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Targeting mTORC1 and AMPK Signaling: Potential Therapeutic Approaches for Idiopathic Pulmonary Fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive disease characterized by increasing incidence and mortality. The underlying mechanisms of IPF remain poorly understood, contributing to the limited availability of effective treatments. Current therapies mainly slow disease progression but fail to provide a cure. Consequently, increasing attention has been directed toward modulating signaling pathways such as mammalian target of rapamycin complex 1(mTORC1) and Adenosine monophosphate–activated protein kinase (AMPK), both of which are key regulators of metabolic reprogramming in IPF. This review summarizes recent advances in therapeutic strategies that target cellular metabolism by modulating mTORC1 and AMPK.

Keywords: Idiopathic Pulmonary Fibrosis; AMPK; mTORC1; Metabolic Reprogramming

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a prototypical interstitial lung disease (ILD) characterized by a progressive respiratory decline of unknown onset, with a median survival of 3–5 years after diagnosis in the absence of treatment (Lederer & Martinez, 2018). Since 2000, the age-standardized mortality rate has ranged from 0.5--12 per 100,000 persons annually, imposing a substantial socioeconomic burden comparable to that of malignancies such as pancreatic or prostate cancer (Ferlay et al., 2015; Zheng et al., 2022). Another study reported that IPF-related mortality has increased across Europe, with more than 17,000 deaths annually between 2013 and 2018 (Gonnelli et al., 2024).

Although the exact etiology of IPF remains idiopathic, several risk factors have been identified that contribute to disease susceptibility and progression. Advanced age (typically over 60 years) is a primary risk factor, with aging-related cellular senescence and telomere shortening playing key roles (Zaman & Lee, 2018). Males are disproportionately affected, potentially due to hormonal or

genetic influences (Kalafatis et al., 2019). Cigarette smoking is the strongest environmental risk factor, causing chronic epithelial injury and promoting fibrosis through oxidative stress and inflammation (Oh et al., 2012). Genetic predispositions, such as polymorphisms in the MUC5B promoter gene or mutations in telomere-related genes (e.g., TERT, TERC), increase familial risk and are found in up to 30% of cases (Park et al., 2021). Occupational and environmental exposures, including metal dust, wood dust, air pollution, and agricultural work, have also been linked to increased incidence, likely via repetitive microinjuries to the lung epithelium (Sack & Raghu, 2019). Additionally, comorbidities such as gastroesophageal reflux disease (GERD) may exacerbate fibrosis through microaspiration (Mei et al., 2022). The major risk factors contributing to IPF pathogenesis are summarized in Figure 1.

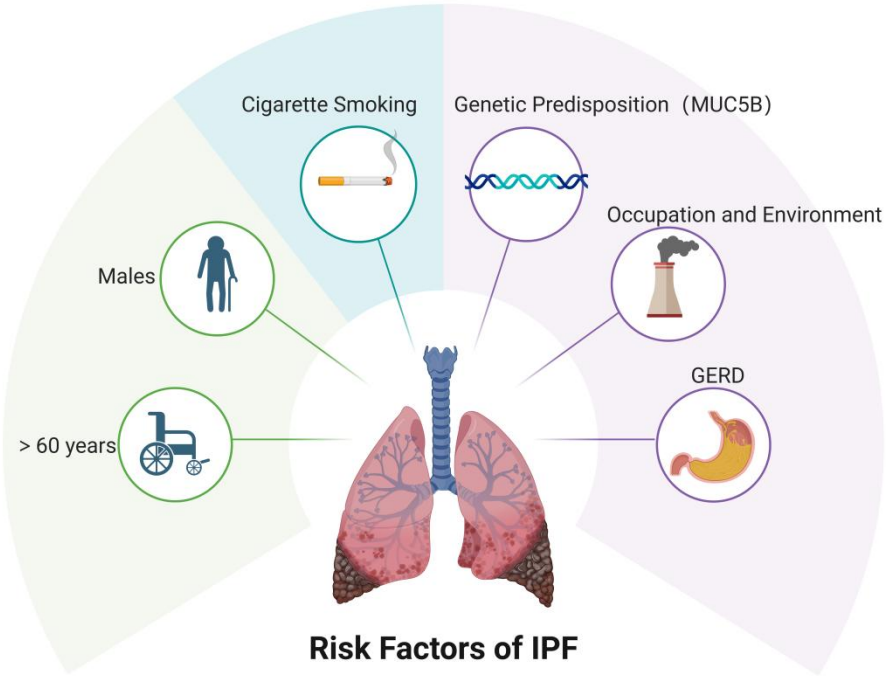

Figure 1.This diagram centers on the lungs and illustrates the primary risk factors for IPF

The main pathological features of IPF include diffuse alveolitis, extracellular matrix deposition, and fibroblast proliferation. These processes lead to characteristic histopathological findings, such as honeycomb cysts, fibroblastic foci, and hyperplastic epithelial cells, which reflect recurrent remodeling of the interstitium, distal airways, and alveolar spaces following abnormal injury and repair.

