Pathological regulatory roles of lysine acylation modifications in idiopathic pulmonary fibrosis (Review)

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Abstract. Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and fatal interstitial lung disease pathologically defined by progressive fibrosing remodeling of the pulmonary interstitium and irreversible destruction of normal alveolar architecture. IPF has a complex pathogenesis involving three consecutive stages: Initial alveolitis, chronic fibrosis and end-stage lung tissue destruction. Metabolic reprogramming is considered a key pathological feature throughout the disease process. Changes in the availability of intracellular metabolites caused by metabolic reprogramming may further influence the dynamic balance of acetylation modifications, thereby linking metabolic dysregulation to the fibrotic phenotype. However, its relationship with key pathological regulatory networks remains to be further elucidated. The present review summarizes seven acylation modifications in IPF, namely, lactylation, succinylation, acetylation, β-hydroxybutyrylation, palmitoylation, citrullination and formylation, including their stage-specific roles, crosstalk and therapeutic potential. The review further examines the links between different acylation modifications and metabolic reprogramming and fibrotic progression, identifies key regulatory nodes such as SIRT3 and establishes an integrated regulatory network of acylation modifications in IPF. By integrating the dynamic changes and crosstalk among distinct acylation modifications, the present review aims to advance our understanding of the metabolic-acylation regulatory mechanisms underlying IPF and provide a theoretical basis for therapeutic approaches targeting acylation homeostasis.

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1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and fatal interstitial lung disease (1). The defining pathological hallmarks of IPF include persistent interstitial fibrosis and irreversible destruction of the alveolar architecture (1,2). Available clinical therapies for IPF, including pirfenidone and nintedanib, attenuate disease progression but fail to reverse established fibrotic lesions. Although these agents slow the decline in forced vital capacity, they do not reverse honeycomb remodeling or restore normal alveolar architecture (3,4). Elucidation of the core molecular mechanisms driving IPF pathogenesis is critical for the development of more effective, disease-modifying therapies for IPF (5).

IPF progression proceeds through three well-characterized sequential phases: Initial alveolitis, chronic fibrogenesis and

end-stage lung destruction (6). The initial alveolitis phase is defined by alveolar epithelial injury, immune cell infiltration and sustained activation of pro-inflammatory signaling pathways. The chronic fibrogenesis phase is marked by aberrant fibroblast proliferation, fibroblast-to-myofibroblast differentiation and excessive deposition of extracellular matrix components. The end-stage phase culminates in diffuse destruction of the lung parenchyma alongside honeycomb lung remodeling (7). Across the full pathological continuum of IPF, metabolic reprogramming emerges as a consistent, core pathological feature. Dysregulated glycolysis, lactate accumulation, mitochondrial dysfunction and altered acyl-donor metabolism converge to establish a unique metabolic microenvironment that dynamically regulates acylation-related signaling networks across all stages of IPF progression (8). Table I further delineates the stage-specific predominance of different acylation modifications. Lactylation, citrullination and formylation predominate during initial alveolitis, consistent with innate immune activation and pro-inflammatory signaling. Chronic fibrogenesis is characterized by the predominance of lactylation, succinylation, acetylation and palmitoylation, which coordinate fibroblast activation, myofibroblast differentiation and ECM deposition. End-stage lung destruction is characterized by formylation, succinylation and acetylation, which are associated with irreversible parenchymal remodeling and functional loss. Thus, the acylation landscape is dynamically reconfigured throughout IPF progression (Fig. 1) (9).

Post-translational modifications (PTMs) act as core regulators of protein function and form a direct molecular link between metabolic dysregulation in IPF and the establishment of the fibrotic phenotype (9). Among the IPF-associated PTMs, reversible lysine acylations, such as acetylation, succinylation, lactylation and β-hydroxybutyrylation, are directly governed by intracellular metabolite availability and have attracted increasing attention in fibrosis research. These modifications use acyl-CoA species as acyl donors. Other PTMs discussed herein, including S-palmitoylation, citrullination and formylation, are not classical lysine acylations but likewise contribute to fibrotic signaling (9-11). Acyl groups are conjugated to lysine residues of target proteins by acyltransferases (writers) and removed by deacylases (erasers), including HDACs and SIRTs. This applies to reversible lysine acylations such as acetylation, succinylation, lactylation and β-hydroxybutyrylation, but not to S-palmitoylation, citrullination or formylation (Fig. 2) (12). Within the IPF pathological microenvironment, metabolic reprogramming drives shifts in the abundance of discrete acyl-CoA species, which drive widespread alterations in acylation profiles across both histone and non-histone proteins (9). These acylation-modified proteins directly regulate core IPF pathological processes, including aberrant fibroblast activation and alveolar epithelial cell dysfunction, via regulation of pro-fibrotic gene transcription, dysregulation of TGF-β signaling cascades, and disruption of mitochondrial homeostatic control (9).

Most published studies to date have centered on individual acylation marks in discrete pathological contexts, with the majority of associated analyses relying on static observations captured at single time points (9,13,14). This body of work has not yielded a clear understanding of how acylation modification profiles shift dynamically across the inflammatory, fibrogenic and end-stage phases of IPF (9). It remains undefined how distinct acylation events, derived from a shared pool of metabolic intermediates, mediate coordinated crosstalk to form stage-specific regulatory networks that ultimately govern IPF progression (9).

The present review provides a systematic summary of acylation modifications in the setting of IPF, including lactylation, succinylation, acetylation, β-hydroxybutyrylation, palmitoylation, citrullination and formylation. The metabolic origins, writer and eraser enzymes, and core modification sites of these modifications are summarized in Table II. The present review details the functional roles of these acylation modifications in core IPF pathological processes, and examines the interconnections between individual modification events, with a focus on shared metabolic precursors, enzymatic crosstalk and synergistic regulatory effects. The present review evaluates the therapeutic potential of targeting key modifying enzymes or specific acylation states, with the dual aims of establishing an integrated framework for understanding IPF pathobiology and informing the development of targeted therapeutics for pulmonary fibrosis.

2. Energy metabolism-sensing and effector acylations

Metabolic reprogramming is a hallmark of IPF pathogenesis. Specific acylation modifications, including lactylation, succinylation, acetylation and β-hydroxybutyrylation, act as direct sensors of shifts in the metabolic environment (15). These modifications tune downstream protein function and modulate fibrogenesis, exemplified by H3K18la-driven M1 macrophage polarization and mitophagy impairment and ITGB1 K238 hyper-succinylation-induced alveolar epithelial senescence via ITGB1/STAT3 (16-18). These four modifications are classified as energy metabolism-sensing and effector acylations, based on their direct link to the cellular metabolic state (19). Collectively, they form an integrated regulatory network that links diverse metabolic inputs (glycolysis, the tricarboxylic acid cycle and ketogenesis) to coordinated functional outputs, including epigenetic reprogramming, mitochondrial quality control and antioxidant defense. The dynamic balance of this network is orchestrated by shared acyl-CoA pools and SIRT-mediated deacylase activities, and its perturbation directly fuels the profibrotic cascade in IPF (Fig. 3) (8,20,21).

Lactylation. Lactylation links glycolytic bursts to epigenetic and signaling reprogramming (22). This modification is driven by lactate, which accumulates to high levels in IPF as a result of aerobic glycolysis in activated immune cells and fibroblasts. This metabolic phenotype is frequently driven by NOD-like receptor family pyrin domain-containing protein 3 inflammasome activation and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3-mediated enhancement of glycolytic flux (23,24). Accumulated lactate acts as a substrate for lysine lactyltransferases, including p300/CREB-binding protein (CBP). These enzymes catalyze the covalent modification of lysine residues on both histone and non-histone proteins (16,25). This process links the cellular metabolic state to epigenetic regulation and protein functional remodeling, and translates glycolytic signals into durable changes in cell phenotype.

