that precisely regulates glycolytic metabolism in PF. Therefore, targeting specific ncRNAs presents a promising strategy to reverse pathological metabolic remodeling and halt disease progression (Fig. 4).

Translational challenges and future directions for glycolysis-targeting therapies. Despite the promising preclinical efficacy of the aforementioned glycolysis-targeting strategies, translating these findings into clinically viable therapies for PF faces substantial challenges that warrant critical consideration.

First, target selectivity and cell-type specificity are challenging. An important consideration emerging from the current literature is the cell-type- and context-dependent nature of glycolytic metabolism in PF. While enhanced glycolysis is predominantly pathogenic in activated fibroblasts and pro-fibrotic macrophages, its role in AECs is more nuanced. Fibroblasts undergo metabolic reprogramming characterized by upregulated glycolytic flux to support the bioenergetic and biosynthetic demands of myofibroblast differentiation and ECM production (116). Macrophages exhibit polarization-dependent metabolic profiles, with classically activated M1 cells favoring glycolysis and alternatively activated M2 cells relying more on oxidative phosphorylation (202). Furthermore, lactate derived from activated fibroblasts can shape macrophage function through histone lactylation, reinforcing a pro-fibrotic metabolic crosstalk (21). In ECs, glycolytic activation promotes EndMT and contributes to vascular remodeling. In AECs, however, glycolysis serves a dual role: A tightly regulated glycolytic flux supports progenitor cell function and regenerative repair, whereas dysregulated glycolysis in the setting of metabolic dysfunction contributes to pathogenic epithelial alterations and fibrosis (203). The varying roles of different cell types highlight a marked therapeutic issue: Global inhibition of glycolysis may effectively reduce profibrotic fibroblast activity, but it could also hinder epithelial regeneration and other essential adaptive responses. Therefore, future therapeutic approaches should focus on selective targeting of specific cell types, by utilizing isoform-specific inhibitors, lung-targeted delivery systems or interventions tailored to the disease stage, in order to enhance antifibrotic effectiveness while minimizing any adverse effects on epithelial repair and immune homeostasis.

Secondly, there are pharmacokinetic and delivery-related challenges. Numerous glycolytic inhibitors demonstrate low oral bioavailability, short half-lives or restricted penetration into lung tissue. For example, 2-DG, a glucose analog that inhibits glycolysis, has been extensively utilized in preclinical PF models; however, its suboptimal pharmacokinetics hinder its therapeutic effectiveness (204,205). Similarly,

3PO and its analogs have demonstrated efficacy in animal models but encounter challenges related to formulation and systemic exposure, such as poor water solubility and rapid clearance (116). Anlotinib, which inhibits PFKFB3-driven glycolysis in myofibroblasts by downregulating poly(rC) binding protein 3 (PCBP3), has shown strong antifibrotic effects in bleomycin-induced mouse models; however, its clinical application for PF remains unestablished (184). Lung-targeted drug delivery methods, such as inhalation, aerosolized nanoparticles or exosome-based delivery, offer a promising approach to achieve elevated local concentrations while minimizing systemic toxicity (206). Recent advancements include inhalable myofibroblast-targeting nanoparticles, which achieved a 117.8% increase in pulmonary drug delivery and a 71.5% increase specifically aimed at fibroblast activation protein-positive myofibroblasts (207), nebulized multi-modular stem cell-derived exosomes for targeted pulmonary delivery and inhalable nanoparticles that restore airway-alveolar homeostasis by inhibiting bronchiolarization and EMT (208). However, the thickened interstitium and reduced vascularity of fibrotic lungs may hinder drug penetration, and the inflammatory microenvironment could affect nanoparticle stability and clearance (209). Addressing these physical and biological barriers is essential for advancing glycolysis-targeting therapies toward clinical translation.