Current standard antifibrotic therapies are limited to pirfenidone and nintedanib. Pirfenidone has been shown to modulate the activity of transforming growth factor-β1 (TGF-β1) and tumor necrosis factor-α (TNF-α) while suppressing collagen synthesis and fibroblast proliferation. Nintedanib acts as a tyrosine kinase inhibitor, targeting the kinase activity of platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor receptors (Wollin et al., 2014). A recent randomized controlled trial demonstrated that pirfenidone- and nintedanib-

treated groups presented no significant differences in overall survival or hospitalization at the 24-month follow-up (Kim et al., 2024). However, frequent acute exacerbations, continued disease progression, and adverse events—such as photosensitivity, nausea, diarrhea, and liver dysfunction—often lead to treatment discontinuation (Takehara et al., 2022). Moreover, although these drugs slow disease progression, they neither halt nor reverse the course of IPF (Noble et al., 2016; Richeldi et al., 2014).

Accurate HRCT pattern classification—usual interstitial pneumonia (UIP), probable UIP, indeterminate UIP, or an alternative diagnosis—directly shapes the diagnostic pathway and the need for surgical/cryobiopsy. Misclassification delays antifibrotic initiation and confounds trial eligibility. Epidemiology indicates a rising global incidence with regional heterogeneity, whereas common comorbidities (e.g., GERD, OSA, metabolic syndrome) modulate trajectories and may intersect with the metabolic rewiring discussed below (Hutchinson et al., 2015; Raghu et al., 2018, 2022).

Therefore, metabolic reprogramming may offer a novel perspective on the mechanisms and treatment of IPF. The increased expression of glycolytic- and glutaminolytic-related enzymes and proteins in lung fibroblasts indicates enhanced glycolysis (Andrianifahanana et al., 2016) and glutaminolysis (Nigdelioglu et al., 2016; Selvarajah et al., 2019) as hallmarks of fibrotic metabolism. In IPF, both fibrotic and nonfibrotic regions show increased 18F-FDG uptake on PET–CT, reflecting enhanced glycolysis (Groves et al., 2009). Moreover, antifibrotic agents reduce this uptake in a bleomycin-induced murine model (Bondue et al., 2019). During fibrogenesis, metabolic reprogramming contributes to collagen synthesis as well as fibroblast proliferation and differentiation.

Adenosine monophosphate–activated protein kinase (AMPK) (Steinberg & Hardie, 2023) and the mammalian target of rapamycin complex 1(mTORC1) (Kim & Guan, 2015) function as master regulators and signal transducers of cellular metabolism and are closely associated with energy homeostasis, cell growth, autophagy, and apoptosis. Emerging experimental evidence indicates that this axis plays a pivotal role in various cancers and nonneoplastic diseases, including IPF. The interactions and regulatory networks among AMPK, mTORC1, and other signaling pathways reveal potential therapeutic targets. Increasing evidence suggests that the antidiabetic drug metformin and the lipid-lowering agent ezetimibe are promising candidates for repurposing in IPF.

2. Detailed Exploration of mTORC1 and AMPK as Central Regulators

AMPK, which is composed of three subunits, is regulated by the intracellular AMP/ATP ratio and functions as a cellular energy sensor by activating catabolic pathways to maintain energy homeostasis. When energy levels decrease, AMPK becomes phosphorylated, thereby stimulating ATP production. AMPK activation not only regulates energy balance through glucose and lipid metabolism but also exerts protective effects in IPF by reducing inflammation, epithelial–mesenchymal transition (EMT), oxidative stress, and extracellular matrix (ECM) production while inhibiting fibroblast activation and promoting fibroblast apoptosis (Yang et al., 2024). For

example, 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), an AMPK activator, enhances p-AMPK expression and reduces α-SMA levels in TGF-β–treated primary lung fibroblasts (Rangarajan et al., 2018).

Several studies have demonstrated the associations among pulmonary fibrosis, agent-induced AMPK phosphorylation, and downstream biomarkers. Alpha-mangostin (α-MG), a compound extracted from mangosteen fruit, increased the p-AMPK/AMPK ratio, inhibited Smad2/3 phosphorylation and NOX4 protein expression, and consequently reduced α-SMA and collagen I levels in the lung tissue of a bleomycin-induced murine model (Li et al., 2019). Similarly, mogrol and bryodulоglucinol modulate AMPK/NOX4 signaling to reduce reactive oxygen species (ROS) production and attenuate fibrosis (Ding et al., 2022; B. Liu et al., 2021). With respect to Smad2/3, one study reported that cereblon-induced Smad3 activation promoted fibrosis by suppressing AMPK activity (Kang et al., 2021).