Table I. Stage-specific acylation in IPF progression.

IPF disease stage	Core pathological hallmarks	Dominant regulatory acylation modifications
Initial alveolitis phase	Recurrent alveolar epithelial injury, innate immune cell infiltration, sustained activation of pro-inflammatory signaling cascades	Lactylation, citrullination, formylation
Chronic progressive fibrogenesis phase	Aberrant fibroblast activation, myofibroblast differentiation, ECM deposition, EMT/EndMT	Lactylation, succinylation, acetylation, palmitoylation
End-stage lung destruction phase	Widespread destruction of lung parenchyma, honeycombing remodeling, irreversible loss of pulmonary function	Formylation, succinylation, acetylation

IPF, idiopathic pulmonary fibrosis; ECM, extraceullar matrix; EMT, epithelial-mesenchymal transition; EndMT, endothelial-mesenchymal transition.

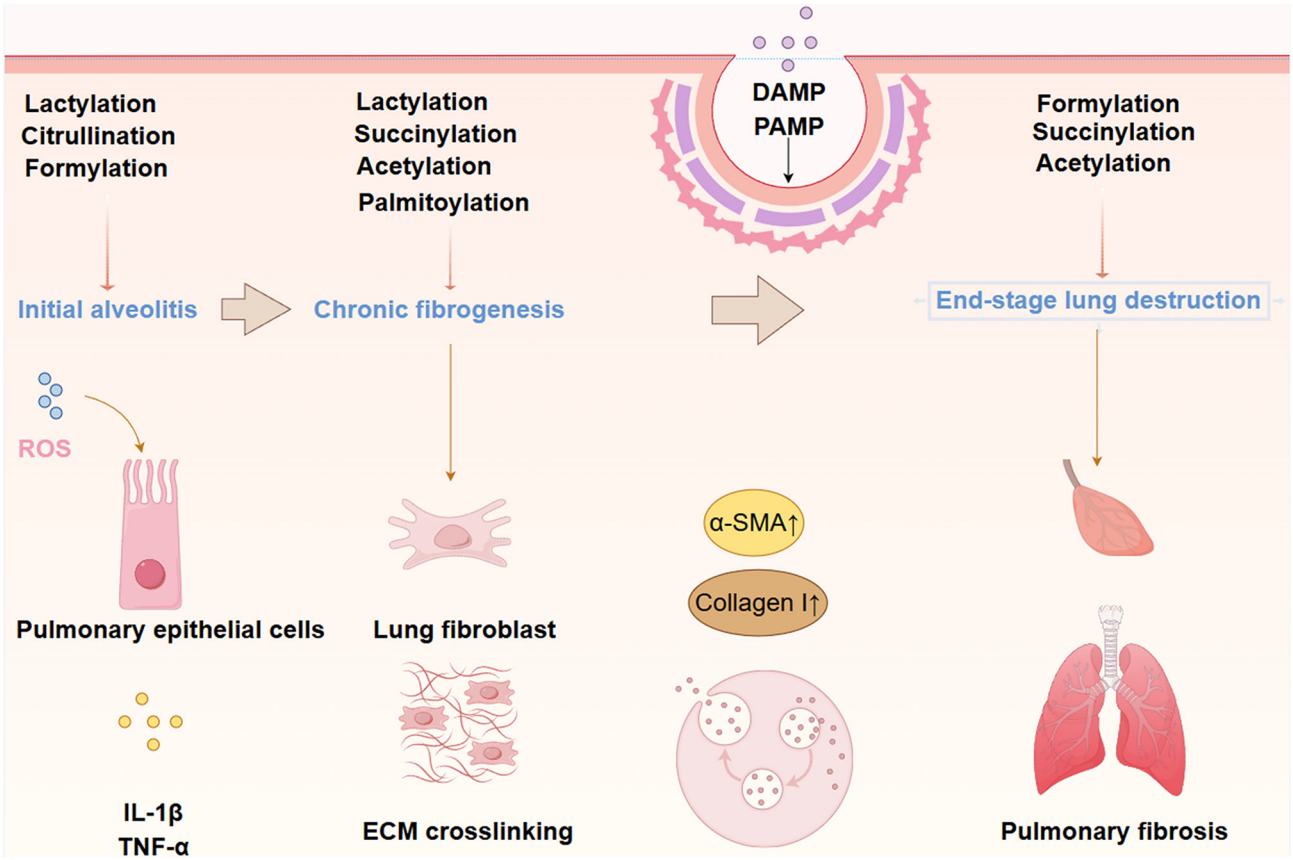

Figure 1. Acylation modifications regulate the progression from alveolitis to end-stage pulmonary fibrosis. Distinct acyl modifications (lactylation, succinylation, formylation, acetylation, citrullination and palmitoylation) govern the pathological progression of pulmonary fibrosis from initial alveolitis through chronic fibrogenesis to end-stage lung destruction, via modulation of pulmonary epithelial and lung fibroblast function, as well as ECM remodeling. Specifically, alveolitis is promoted by activation of DAMP/PAMP signaling, ROS production, and release of IL-1β and TNF-α. Chronic fibrogenesis is mediated by fibroblast activation (evidenced by elevated α-SMA and collagen expression) and ECM crosslinking. These cascading pathological events ultimately culminate in end-stage lung destruction and established pulmonary fibrosis. ECM, extracellular matrix; DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern; ROS, reactive oxygen species; α-SMA, α-smooth muscle actin. Drawn using Figdraw (www.figdraw.com).

Lactylation exerts distinct functional effects in a cell type-dependent manner (22). In macrophages, histone H3 lysine 18 lactylation (H3K18la) accumulates at the promoter regions of genes such as inducible nitric oxide synthase. This accumulation promotes polarization toward a pro-inflammatory M1 phenotype and contributes to cytokine release. The delactylase SIRT3 removes this modification (26). In fibroblasts, lactylation acts through a well-defined epigenetic cascade. H3K18la enhances transcription of methyltransferase-like 3 (METTL3), an RNA N^6-methyladenosine (m^6A) methyltransferase (17). METTL3 mediates m^6A modification of mitochondrial genes, including peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α). This modification reduces expression of the target genes (17). This cascade of events impairs mitophagy and drives pathological activation of lung fibroblasts. Direct lactylation of the transcription factor Snail1