Third, the dependence on disease stage and the optimal timing for intervention are vital considerations. The role of glycolysis in PF is not fixed but rather adapts with disease progression. During the early stages of lung injury, metabolic reprogramming in AECs, including enhanced glycolysis coupled with FAO and glutamine catabolism, meets the energetic demands necessary for the differentiation of AT2 into AT1 and supports alveolar regeneration (210). However, as fibrosis becomes established, the metabolic needs of effector cells change. Activated myofibroblasts develop a marked glycolytic dependency that fuels their bioenergetic and biosynthetic requirements for ECM production. Furthermore, targeting the HIF-1α/PDK1-mediated glycolytic switch with dichloroacetate has been shown to suppress bleomycin-induced PF, highlighting the therapeutic potential of metabolic interventions (137). In models of established fibrosis, inhibiting lactate production through LDHA or blocking lactate transporters has demonstrated efficacy, even when initiated after fibrosis has developed (211). These observations suggest that, while glycolysis in the early disease stage supports epithelial repair, the fibrotic phase presents a therapeutic window for selectively targeting glycolysis and lactate transport in pathogenic fibroblasts and myofibroblasts. Consequently, delayed intervention aimed at addressing the glycolytic dependence of established myofibroblasts, rather than indiscriminate early inhibition, may represent a more effective and safer therapeutic strategy. Accurate patient stratification based on disease stage, distinguishing between the early inflammatory/repair phase and the established fibrotic phase, will be critical for optimizing the timing of interventions targeting glycolysis.

Fourth, there is a potential for interference with immune defense. As discussed in previous sections, glycolysis serves various critical functions across different cell types in PF. While it drives pathogenic activation in fibroblasts, it also plays vital roles in immune cells. Macrophages display metabolic profiles that depend on their polarization: Classically activated M1 cells favor glycolysis, whereas alternatively activated M2 cells preferentially utilize oxidative phosphorylation (85). Additionally, lactate produced by myofibroblasts can lead to histone lactylation in macrophages and enhance profibrotic transcriptional programs (21). This complexity indicates that therapies targeting glycolysis may have varying effects on different immune-cell subsets, depending on their polarization state and the stage of the disease. Patients with PF, who are already more vulnerable to respiratory infections, face an increased risk of pneumonia and other pulmonary infections, which are significant contributors to morbidity and mortality in this population (212). Therefore, although targeting glycolysis shows promise for inhibiting fibroblast activation, it is essential to carefully assess its impact on immune defense in future research.

Fifth, the developmental status of candidate interventions must be considered. Current glycolysis-targeting interventions for PF remain predominantly at the preclinical stage, with evidence largely derived from *in vitro* studies and animal models (bleomycin-, silica-, LPS- and radiation-induced PF models). Among the agents discussed, only a few have progressed toward clinical evaluation, mostly in oncology contexts rather than PF. Gossypol (an LDHA inhibitor) has demonstrated efficacy in preclinical models of radiation- and bleomycin-induced PF, with subcutaneous treatment inhibiting collagen accumulation, myofibroblast differentiation and pro-fibrotic gene expression in the lung, but has not been evaluated in PF clinical trials (128). GNE-140 (an LDHA inhibitor) pretreatment was found effective in alleviating histone lactylation and thus PF in PM2.5-induced models (187). Metformin (an AMPK activator) is an approved antidiabetic agent being repurposed for PF in early-phase trials. Verteporfin (a YAP inhibitor) is approved for ophthalmological use and is being explored preclinically for PF (213). Anlotinib has shown potent antifibrotic effects by downregulating PCBP3, reducing PFKFB3 translation and inhibiting glycolysis in myofibroblasts. Other agents, such as 2-DG, 3PO, compound 3k and BAY876, remain at the *in vitro* or animal model stage, with no human data in PF. The translational gap between preclinical efficacy and clinical benefit remains substantial, and safety, tolerability and pharmacokinetic profiles in patients with PF are largely unknown.