Mammalian target of rapamycin (mTOR), a downstream effector of AMPK, is a serine/threonine kinase belonging to the phosphatidylinositol 3-kinase (PI3K)-related family. It has been reported to mediate TGF-β1–induced profibrotic responses by promoting fibroblast proliferation (Saxton & Sabatini, 2017). mTOR complex 1 (mTORC1), which contains mTOR, is involved in multiple cellular processes, including metabolism, protein synthesis, autophagy, and cell proliferation and growth. Woodcock et al. reported that TGF-β1 activated mTORC1 and its downstream effector 4E-binding protein 1 (4E-BP1) (Woodcock et al., 2019). The subsequent activation of mTORC1 and 4E-BP1 induces the synthesis of activating transcription factor 4 (ATF4), which enhances the de novo serine–glycine biosynthetic pathway to meet increased collagen production demands (Selvarajah et al., 2019). Moreover, mTORC1 and ATF4 play central roles in TGF-β1–induced metabolic reprogramming. Rapamycin, an allosteric inhibitor of mTORC, was unable to suppress ATF4 activation. In contrast, Rapalink-1, which specifically inhibits the mTORC1 kinase domain, effectively prevents ATF4 activation and collagen accumulation (O'Leary et al., 2020).

These data place the 4E-BP1–ATF4 axis at the center of collagen anabolism: ATF4-driven serine–glycine/one-carbon metabolism supplies glycine for procollagen, whereas selective 4E-BP1 control of translation explains why rapamycin underperforms ATP-competitive mTORC1 inhibitors against matrix accumulation (Kang et al., 2013a; O'Leary et al., 2020; Selvarajah et al., 2019; Woodcock et al., 2019).

The interplay between AMPK and mTORC1 was partially elucidated in a previous study (Y. C. Kim & Guan, 2015). On the one hand, when the AMP/ATP ratio is elevated, AMPK becomes phosphorylated and activates tuberous sclerosis complex 2 (TSC2), which subsequently regulates Ras homolog enriched in the brain (Rheb), a potent activator of mTORC1. Rheb, in turn, activates mTORC1. On the other hand, AMPK directly regulates mTORC1 by phosphorylating RAPTOR, a key component of the complex (Gwinn et al., 2008).

Mechanistically, AMPK imposes dual brakes on mTORC1 via TSC2 and RAPTOR and couples energy stress to autophagy through ULK1. This forms a tractable 'push–pull' model in which AMPK agonism restores collagen turnover, whereas ATP-competitive mTORC1 blockade

suppresses ATF4-dependent translation—providing rational synergy (Gwinn et al., 2008; Hardie, 2011; Zhao & Klionsky, 2011).

Independent of AMPK activation, the PI3K–AKT–mTOR pathway lies downstream of receptor tyrosine kinases (RTKs) and has previously been proposed as an important therapeutic target in non-small cell lung cancer (NSCLC) (Zeng et al., 2025). The inhibition of mTOR through this pathway may also provide new therapeutic strategies against pulmonary fibrosis. A previous study demonstrated that omipalisib, a pan-PI3K and dual mTOR inhibitor, reduced AKT phosphorylation in IPF lung slices, thereby attenuating fibroblast proliferation and TGF-β1–induced collagen production (Mercer et al., 2016). A randomized, placebo-controlled trial confirmed the pharmacological effects of short-term oral omipalisib administration in IPF patients and further demonstrated limited adverse events with notable tolerability (Lukey et al., 2019). However, another study from the same period reported that mTOR did not depend primarily on upstream PI3K–AKT signaling for its fibrogenic effects, challenging earlier mechanistic assumptions (Woodcock et al., 2019). In support of this view, during TGF-β1 signaling, maximal phosphorylation of mTORC1 substrates occurs approximately 10 hours before peak AKT phosphorylation. Moreover, inhibition of PI3K or AKT alone did not affect downstream mTORC1 activity. Furthermore, 4E-BP1, but not p70S6K, was identified as the key downstream effector of mTORC1 that is responsible for promoting collagen synthesis. Conclusive evidence has shown that rapamycin, an allosteric inhibitor that selectively attenuates the phosphorylation of p70S6K and 4E-BP1 (Ser65), has no effect on TGF-β1–induced collagen deposition. In contrast, ATP-competitive mTOR inhibitors profoundly suppressed fibrosis by completely blocking 4E-BP1 phosphorylation at Thr37/46 and Ser65 (Kang et al., 2013b).

In summary, simultaneous activation of AMPK, suppression of mTORC1, and modulation of the AMPK/mTORC1 axis represent feasible strategies for agents to exert antifibrotic effects.

3. Emerging Therapeutic Strategies

3.1. Effects of Metformin in IPF Treatment

The first-line antidiabetic drug metformin exerts pleiotropic pharmacological effects and has been shown to reverse established fibrosis in IPF lungs as well as in models of bleomycin- or TGF-β1–induced lung injury.

Metformin was previously shown to attenuate TGF-β–induced lung fibrosis in vitro, as evidenced by immunofluorescence staining of α-smooth muscle actin (α-SMA) and concomitant decreases in phosphorylated SMAD2/3, STAT3, AKT, and ERK1/2 (L. Li et al., 2015). Although metformin downregulated TGF-β downstream signaling and associated biomarkers, this effect was abolished in the presence of an AMPK inhibitor. Thus, metformin attenuates TGF-β–induced fibrosis in an AMPK-dependent manner. NADPH oxidase 4 (NOX4), an isoform of the NOX family, has been identified as a modulator of TGF-β1/SMAD signaling through the regulation of intracellular reactive oxygen species (ROS) levels. Elevated NOX4 expression has been observed in myofibroblasts from IPF patients. Despite substantial NOX4 expression, bleomycin induced increased SMAD2/3 phosphorylation and ROS production. Metformin treatment, similar to

NOX4 knockdown or AMPK activation–mediated NOX4 suppression, significantly counteracted these effects (Sato et al., 2016). This study explicitly demonstrated that the inhibition of NOX4-induced ROS production and p-SMAD expression is a key component of the antifibrotic mechanism of metformin.