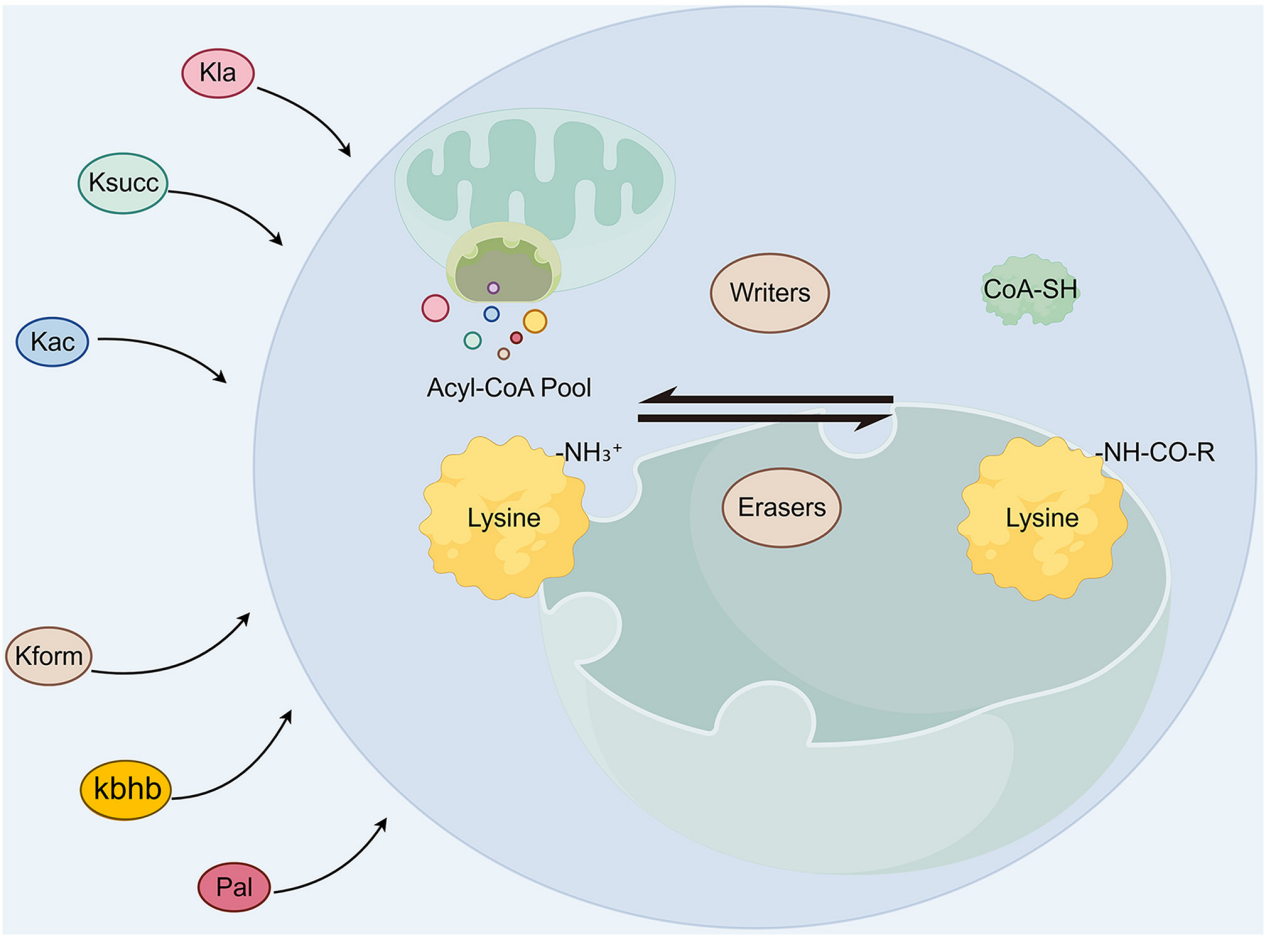

Figure 2. Lysine acylation modifications and their regulation. This schematic outlines the key subtypes of lysine acylation in eukaryotic cells, the metabolic origins of their acyl donors and their enzymatic regulatory network. A diverse pool of acyl-CoA species, derived from carbohydrate, lipid and ketone body metabolism, serves as the source of acyl groups for modifications such as Kac, Kla, Ksucc and Kbhb. The dynamic equilibrium of these modifications is maintained by the coordinated activities of lysine acyltransferases and lysine deacylases, which ensures modification homeostasis. Acyl-CoA, acyl-coenzyme A; Kac, lysine acetylation; Kla, lysine lactylation; Ksucc, lysine succinylation; Kbhb, lysine β-hydroxybutyrylation; Kform, lysine formylation; Kla, lysine lactylation; Ksucc, lysine succinylation; NH_3, ammonia; NH-CO-R, amide linkage (N-H-C(=O)-R); Pal, palmitoylation (S-palmitoylation). Drawn using Figdraw (www.figdraw.com).

stabilizes the protein and promotes epithelial-mesenchymal transition (EMT) (27).

Lactylation contributes to endothelial-mesenchymal transition and vascular remodeling in endothelial cells through upregulation of genes such as insulin-like growth factor binding protein 7 and chaperonin containing TCP1 subunit 2 (28). This modification competes with other lysine acylations. Specific lysine residues, such as H3K18, serve as substrates for alternative acetylation or succinylation, and the competitive occupancy of these sites modulates chromatin activity and transcriptional output (26). SIRT3, a deacetylase that also exhibits delactylase and desuccinylase activities, functions as a central integrator responsive to cellular metabolic status and balances these modifications (26). Pyruvate generated from glycolysis not only supplies the precursor for lactate production but also enters mitochondria to support acetyl-CoA synthesis or influences succinyl-CoA pools through anaplerotic pathways. Such metabolic coupling effectively integrates distinct acylation systems into a coordinated regulatory network (29).

Beyond histones, lactylation directly modulates non-histone proteins to regulate proteostasis, enzymatic activity and signal transduction in IPF. Lactylation of the transcription factor Snail1 at lysine residues impedes its ubiquitin-proteasome degradation, stabilizes the protein and potentiates its transcriptional repression of E-cadherin, thereby promoting EMT in alveolar epithelial cells (30). Lactylation of metabolic enzymes such as pyruvate kinase M2 has been shown to govern tetramer assembly and catalytic efficiency, although its precise role in IPF remains to be elucidated (31). Furthermore, lactylation of signaling adaptors or kinases can modulate phosphorylation cascades and downstream effector activation, thereby amplifying or attenuating pro-fibrotic outputs. These non-histone events often converge with acetylation or succinylation on shared substrates, constituting a multilayered post-translational code that fine-tunes cellular responses to metabolic stress (32). Thus, non-histone lactylation operates as a direct effector arm of metabolic reprogramming, controlling protein function at multiple levels, including stability, activity and signaling, and represents a critically underappreciated regulatory layer in IPF pathogenesis.

Current therapeutic strategies against lactylation aim to either disrupt lactate biosynthesis or directly modulate the modification machinery (29,30). At the upstream metabolic level, glucagon-like peptide-1 receptor agonists suppress

Table II. IPF and protein acylation modifications.

Acylation modification type	Metabolic origin	Writer enzyme	Eraser enzyme	Core modification site	(Refs.)
Lysine lactylation	Lactate (product of glycolysis)	p300, CBP	SIRT3	Histone H3K18, non-histone protein Snail1	(26,133, 134)
Lysine succinylation	Succinyl-coenzyme A	Acyltransferase family	SIRT5, SIRT3	Mitochondrial metabolic proteins, integrin β1, STAT1	(135-138)
Lysine acetylation	Acetyl-coenzyme A	p300, CBP	Histone deacetylases, SIRT3	Histones, non-histone proteins (for example, STAT1 and p53)	(139,140)
Lysine β-hydroxybutyrylation	β-hydroxybutyrate (product of ketone metabolism)	Not yet identified	Not yet identified	Lysine residues	(141)
Protein S-palmitoylation	Palmitoyl group	zDHHC5, zDHHC11	Not yet identified	Cysteine residues	(142)
Protein citrullination	Conversion from arginine residues	PAD2, PAD4	Not yet identified	Arginine residues (histones, MZB1, vimentin, fibrinogen and α-enolase)	(81,143)
Protein formylation	Formyl group	Methionyl-tRNA formyltransferase	Not yet identified	N-terminal methionine,	(144)

PAD, peptidylarginine deiminase; zDHHC, zinc finger DHHC domain-containing palmitoyltransferase; MZB1, marginal zone B and B1 cell-specific protein; CBP, cAMP response element-binding protein; SIRT, sirtuin; H3K18, histone H3 lysine 18; Snail1, zinc finger transcription factor SNAI1.

glycolytic flux, thereby reducing lactate production and limiting the availability of lactate as a substrate for lactylation (33). At the direct regulatory level, small-molecule inhibitors of writers (such as p300/CBP) or activators of erasers (such as SIRT3) are being developed to reduce pathological lactylation (34). The natural compound wogonoside illustrates this strategy, exerting antifibrotic effects through a dual mechanism that simultaneously inhibits Snail1 lactylation and activates PGC-1α/PTEN induced kinase 1-mediated mitophagy (30). Despite these promising preclinical findings, clinical translation faces major hurdles: Most enzyme inhibitors lack sufficient target specificity, there are no validated biomarkers to monitor modification dynamics *in vivo* and targeted delivery to fibrotic lung lesions remains technically challenging (29). Table III summarizes the currently explored therapeutic strategies targeting acylation modifications in IPF.