Sixth, strategies to address translational barriers must be explored. Despite the aforementioned challenges, several strategies could enhance the translational potential of therapies targeting glycolysis, including: i) Development of isoform-selective inhibitors that offer improved target specificity, such as HK2- and PFKFB3-selective compounds; ii) use of lung-targeted delivery systems (such as inhalation, nanoparticles and exosomes) to achieve organ-specific exposure while minimizing systemic toxicity; iii) biomarker-driven patient selection based on glycolytic activity in fibrotic tissue or plasma lactate levels; iv) disease-stage stratification to differentiate between the early inflammatory/repair and established fibrotic phases, allowing for intervention at the optimal therapeutic window; v) combination regimens with current standard-of-care agents, such as nintedanib and pirfenidone, to achieve additive or synergistic effects; and vi) adaptive trial designs that incorporate close monitoring for infectious complications and facilitate

early detection of safety signals, particularly those related to immune function and epithelial repair.

In summary, while glycolysis-targeting therapies hold considerable promise for PF, their successful translation requires careful attention to target selectivity, delivery strategies, therapeutic timing and patient stratification. Addressing these challenges through innovative drug design, formulation technology and personalized medicine approaches will be essential to realize the full therapeutic potential of metabolic reprogramming in PF.

8. Conclusions and perspective

PF is a progressive and often fatal chronic lung disease characterized by complex pathogenesis and limited therapeutic options. In recent years, metabolic reprogramming, particularly aberrant activation of glycolysis, has been identified as a critical factor in the initiation and progression of PF. The present review has systematically elucidated the central role of glycolysis in PF, including the upregulation of key metabolic enzymes such as GLUTs, HK2, PFKFB3, PKM2 and LDHA, as well as lactate accumulation and the regulatory mechanisms of associated signaling pathways, including TGF-β1, HIF-1α, PI3K/AKT/mTOR, Hippo, AMPK and SIRT. Collectively, these metabolic shifts facilitate fibroblast-to-myofibroblast differentiation, promote ECM deposition and disrupt immune cell functions and energy homeostasis, thereby driving the fibrotic process.

A more nuanced understanding of glycolysis in PF has emerged, moving beyond the earlier perspective that enhanced glycolysis serves as a universal pathogenic driver. Increasing evidence indicates that its functional consequences differ across various cell types, microenvironmental contexts and disease stages. In summary, enhanced glycolysis in mesenchymal and pro-fibrotic immune cells generally promotes activation, amplifies inflammation and facilitates matrix deposition. Conversely, in AECs, it plays a role in progenitor function and epithelial repair. This functional duality presents a remarkable therapeutic challenge: While global suppression of glycolysis may diminish fibrotic activation, it could also hinder alveolar regeneration, compromise barrier integrity and weaken antimicrobial immune responses. Consequently, the central challenge lies not in whether to target glycolysis, but in how to selectively inhibit it within pathogenic cell populations and at the appropriate disease stage, all while preserving essential protective metabolic processes. Progress in this area may be enhanced by using isoform-selective inhibitors, implementing lung-targeted and spatiotemporally controlled delivery systems, stratifying by disease stage and employing reliable biomarkers of glycolytic activity. These unmet needs set the stage for the therapeutic strategies and translational challenges outlined below.

Building on these mechanistic insights, inhibitors targeting key glycolytic nodes have demonstrated promising anti-fibrotic efficacy in preclinical studies. Concurrently, ncRNAs, which serve as crucial regulators of both glycolysis and fibrotic signaling pathways, have emerged as prospective diagnostic biomarkers and therapeutic targets. Addressing metabolic reprogramming, with particular emphasis on glycolysis, offers novel perspectives and strategies for the treatment of PF. Furthermore, fibrotic diseases are also associated with other metabolic pathways, such as glutaminolysis and lipid metabolism. The interplay and crosstalk between glycolysis and these pathways warrant further comprehensive investigation. As the current understanding of the metabolic mechanisms underpinning PF continues to advance, future research is expected to facilitate the development of more effective and less toxic personalized therapies, ultimately improving patient outcomes.

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Authors' contributions

All authors contributed to the study conception and design. CY was involved in conceptualization and writing-original draft preparation. HY was responsible for methodology, software and writing-reviewing and editing. MH provided visualization and supervision. QX provided guidance on writing and performed funding acquisition and supervision. 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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