Another study revealed that bleomycin treatment resulted in increased inflammatory cell infiltration, alveolar remodeling, and fibrotic deposition, as evidenced by H&E staining. However, low- and medium-dose metformin pretreatment had minimal effects on extracellular matrix deposition, whereas only the highest dose significantly suppressed fibrotic pathology (Gamad et al., 2018). Moreover, unlike lower doses, high-dose metformin (500 mg/kg/day) markedly mitigated bleomycin-induced weight loss in rats. Both medium- and high-dose metformin reduced inflammatory cell infiltration. The dose-dependent effects of metformin on weight loss and inflammatory cell infiltration are summarized in Figure 2. Further studies are needed to clarify the optimal dosing regimen and initiation time of metformin treatment.

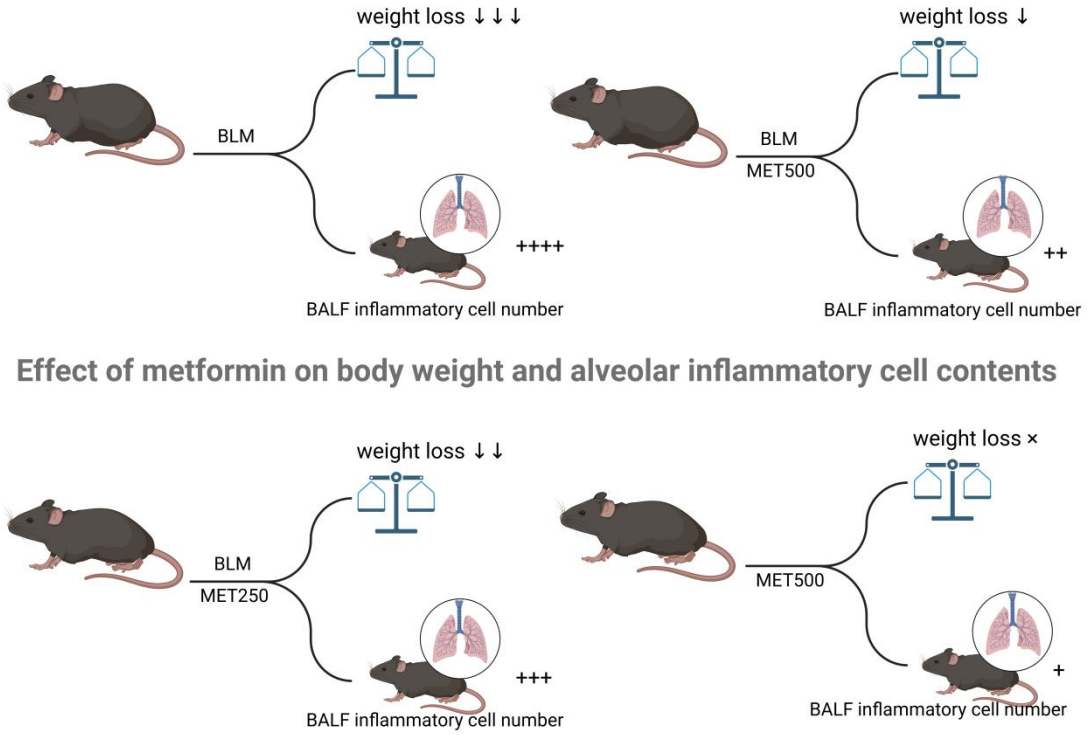

Figure 2. Dose-Dependent Effects of Metformin on Bleomycin-Induced Weight Loss and BALF Inflammatory Cell Infiltration in Rats.

Rangarajan et al. demonstrated that autophagy was partly dependent on AMPK activation and contributed to the regulation of collagen accumulation. When autophagy is inhibited by chloroquine in TGF-β1–treated fibroblasts, collagen turnover within autophagosomes increases (Rangarajan et al., 2018). Silencing the well-recognized upstream regulator AMPK consequently enhances extracellular matrix (ECM) deposition. In addition, AMPK activation reversed resistance to apoptosis by promoting mitochondrial biogenesis. In summary, AMPK-induced

autophagy and the restoration of apoptosis play important roles in fibroblast regulation, although downstream signaling events require further elucidation.

Micrometer-thick precision-cut lung slices (PCLS), derived from fibrotic regions of IPF patient lung tissue, serve as an ex vivo culture system. Compared with conventional cell culture systems, PCLS closely mimics the complex architecture of the respiratory system and provides more flexible, well-ventilated spaces. Another original research study replicated the effects of metformin in PCLS models (Kheirollahi et al., 2019). After 5 days of metformin treatment, significant improvements in lung structure and reduced collagen deposition were observed via hematoxylin and eosin staining, Masson's trichrome staining, and COL1A1 immunostaining. Three-dimensional reconstruction and flow cytometry–based quantification revealed an increased abundance of lipid droplets and lipid-containing cells. Further investigation via genetic labeling revealed that metformin promoted myogenic-to-lipogenic conversion of cells, an effect not observed with pirfenidone or nintedanib. However, this lipogenic differentiation is dependent on the BMP2 and PPARγ signaling pathways and is largely independent of AMPK, which is closely associated with ECM regulation.