Succinylation. Succinylation is a lysine acylation modification derived from succinyl-CoA, an intermediate of the tricarboxylic acid cycle (35). Dysregulation of this modification is closely associated with mitochondrial dysfunction and metabolic reprogramming observed in IPF (36). Within the fibrotic pulmonary microenvironment, metabolic disturbances induce alterations in succinyl-CoA availability, which in turn drive widespread remodeling of the protein succinylome (37).

A quantitative succinylome analysis of IPF lung tissue identified 1,964 lysine succinylation sites across 628 proteins, with marked enrichment in mitochondrial metabolic proteins (675 sites on 124 polypeptides); notable targets included kynurenine aminotransferase 3, hydroxysteroid 17-β dehydrogenase 8, glyoxylate and hydroxypyruvate reductase and isocitrate dehydrogenase [NADP(+)] (37). This modification landscape exhibits particular enrichment in mitochondrial metabolic proteins, encompassing 675 sites on 124 polypeptides. Notable targets include key enzymes such as kynurenine aminotransferase 3, hydroxysteroid 17-β dehydrogenase 8, glyoxylate and hydroxypyruvate reductase and isocitrate dehydrogenase [NADP(+)] 2 (37).

Aberrant succinylation of specific substrate proteins is sufficient to drive key profibrotic processes in the lung (18). In alveolar epithelial cells, hyper-succinylation of integrin β1 (ITGB1) at lysine 238 promotes cellular senescence through activation of the ITGB1/STAT3 signaling axis. This aberrant modification results from downregulation of the desuccinylase SIRT5; restoration of SIRT5 function attenuates ITGB1 succinylation and alleviates the fibrotic phenotype (18). Beyond ITGB1, this regulatory mechanism extends to other signaling mediators (38). For example, STAT1 activity is tightly regulated by crosstalk between its acetylation and succinylation, and preclinical work has found that pharmacological targeting of these STAT1 modifications with geranylgeranylacetone reduces the fibrotic burden *in vivo* (38).

At the enzymatic level, overlapping substrate specificity among deacylases such as SIRT3 enables competitive interactions between distinct acylation marks. For example, SIRT3 and SIRT5 exhibit overlapping substrate specificity, SIRT3

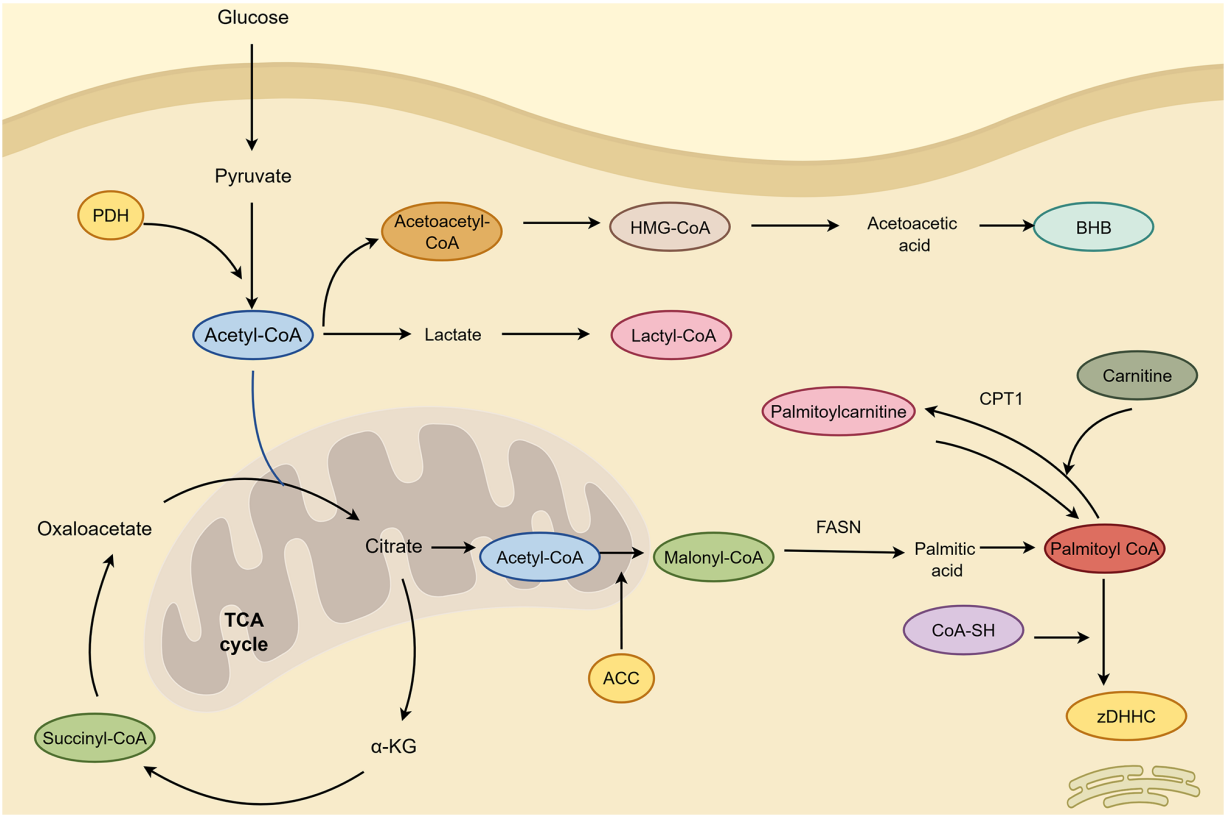

Figure 3. Acyl donor metabolism of lysine acylation modifications. The metabolic pathways that synthesize various acyl-CoA donors for lysine acylation in mammalian cells, establishing the biochemical foundation for metabolic regulation in pulmonary fibrosis. Glucose is processed through core pathways, including glycolysis, the TCA cycle, ketogenesis and *de novo* fatty acid synthesis, to generate a range of acyl-CoAs, such as acetyl-CoA, succinyl-CoA, and lactyl-CoA. These molecules serve as the substrates for their respective lysine acylation modifications. Dysregulation in the expression or activity of key rate-limiting enzymes within this network, such as PDH, ACC and FASN, is central to cellular metabolic reprogramming. This reprogramming drives the progression of pulmonary fibrosis by altering the composition and homeostasis of the intracellular acyl-CoA pool. PDH, pyruvate dehydrogenase complex; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; acyl-CoA, acyl-coenzyme A; BHB, β-hydroxybutyrate; CoA, coenzyme A; TCA, tricarboxylic acid cycle. Drawn using Figdraw (www.figdraw.com).

deacetylates, delactylates and desuccinylates lysine residues, whereas SIRT5 preferentially removes succinyl, malonyl and glutaryl groups, enabling direct competition at shared residues such as VLCAD K507 and MAVS K7 (39). At the metabolic level, succinyl-CoA and acetyl-CoA pools show tight metabolic interdependence. Shifts in the abundance of one metabolite can directly influence the other and shape the global cellular acylation landscape (38). Accumulation of mitochondrial acetyl-CoA, for example, may indirectly suppress succinyl-CoA generation through feedback inhibition of enzymes, including pyruvate dehydrogenase (36). This interaction creates dynamic crosstalk between acetylation and succinylation (40).

Therapeutic strategies designed to target succinylation focus on restoring modification homeostasis, either through activation of desuccinylases such as SIRT5 or modulation of upstream succinyl-CoA metabolism. However, a major limitation of this approach is the shared substrate specificity of deacylases: SIRT3, for example, regulates acetylation, succinylation and lactylation simultaneously, meaning non-selective targeting of this enzyme could cause widespread, off-target effects across multiple acylation pathways (18) (Table II).

Acetylation. Dysregulated protein acetylation is a well-documented epigenetic driver of IPF progression (41). This modification governs gene transcription and signal transduction through coordinated modulation of histone and non-histone protein acetylation. Inhibition of acetylation exerts antifibrotic effects through crosstalk with other epigenetic marks and facilitation of an open chromatin configuration (42). Combined inhibition of hypoxia-inducible factor-1α and GSK-3β has been shown to reverse TGF-β1-induced endothelial-to-mesenchymal transition *in vitro* and attenuate pathological injury in murine models of pulmonary fibrosis (43). At the non-histone level, acetylation of STAT1 precisely modulates its transcriptional activity (44). Activation of the mitochondrial deacetylase SIRT3 reduces acetylation of p53, promoting nuclear export of this transcription factor and enhancing glutathione synthesis. This cascade ultimately suppresses ferroptosis in alveolar epithelial cells, contributing to an antifibrotic effect (45).

Within the integrated acylation regulatory network, acetylation acts as a central signaling hub, and its crosstalk with other acyl modifications is essential for coordinating the overall functional output of the network. On one level, acetylation directly competes with lactylation and succinylation for the same lysine residues on histones; this competition is a core mechanism for cellular integration of metabolic signals to fine-tune gene transcription (9). On another level, the 'writers' and 'erasers' of acetylation often possess broad

Table III. Acylation modification-targeted therapeutic strategies for IPF.

Acylation modification and intervention	Intervention agent	(Refs.)
Lactylation		
Lactate synthesis metabolic pathway	GLP-1 receptor agonist	(33)
Acyltransferase p300/CBP, delactylase SIRT3	Wogonoside (natural small molecule compound)	(30)
Succinylation		
Desuccinylase SIRT5	SIRT5 agonist	(145)
STAT1 acylation modification site	Teprenone	(38)
Acetylation		
HDACs	Vorinostat (broad-spectrum HDAC inhibitor)	(146)
Deacetylase SIRT3	SIRT3 agonist	(147)
β-hydroxybutyrylation		
β-hydroxybutyrate substrate supply pathway	Exogenous β-hydroxybutyrate supplementation, ketogenic diet, regulation of 3-hydroxybutyrate-producing gut microbiota	(148)
Palmitoylation		
zDHHC family palmitoyltransferases	2-bromopalmitate (broad-spectrum zDHHC inhibitor), zDHHC5/11 selective inhibitor	(54,56,149)
Palmitoyltransferase zDHHC11	Selenium supplement	(70)
Citrullination		
PAD2/4	Cl-amidine (pan-PAD inhibitor), GSK484 (PAD4-selective inhibitor)	(143)
NET structure	Deoxyribonuclease I	(150)
Formylation		
Methionine/lysine formyltransferase	Formylation inhibitor	(144)
FPR2	WRW4 (FPR2 antagonist)	(151)

GLP-1, glucagon-like peptide-1; SIRT, sirtuin; HDAC, histone deacetylase; zDHHC, zinc finger DHHC domain-containing palmitoyltransferase; FPR2, formyl peptide receptor 2; PAD, peptidylarginine deiminase; NET, neutrophil extracellular trap; CBP, cAMP response element-binding protein; GSK484, PAD4-selective inhibitor GSK484; WRW4, FPR2 antagonist WRW4.

substrate specificity, enabling them to regulate other acylation events and establish functionally antagonistic or synergistic relationships (41,46,47).

Targeting the acetylation machinery has emerged as a promising therapeutic strategy for pulmonary fibrosis, with most preclinical work focusing on HDAC inhibitors (48,49). The broad-spectrum HDAC inhibitor vorinostat shows combined antifibrotic and anti-inflammatory properties, suppressing TGF-β1-induced myofibroblast differentiation, promoting apoptosis of fibrotic cells and downregulating genes involved in collagen biosynthesis (50). Notably, however, the efficacy of HDAC inhibitors is highly model- and context-dependent, and their broad-spectrum activity can cause unintended off-target effects, including paradoxical upregulation of pro-inflammatory genes that limit their clinical utility (51). In summary, acetylation acts as the core signaling hub of the acylation regulatory network in IPF, with its dual roles in epigenetic and non-histone protein regulation making it a double-edged sword for therapeutic intervention.

β-hydroxybutyrylation. β-hydroxybutyrylation is a recently identified lysine acylation modification derived from β-hydroxybutyrate (BHB), a ketone body produced predominantly during fasting or ketogenic states (52). BHB is metabolized to β-hydroxybutyryl-CoA, which serves as the acyl donor for this modification. Although the specific writers and erasers of β-hydroxybutyrylation have not yet been definitively identified, emerging evidence suggests that this modification is dynamically regulated and responds to shifts in systemic ketone body metabolism (53).

In the context of pulmonary fibrosis, β-hydroxybutyrylation exerts protective effects primarily through suppression of ferroptosis in alveolar epithelial cells (54,55). BHB treatment has been shown to reduce lipid peroxidation and mitochondrial oxidative stress, thereby preserving alveolar epithelial integrity and attenuating bleomycin-induced fibrotic remodeling (54). Mechanistically, this anti-ferroptotic function converges with acetylation-mediated suppression of ferroptosis through the SIRT3/p53 axis, as both pathways operate by enhancing cellular antioxidant capacity. This convergence suggests that distinct upstream regulatory events, ketone body metabolism vs. acetyl-CoA flux, may coordinate through shared downstream effector mechanisms to reinforce protective responses against fibrotic injury (54).

Therapeutic interventions aimed at augmenting β-hydroxybutyrylation include exogenous BHB administration,

implementation of a ketogenic diet and modulation of gut microbiota composition to enrich for 3-hydroxybutyrate-producing bacterial strains (56). Direct targeting of downstream effector proteins, such as pharmacological activation of glutathione peroxidase 4 or inhibition of indoleamine 2,3-dioxygenase 1, also represents a viable therapeutic approach (57,58). Together, these strategies offer promising avenues for treating pulmonary fibrosis by harnessing this protective modification pathway (Table III). Overall, β-hydroxybutyrylation exerts mitochondria-protective and antifibrotic effects in IPF, offering a metabolically targeted strategy to alleviate alveolar epithelial injury.

Collectively, metabolite-driven acylation modifications, including lactylation, succinylation, acetylation and β-hydroxybutyrylation, form an integrated regulatory network in IPF. These modifications engage in extensive crosstalk through competition for shared lysine residues and common eraser enzymes, such as SIRT3, thereby coordinately regulating histone and non-histone proteins, and modulating inflammation, mitochondrial homeostasis and fibrotic progression. Such competitive occupancy poses a major therapeutic challenge, as targeting a single acylation type or enzyme may trigger compensatory network-wide remodeling and compromise antifibrotic efficacy. Although strategies targeting individual modifications or enzymes, such as HDAC inhibition and SIRT5 activation, have shown preliminary therapeutic promise, limited enzyme specificity, a lack of dynamic biomarkers and challenges in lesion-targeted delivery remain major barriers to clinical translation (59-61).

3. Palmitoylation as an acylation modification regulating membrane dynamics and signal transduction

In addition to their well-defined roles in sensing and mediating the metabolic state, several acylation modifications drive IPF pathogenesis via regulation of core cellular processes (53). These processes include protein membrane trafficking, regulation of protein stability and intracellular signal transduction (19).