Integrating across models, metformin engages at least three axes: (i) NOX4–ROS–SMAD dampening; (ii) AMPK–ULK1–autophagy restoration with reversal of apoptosis resistance; and (iii) BMP2–PPARγ-driven myogenic–to-lipogenic conversion in human PCLs, largely AMPK light. These programs explain both the reduction in the ECM and the reprogramming of the cell state (Kheirollahi et al., 2019; Rangarajan et al., 2018; Sato et al., 2016).

Fibroblast proliferation is considered one of the prominent features of pulmonary fibrosis. Forkhead box M1 (FOXM1), a member of the transcription factor family, is a key regulator of fibroblast activation and fibrotic progression (Penke et al., n.d.). Xuan Gu et al. further clarified the relationships among AMPK, FOXM1, and fibroblasts. In bleomycin-induced pulmonary fibrosis in mice, metformin treatment suppressed the expression of FOXM1 and Cyclin D1, a marker of the proliferative phenotype (Gu et al., 2021). In contrast, treatment with the AMPK inhibitor compound C led to AMPK deactivation and increased FOXM1 expression. Therefore, it was concluded that metformin-induced AMPK activation suppresses pathological fibroblast proliferation by downregulating FOXM1.

Recently, another AMPK downstream signaling pathway has been partially elucidated. Bone morphogenetic protein 9 (BMP9) promotes fibroblast activation through activin receptor-like kinase 1 (ALK1) and Smad1/5 signaling (Wang et al., 2021). Metformin promoted AMPK activation, suppressed BMP9 signaling, and subsequently downregulated ALK1 and Smad1/5, thereby reducing fibroblast proliferation and differentiation in vitro (Chen et al., 2022).

Elevated S100A4 expression—formerly regarded as a marker of fibroblast presence—has been reported in the bronchoalveolar lavage fluid (BALF) of IPF patients and in fibroblasts from bleomycin-induced rats, suggesting that S100A4 contributes to IPF pathogenesis (Gu et al., 2021; Lee et al., 2020). A recent study by Huimin Ji et al. elucidated how metformin attenuates fibrosis through the AMPK–STAT3–S100A4 axis, with STAT3 being a member of the STAT family activated by TGF-β1 (Ji et al., 2023). They first confirmed that metformin-mediated antifibrotic

effects in vivo were accompanied by reduced S100A4 protein levels and decreased STAT3 phosphorylation. Both pharmacological inhibition of STAT3 phosphorylation by the small-molecule inhibitor stattic and AMPK activation by metformin suppressed S100A4 expression and ultimately reduced α-SMA deposition.

Moreover, a meta-analysis demonstrated that metformin significantly reduced inflammation, fibrosis, and fibrosis-associated biomarkers (Wu et al., 2022). Furthermore, compared with the control diet, metformin significantly reduced mortality.

Future clinical studies should compare the side-effect profiles of metformin with those of pirfenidone and nintedanib and address potential safety concerns. The most common side effects are gastrointestinal (GIT) disturbances, including diarrhea, nausea, and abdominal pain, which are dose dependent and generally transient. These effects can be minimized by gradually increasing the metformin dosage (Akhter & Uppal, 2020; Feng et al., 2022). Rarely, metformin may cause lactic acidosis (MALA), a serious condition that can result in cardiovascular or renal failure, particularly in patients with hepatic or renal impairment (Brackett, 2010). The long-term use of vitamin B12 has been associated with vitamin B12 deficiency, although its clinical significance remains unclear (Aroda et al., 2016). In addition, the relatively low cost of metformin may make it a more sustainable option for patients than the considerably more expensive pirfenidone and nintedanib (Teague et al., 2022).

Clinical translation should prioritize lung tissue exposure mapping, stratification by metabolic comorbidity, and combination with pirfenidone or nintedanib. In human data, the results are mixed: a national claims-based cohort of IPF patients with T2D reported an association between metformin use and lower mortality/hospitalization (Teague et al., 2022), whereas a post hoc analysis of three phase III pirfenidone trials revealed no effect on clinically relevant outcomes (Spagnolo et al., 2018). Embedding pharmacodynamic biomarkers—LC3-II in PCLS, circulating long-chain acyl-carnitines/metabolomic signatures, and quantitative HRCT metrics (CALIPER/DTA)—can reduce the risk in phase II/III trials (Humphries et al., 2017; Kheirollahi et al., 2019; Maldonado et al., 2014; Rindlisbacher et al., 2018).

3.2. Ezetimibe in IPF Treatment

Ezetimibe, a drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of hypercholesterolemia, acts by inhibiting the intestinal cholesterol transporter Niemann-Pick C1-like 1 (NPC1L1) (Garcia-Calvo et al., 2005).