Protein S-palmitoylation is a reversible, dynamic PTM catalyzed by zinc finger DHHC domain-containing palmitoyltransferases (zDHHCs) (62). This modification enables precise control over protein membrane trafficking, stability and signal transduction through covalent attachment of palmitoyl groups to specific cysteine residues (63). In the context of pulmonary fibrosis, specific members of the zDHHC family exhibit upregulation, leading to aberrant palmitoylation of key profibrotic proteins and subsequent amplification of fibrotic signaling cascades (64). For example, aberrant palmitoylation of metal transporters is a critical upstream event that initiates profibrotic signaling in the lung. Zinc transporter 14 (ZIP14) and zinc transporter 1 (ZNT1), which serve as key substrates for zDHHC family members, show enhanced membrane localization and transport capacity after palmitoylation. This modification facilitates cellular uptake of environmental toxins such as cadmium, establishing a microenvironment conducive to fibrotic signaling (64). Within the TGF-β pathway, palmitoylation is extensively integrated into the fibrotic cascade. Upstream components, including fibrillin-1 and integrin α-5, undergo palmitoylation, which promotes maturation and release of the TGF-β precursor. Downstream signal transduction is enhanced through modification of cytoskeletal proteins, including desmoplakin and vimentin, ultimately driving myofibroblast differentiation (64). Aberrant palmitoylation further amplifies fibrotic responses by suppressing degradation of the autophagy substrate p62, leading to enhanced release of pro-inflammatory cytokines (65).

Although palmitoylation targets cysteine residues rather than the lysine sites modified by other acylations, these two classes of modification display substantial functional interplay (66). Through regulation of the TGF-β signaling pathway, palmitoylation governs the activity and membrane localization of key receptors and signaling mediators, including TGFβR1and Smad7 (67). This provides critical upstream input that influences subsequent lysine acylation events on transcription factors and metabolic enzymes. Additionally, palmitoylation of zinc transporters modulates intracellular zinc homeostasis, which indirectly affects the function of numerous zinc-dependent proteins and establishes potential points of coupling with the lysine acylation network (68).

In preclinical cellular models, the broad-spectrum zDHHC inhibitor 2-bromopalmitate markedly reduces palmitoylation of ZIP14, ZNT1 and TGF-β pathway proteins, inhibiting cadmium uptake and downregulating pro-fibrotic gene expression (64). The development of substrate-specific targeting strategies is another promising direction. Selective inhibition of key zDHHC isoforms, such as zDHHC5 and zDHHC11, may enable precise blockade of pro-fibrotic signaling while minimizing off-target effects (69). Additionally, selenium supplementation has been shown to indirectly suppress fibrotic signaling through downregulation of zDHHC11 expression, suggesting potential utility in combination therapeutic approaches (Table III) (70). In summary, aberrant palmitoylation contributes to IPF progression by regulating membrane protein localization, metal homeostasis and TGF-β signaling, while interacting with other acylation modifications to form a complex regulatory network. Based on this, modulation of aberrant palmitoylation may provide a potential new therapeutic direction for IPF.

4. Damage-associated molecular patterns and immune-activating PTMs

In the IPF alveolar microenvironment, persistent innate immune activation driven by damage-associated molecular patterns is a key driver of fibrogenesis (71,72). The aberrant activation of specific enzymes frequently underlies associated protein modifications, including citrullination. By modulating the function of both histone and non-histone proteins, these modifications reshape innate and adaptive immune responses in the lung, creating a self-amplifying feedforward loop that exacerbates tissue injury (73).

Citrullination. Citrullination is a PTM in which peptidylarginine deiminase (PAD) enzymes convert arginine residues to citrulline (74). This modification is a critical regulatory mechanism in the pathogenesis of both rheumatoid arthritis-associated interstitial lung disease (RA-ILD) and IPF (75). PAD4 expression is upregulated in bronchoalveolar lavage fluid cells isolated from >80% of patients with

RA-ILD and IPF. PAD2 expression exhibits a close association with smoking history and remains persistently elevated in lung tissue from smokers (76). These findings define the enzymatic basis for increased citrullination in IPF. They also directly link environmental risk factors, including smoking, to dysregulation of this modification pathway.

Citrullination drives pulmonary fibrosis primarily by promoting the formation of neutrophil extracellular traps (NETs), which in turn amplify inflammatory responses and drive immune dysregulation in the fibrotic lung (77). Histone citrullination catalyzed by PAD4 is an essential step in NET release (78). The extruded NETs directly injure alveolar epithelial cells while simultaneously presenting inflammatory mediators that recruit additional immune populations and facilitate fibroblast activation (79). Citrullinated substrates and their corresponding autoantibodies can activate the NF-κB pathway, further potentiating pro-fibrotic signaling. PAD2-mediated citrullination of marginal zone B and B1 cell-specific protein disrupts mucosal immune homeostasis by affecting IgM and IgA secretion, and local deposition of immune complexes may trigger complement activation, exacerbating tissue damage (80,81). Smoking is a major risk factor for IPF and can upregulate PAD2 and PAD4 expression, thereby enhancing protein citrullination in the lung parenchyma and promoting NET formation and immune dysregulation. This aberrant citrullination may contribute to a vicious cycle of tobacco exposure, PAD activation, and pulmonary fibrosis, linking environmental exposure to IPF progression (76,82).

Therapeutic strategies directed at citrullination primarily involve inhibition of PAD enzyme activity (83). These approaches encompass both pan-PAD inhibitors, such as Cl-amidine, and isoform-selective compounds, including the PAD4-specific inhibitor GSK484 and the PAD2-selective inhibitor AFM-30a, all designed to reduce citrullination levels and suppress NET formation (84-86). Agents capable of degrading existing NETs, such as DNase I, function through enzymatic cleavage of the DNA scaffolding that maintains NET structure (87). Developing neutralizing antibodies against pathogenic citrullinated epitopes is another promising therapeutic avenue, while repurposing clinically approved antifibrotics such as nintedanib to target this pathway represents an important complementary research direction (88,89).

Formylation. Formylation is a PTM that can mediated by methionine formyltransferase and lysine formyltransferase, both of which are upregulated in lung tissue and primary fibroblasts from patients with IPF and RA-ILD (90-92). This modification regulates substrate function through covalent attachment of a formyl group to either the N-terminal methionine residue or internal lysine residues of target proteins (93).

Dysregulated formylation promotes fibrotic progression through several distinct, non-redundant mechanisms. Specifically, lysine residues in collagen Iα1 can undergo formylation, enhances intermolecular cross-linking and reduces susceptibility to proteolytic degradation, thereby promoting pathological extracellular matrix accumulation. The extent of this modification is inversely associated with pulmonary function parameters such as forced vital capacity in affected patients (92). At the signaling level, formylation of TNF-α at K65 increases its binding affinity for TNF receptor 1, leading to NF-κB pathway activation and subsequent induction of myofibroblast differentiation (94,95). N-terminal formylation of annexin A1 generates the isoform N-terminal formylated annexin A1 (fMet-AnxA1), which stimulates fibroblast proliferation and migration through engagement of formyl peptide receptor 2 and activation of its downstream PI3K/Akt signaling cascade (96,97). Meanwhile, K194 of E-cadherin is a potential site of post-translational modification, and the putative modification at this site may disrupt intercellular adhesion and promote EMT (98,99).