Lee YS et al. further demonstrated that ezetimibe inhibited adipogenesis primarily by increasing AMPK activation and subsequently suppressing mTORC1 signaling, thereby halting cell proliferation and exerting antiobesity effects (Lee et al., 2020).

A recent article published in the European Respiratory Journal highlighted the therapeutic potential of the old drug ezetimibe for IPF, drawing extensively on findings from three major studies(Lee et al., 2024). Ezetimibe counteracted TGF-β1–induced COL1A1 expression in human and murine lung fibroblasts (hLFs/mLFs) in a dose- and time-dependent manner, with 20 μM treatment for 24 hours restoring COL1A1 and ACTA2 levels to near baseline. mRNA sequencing further revealed that ezetimibe reduced the expression of TGF-β1–induced myofibroblast markers

and increased the expression of autophagy-related genes. Gene set enrichment analysis revealed downregulation of fibrosis-associated genes and upregulation of autophagy-related genes. Using fluorescent protein–tagged LC3 transgenic mLFs, researchers reported increased LC3 conversion, accumulation of free GFP fragments, and increased numbers of autophagosomes and autolysosomes, indicating increased autophagic flux. Serum response factor (SRF) was subsequently identified as an autophagic substrate that is degraded through ezetimibe-induced autophagy. The study also demonstrated reduced phosphorylation of P70S6K and RPS6, downstream targets of the mTORC1 axis. mTORC1 activity was shown to be regulated by lysosomal cholesterol, whereas ezetimibe redistributed intracellular cholesterol without altering total cellular cholesterol levels. Additionally, a second study effectively replicated the in vitro findings in vivo, yielding consistent results. A third study suggested that ezetimibe, either as monotherapy or in combination with pirfenidone, may improve overall survival and reduce all-cause mortality in IPF patients. Ezetimibe also showed potential as a standalone therapy to improve lung function, with better FVC and DLCO outcomes than pirfenidone alone. Collectively, ezetimibe inhibits myofibroblast differentiation by targeting the mTORC1–autophagy axis and regulating cholesterol distribution. In IPF patients, it reduces mortality and slows the decline in lung function.

Mechanistic nuance: ezetimibe alters lysosomal cholesterol distribution without lowering total cholesterol, thereby tuning lysosomal mTORC1 signaling and permitting SRF degradation via increased autophagic flux—distinct from statins. These findings are consistent with those of fundamental studies on NPC1L1 targeting and lysosomal cholesterol–mTORC1 coupling (Castellano et al., 2017; Eid et al., 2017; Garcia-Calvo et al., 2005; Shin et al., 2022; Weinglass et al., 2008).

Notably, ezetimibe has a favorable safety profile and is characterized by mild and transient gastrointestinal side effects and rare serious adverse events. It is well tolerated and does not significantly increase the risk of major adverse events (Olmastroni et al., 2024).

3.3. AMPK-mTOR in IPF

The AMPK–SMAD/NOX4/FOXM1/BMP9/STAT3 pathways targeted by metformin are largely independent of mTOR. A previous study demonstrated that Smad3 knockdown attenuated mTORC1-mediated phosphorylation of p70S6K and 4E-BP1 while also reducing COL1A1 mRNA levels (Woodcock et al., 2019). On the basis of these findings, a pathway model in which Smad3 activation directly promotes early COL1A1 mRNA transcription while influencing 4E-BP1 through mTORC1 activation was proposed. This dual regulation further enhances COL1A1 expression and ultimately collagen synthesis (Verrecchia et al., 2001). Since AMPK activation inhibits mTOR through multiple routes—including the AMPK–Smad3–mTOR, AMPK–TSC–mTOR, and AMPK–RAPTOR–mTOR pathways—the AMPK–mTOR axis should be considered an important regulatory pathway.

The lipopolysaccharide (LPS)-induced cellular pulmonary fibrosis model is a promising system for studying IPF mechanisms and therapeutics, as LPS acts as an autophagy inhibitor that

promotes fibroblast proliferation through the mTOR pathway (Xie et al., 2019). Metformin was found to attenuate PFKFB3-catalyzed glycolysis following AMPK phosphorylation and mTORC1 inhibition, thereby reducing collagen production in LPS-induced lung fibroblasts, although this specific effect has not yet been validated in animal models (Tang et al., 2021). Given the extensive studies on the AMPK–mTOR pathway in relation to metformin, further efforts are needed to validate this signaling pathway and establish additional well-substantiated pathways. With respect to ezetimibe, previous studies have demonstrated that its effects on fibroblast autophagy are dependent mainly on lysosomal cholesterol distribution–regulated mTORC1 modulation. In contrast, ezetimibe-mediated regulation of the AMPK–mTOR pathway has been proposed to counteract adipogenesis and reduce lipogenesis. Therefore, no evidence currently supports an antifibrotic role of ezetimibe through the AMPK–mTORC1 pathway.