Formylation operates in functional conjunction with other acylation modifications. This modification primarily influences fibrotic processes within the extracellular milieu through direct modification of extracellular matrix components and inflammatory cytokines, whereas most lysine acylations exert their effects on intracellular proteins (9,100). The NF-κB and TGF-β signaling cascades activated by formylation serve as critical upstream regulators of genes encoding enzymes responsible for intracellular modifications, including acetylation and lactylation (19,101). Therefore, this functional coupling links extracellular inflammatory signals to intracellular acylation network reprogramming, creating a feedforward loop that amplifies fibrogenesis (102).

Therapeutically, strategies targeting formylation include inhibiting methionine formyltransferase or lysine formyltransferase, to reduce fMet-AnxA1 generation or block collagen type I α1 chain formylation, respectively (102,103). Administration of formyl peptide receptor 2 (FPR2) antagonists, such as the synthetic hexapeptide WRW4 (Trp-Arg-Trp-Trp-Trp-Trp-NH2), can attenuate fibrotic responses through competitive blockade of downstream signal transduction (104). Development of neutralizing antibodies targeting specific formylation sites is also a promising approach, with the potential for highly selective intervention (92,105).

Beyond formylation, environmental insults, particularly cigarette smoking and cadmium exposure, exert profound influences on the pulmonary metabolic microenvironment, thereby eliciting broad-spectrum alterations in the lysine acylation landscape. Cigarette smoking upregulates PAD2 and PAD4 expression while suppressing the NAD^+-dependent deacetylase SIRT1 through oxidant-mediated inactivation and proteasomal degradation, leading to hyperacetylation of substrates, including RelA/p65 and FOXO3 (106,107). Cadmium, a toxic heavy metal found in cigarette smoke, downregulates histone H3 lysine 9 acetylation/serine 10 phosphorylation (H3K9acS10ph) and histone H4 lysine 5, 8 and 12 acetylation (H4K5ac, H4K8ac and H4K12ac), suppresses histone H3 acetylation at the lysyl oxidase gene promoter and potentiates protein S-palmitoylation via zDHHC11-mediated mTOR complex 1 activation (64,108-111). Furthermore, cadmium induces secretion of citrullinated vimentin through an Akt1- and PAD2-dependent mechanism, which activates Toll-like receptor 4/NF-κB signaling and promotes TGF-β1 production, establishing a feedforward loop that amplifies both inflammatory and fibrotic responses (73). Collectively, these observations establish a coherent pathogenic framework: Environmental exposures perturb cellular metabolism, altering glycolytic flux, mitochondrial redox homeostasis, NAD^+/NADH balance and acyl-CoA precursor availability,

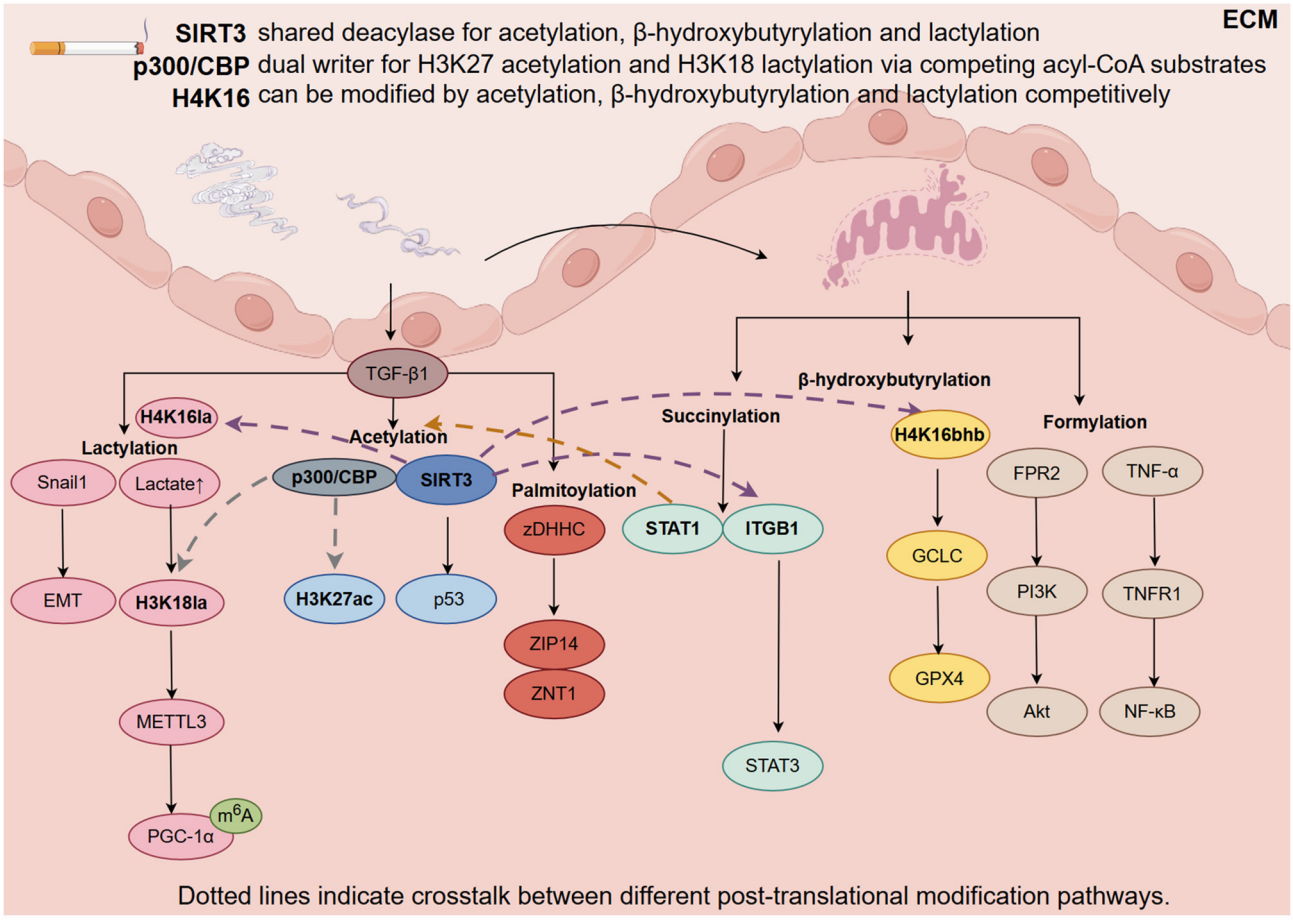

Figure 4. Integrated regulatory network linking mitochondrial dysfunction, TGF-β1 signaling and lysine acylation crosstalk in pulmonary fibrosis. Metabolic reprogramming remodels the intracellular acyl-CoA pool and fuels competing acylations at shared lysine residues. The dual writer p300/CBP catalyzes both H3K27 acetylation and H3K18 lactylation; the shared eraser SIRT3 removes acetyl, lactyl and succinyl groups, and erases H4K16 lactylation and β-hydroxybutyrylation. At H4K16, lactylation and β-hydroxybutyrylation compete for the same residue, and both marks can be removed by SIRT3. Downstream, acylation cascades drive Snail1-mediated EMT, H3K18la-METTL3-PGC-1α-dependent fibroblast activation, ITGB1 succinylation-STAT3-mediated epithelial senescence, STAT1 acetylation/succinylation crosstalk, zDHHC-dependent palmitoylation governing ZIP14/ZNT1-mediated zinc homeostasis, SIRT3/p53- and β-hydroxybutyrylation-mediated ferroptosis resistance, and formylation-driven profibrotic and inflammatory signaling, including FPR2-PI3K/Akt cascades promoting fibroblast proliferation and migration, as well as TNF-α formylation triggering TNFR1-dependent NF-ssssB inflammatory activation. Dotted lines denote crosstalk between distinct PTM pathways. ECM, extracellular matrix; EMT, epithelial-mesenchymal transition. Drawn using Figdraw (www.figdraw.com).

which in turn remodels the activities of acylation-modifying enzymes and reshapes the substrate pools for lysine acylation reactions, ultimately driving a coordinated reprogramming of the acylation network that sustains fibrogenesis (15,112). Thus, environmental factors and metabolic dysregulation constitute an integrated pathogenic axis that links external insults to the core post-translational machinery of IPF.