Other antifibrotic drugs also target the AMPK/mTOR pathway. M2 macrophages, which are derived from alveolar macrophages, secrete profibrotic mediators that promote fibrosis. Nobiletin (NOB), a flavonoid isolated from citrus peels, has been shown to protect the liver from damage and ameliorate lung fibrosis (Dusabimana et al., 2019). One study demonstrated that NOB activated AMPK phosphorylation and inhibited mTOR, thereby enhancing autophagy. As a result, increased autophagy reduces M2 macrophage polarization and alleviates pulmonary fibrosis (Cheng et al., 2024). Furthermore, fenbendazole (FBZ), a benzimidazole compound used to treat parasitic infections and suppress cancer cell proliferation, is noteworthy for its mild side effects and durable efficacy (DUAN et al., 2013). Previous studies have shown that, in fibroblasts, FBZ activated AMPK and suppressed mTOR, thereby reprogramming glycolysis and the glycolytic capacity. This process, in turn, inhibits fibroblast proliferation and differentiation (Wang et al., 2022). The integrated AMPK–mTORC1 signaling network and its pharmacological modulators are schematically illustrated in Figure 3.

Taken together, these findings indicate that mTORC1 activity is elevated, whereas AMPK is deactivated in the lung tissue of IPF patients (Rangarajan et al., 2018). Only a few studies have investigated how drugs or reagents influence mTOR through AMPK and whether their mechanisms rely on AMPK activation, direct mTOR inhibition, or both. Moreover, no evidence has yet clarified which specific AMPK–mTOR pathway exerts the most potent antifibrotic effect. In addition, further studies are needed to explore the potential side effects associated with prolonged AMPK activation and/or mTOR inhibition and to determine whether long-term modulation of mTOR or other AMPK downstream pathways alone would result in fewer adverse effects than multipathway interventions. Furthermore, whether there is a connection between Smad3 downstream of AMPK and PFKFB3 downstream of mTORC1 and whether Smad3 is involved in mTORC1-associated autophagy remain unknown. Finally, comparisons between antifibrotic agents targeting AMPK and/or mTOR require further validation through meta-analyses, randomized controlled trials, and cohort studies. For example, ezetimibe induces autophagy via lysosomal cholesterol–mediated modulation of mTORC1, whereas metformin induces autophagy via AMPK activation. Future research should therefore compare the therapeutic efficacy of these two drugs and evaluate their long-term effects.

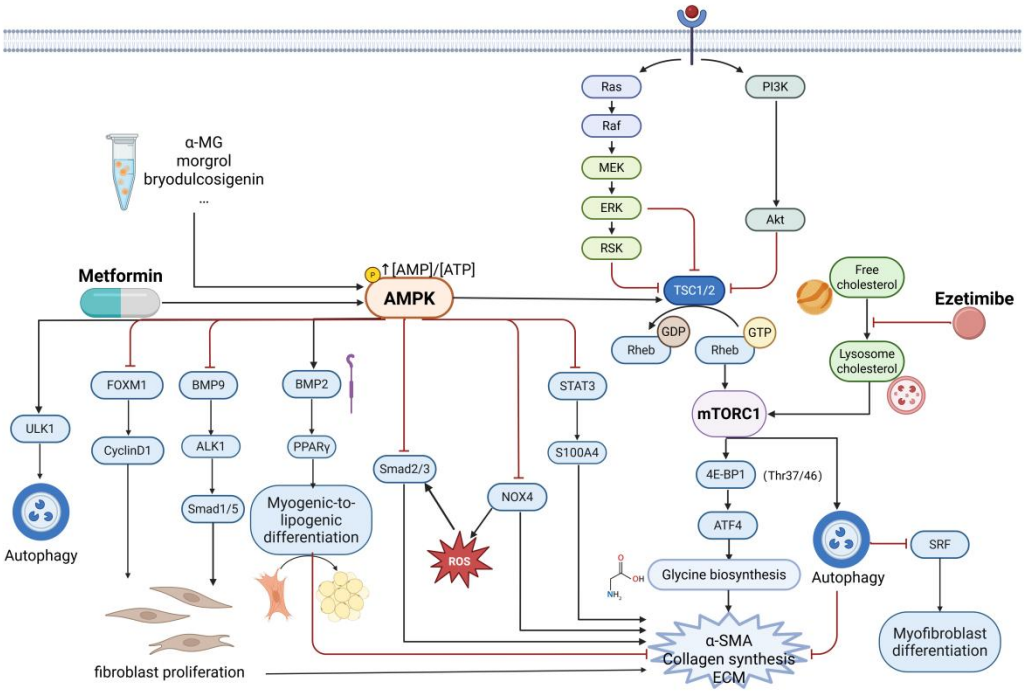

Figure 3. Schematic Overview of AMPK-mTORC1 Signaling Axis in Pulmonary Fibrosis and Pharmacological Modulators.