5. Targeted therapeutic strategies

It is now clear that the various acylation modifications do not act in isolation, but instead form a dynamic, interconnected regulatory network with extensive crosstalk and functional overlap (Fig. 4). SIRT3 acts as an eraser of both H4K16 lactylation and β-hydroxybutyrylation. Since these two acyl modifications compete for the same lysine residue, fluctuations in cellular acyl-CoA pools can alter their relative abundance, thereby establishing crosstalk between the two acylation marks and modulating pro-fibrotic gene transcription (113,114). p300/CBP possesses both acetyltransferase and lactyltransferase activities. Increased glycolytic flux promotes lactyl-CoA accumulation, which may compete with acetyl-CoA for the catalytic pocket of p300, thereby shifting histone modification from acetylation toward lactylation and contributing to the reprogramming of pro-inflammatory transcription in macrophages (115). Metabolic reprogramming governs this network through coordinated modulation of shared precursor pools and the activities of modifying enzymes (60). This coordinated regulation of multiple acylation pathways gives rise to higher-order regulatory modules that function in concert to shape the fibrotic phenotype (116). The desuccinylase SIRT3, for example, has been identified as a key eraser for histone H3K18la, demonstrating that perturbation of a single node can propagate widespread effects throughout the network (26). Deciphering the mechanisms that govern cross-modification crosstalk thus remains essential for the development of therapeutic strategies aimed at restoring homeostatic equilibrium within the acylation network.

The competitive occupancy of shared lysine residues by distinct acyl modifications, acetylation, succinylation

and lactylation, poses a fundamental challenge for therapeutic intervention. This competitive dynamic precludes a simple 'one modification, one function' paradigm, as the functional outcome depends on the dynamic equilibrium among competing modifications rather than on any single mark. Selective inhibition of one acyltransferase or activation of one deacylase may inadvertently shift the equilibrium toward alternative, potentially pathogenic, acylation states on the same substrate (19,117). The functional pleiotropy of central regulators, such as SIRT3, which exerts deacetylase, desuccinylase and delactylase activities, further compounds this complexity: Pharmacological modulation of such a multifunctional node can propagate unintended consequences across multiple acylation circuits simultaneously (113,117). Addressing this challenge necessitates a paradigm shift from single modification-focused approaches toward combinatorial regimens that co-target converging nodes within the network, with restoration of global acylation homeostasis as the therapeutic endpoint.

Small-molecule inhibitors targeting acylation enzymes. Work on acylation-targeted therapies has moved well beyond the classical p300/CBP and SIRT/HDAC enzyme families and has identified a wide range of novel, highly specific regulatory nodes for therapeutic intervention (118). This progress includes identification of lysine lactyltransferases and their corresponding deacylases, which offer novel opportunities for the development of selective inhibitors (119). In the succinylation field, therapeutic strategies now extend beyond modulation of the desuccinylase SIRT5 (120). Small-molecule regulators targeting upstream metabolic enzymes, including succinyl-CoA synthetase, offer alternative approaches to achieve precise control of local precursor pools (121). For S-palmitoylation, allosteric inhibitors of membrane-localized depalmitoylases enable spatiotemporally specific modulation of substrate depalmitoylation (122). β-hydroxybutyrylation is considered to be catalyzed by a novel class of short-chain acyltransferases, whose unique enzymatic properties may enable the design of precision tools for metabolic intervention in IPF (119).

The coordinated regulation of metabolic enzymes and modification enzymes is a distinct emerging frontier in therapeutic development (123). Inhibition of phosphoglycerate dehydrogenase, for instance, disrupts flux through the serine metabolic pathway and subsequently reduces NAD^+ availability (124). This decline in NAD^+ levels selectively attenuates the catalytic activity of NAD^+-dependent SIRTs SIRT1 and SIRT2 while leaving other family members such as SIRT3 and SIRT5 largely unaffected (125). These findings highlight a key shift in next-generation antifibrotic drug discovery: Moving away from non-selective broad-spectrum inhibition toward the rational design of precision small molecules that target tissue- or pathway-specific regulatory nodes (126).

Functional regulation of acylated substrate proteins. To circumvent the key limitations of broad-spectrum enzyme inhibition, an emerging strategy for precision antifibrotic therapy is to directly target substrate proteins in a manner that depends on their acylation state (19,127). This approach integrates chemical proteomics with structure-guided drug design to enable selective targeting of pathologically relevant modified protein states (128). Small-molecule allosteric modulators (forsythoside E) engineered to recognize the β-hydroxybutyrylated form of lysine 311 on pyruvate kinase M2, for instance, can precisely modulate its tetramerization dynamics and metabolic flux. This type of intervention can selectively reverse aberrant metabolic reprogramming in macrophages, without disrupting the basal activity of the enzyme in homeostatic conditions (129). Similarly, competitive inhibitory peptides that mimic S-palmitoylation could potentially be designed in the future to interfere with the membrane localization and endocytosis of TGF-β receptors, thereby effectively blocking downstream profibrotic signaling (64).

The advancement of such strategies depends critically on elucidation of the intrinsic relationships linking modification state, protein conformation and functional outcome at atomic resolution (130). Building on this principle, contemporary research efforts increasingly concentrate on development of antibody-based therapeutics directed against conformational epitopes that are uniquely presented by modified substrates. Monoclonal antibodies targeting a neo-antigenic epitope generated upon annexin A1 formylation, for example, have demonstrated the capacity to block receptor engagement and attenuate inflammatory infiltration in preclinical models (131). These highly targeted approaches offer a promising alternative to conventional enzyme inhibition, enabling selective modulation of protein function without disrupting global acylation homeostasis (132).

6. Conclusion and future perspectives

The present review systematically summarizes the roles of diverse protein acylation modifications in IPF, outlining their core molecular mechanisms, pathological functions and therapeutic potential. The current review also presents a comprehensive analysis of the integrated regulatory networks formed by these modifications, clarifying their distinct and overlapping roles in driving IPF pathogenesis.

Going forward, key studies will need to employ spatiotemporal multi-omics approaches, including single-cell acylation profiling, spatial proteomics and time-series metabolomics, to map these dynamic changes. The goal is to achieve precise mapping of the dynamic acylation landscape across defined cellular populations and sequential phases of IPF progression. These efforts should prioritize resolution of several fundamental scientific questions. These include: i) The principles governing allocation of shared metabolite pools among competing modification pathways and the determinants of modification specificity; ii) the molecular mechanisms by which the pathological microenvironment modulates substrate selectivity and catalytic activity of multifunctional enzymes such as SIRT3; and iii) the integrated functional consequences arising from competitive, cooperative or sequential modifications on individual protein substrates.

The main challenges in the field currently include enhancing inhibitor selectivity and improving tissue-specific targeting, while mitigating the network-level compensatory responses that may arise from single-node intervention. A central opportunity lies in exploiting a more comprehensive understanding of network logic to design combination

regimens that coordinately regulate metabolic flux and critical enzyme activities. Development of intelligent nanoscale delivery systems capable of responding to pathological metabolic cues is another promising direction, potentially enabling precise spatiotemporal intervention at sites of active fibrosis. Ultimately, shifting the therapeutic paradigm from single-target modulation to restoring the homeostatic balance of the entire acylation regulatory network may support the development of disease-modifying therapies for IPF and other progressive fibrotic diseases.

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Competing interests

The authors declare that they have no competing interests.

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