4. Strategic Targeting of the AMPK–mTORC1 Axis: Comparative Evaluation and Therapeutic Prioritization

The evidence above suggests that AMPK activation and mTORC1 inhibition exert their anti-fibrotic effects through interconnected but mechanistically different pathways. These interventions are not isolated pharmacological approaches, but rather can be viewed as complementary strategies targeting different regulatory levels of the AMPK-mTORC1 axis. AMPK activators, including metformin and several natural compounds, primarily restore cellular energy balance and enhance autophagic flux, thereby inhibiting fibroblast proliferation and extracellular matrix accumulation. In contrast, ATP-competitive mTORC1 inhibitors more directly inhibit collagen biosynthesis by blocking the 4E-BP1-ATF4 translational program, acting on the synthetic core of fibrosis formation. Ezetimibe represents a different mechanism, promoting the autophagic degradation of pro-fibrotic mediators by modulating lysosomal cholesterol-dependent mTORC1 activation without globally activating AMPK. From a translational medicine perspective, AMPK activation currently has the broadest experimental support, particularly in models that partially reverse established fibrosis. Direct inhibition of mTORC1 has strong mechanistic potency, but long-term safety needs careful evaluation, as sustained inhibition of mTOR may interfere with epithelial regeneration and host defense. Repositioned drugs such as metformin and ezetimibe benefit from their established human safety profiles, supporting their priority consideration in combination strategies. In summary, the development of effective treatments for idiopathic pulmonary fibrosis (IPF) may not depend on the inhibition of a single node, but rather on the strategic modulation of the AMPK-mTORC1 axis

to achieve a balance between restoring metabolism and inhibiting the synthesis of pathological proteins.

5. Challenges in Translating Preclinical Findings to Clinical Applications

To better simulate human IPF, complementary models are needed. Silica and radiation injury yield more persistent lesions than bleomycin does, whereas telomerase-deficient mice recapitulate aging-related susceptibility. Human organoids and precision-cut lung slices (PCLS) preserve epithelial–mesenchymal interactions and allow the quantification of autophagy and ECM remodeling under defined metabolic cues. Importantly, translational feasibility is underscored by pan-PI3K/mTOR inhibitors such as omipalisib, where preclinical antifibrotic efficacy has been bridged into early-phase clinical trials (Lukey et al., 2019; Mercer et al., 2016).

First, primary fibroblast cultures from healthy donors or IPF patients exhibit variability in growth and gene expression. Thus, the use of more practical and stable fibroblast lines is limited. A recent study proposed WI-38 cells, a human embryonic lung fibroblast line, as a reliable and consistent model for investigating fibroblast biology in lung fibrosis(Vásquez-Pacheco et al., 2024). This study compared WI-38 cells with primary IPF fibroblasts by inducing myofibroblast differentiation with TGF-β1 and lipofibroblast transition with metformin, followed by phenotypic and transcriptomic analyses using fibroblast-specific markers to validate and replicate research on the antifibrotic effects of metformin. Moreover, although the bleomycin-induced lung injury mouse model is the most commonly used model for studying lung fibrosis, it tends to heal spontaneously over time. In future studies, more stable models that closely mimic the pathology of IPF or patient-derived fibroblasts will be essential.

In addition, further studies are needed to explore the effects of metformin (MET) on downstream AMPK mechanisms and additional antifibrotic actions, although previous research has clarified some aspects of AMPK downstream signaling.

A key challenge in transitioning to clinical trials is optimizing the drug dosage, as metformin (MET) must be effectively delivered to the lungs for IPF treatment. Previous in vitro studies have shown that low doses of MET have minimal effects on reducing collagen deposition and lung structural deformation. Preclinical studies have used higher doses to achieve adequate lung concentrations, highlighting the need for tailored dosing strategies in clinical practice. IPF patients also exhibit individual variability in disease progression, family history, imaging features, comorbidities, and other relevant factors. A cohort analysis demonstrated that MET therapy was superior to pirfenidone and nintedanib in reducing all-cause mortality and hospitalization among IPF patients with diabetes (Teague et al., 2022). Future efficacy studies of MET should incorporate a broader range of comorbidities, allowing MET to be prioritized over traditional medications in IPF patients with specific coexisting conditions.

Moreover, a retrospective analysis revealed no effect of MET on the prognosis of IPF patients, which conflicts with findings from clinical trials (Spagnolo et al., 2018). Unfortunately, the study had several limitations, including a small sample size, the exclusion of late-stage patients and those with comorbidities, inconsistent durations of MET use (with some patients using it for only

a few days), and uncertainty regarding treatment adherence and potential drug interactions. In summary, future observational or experimental studies on MET for IPF should include larger, more comprehensive patient cohorts to ensure that findings are generalizable to the broader IPF population. Standardizing the duration of MET treatment, monitoring adherence to MET regimens under real-world conditions, and examining potential interactions with other commonly used medications in IPF patients will be crucial for understanding its long-term effects.

With respect to ezetimibe, studies on its antifibrotic efficacy are limited. The aforementioned research suggests that ezetimibe may act through the mTORC1–autophagy axis; however, its exact molecular targets and pathways remain incompletely understood. Since AMPK is involved in autophagy regulation, further investigation is needed to determine whether ezetimibe activates AMPK to influence autophagic degradation. Given that ezetimibe reduces lysosomal cholesterol content, future studies should examine how lysosomal cholesterol levels affect fibroblast differentiation, autophagic activity, and extracellular matrix (ECM) remodeling. The effects of ezetimibe on the SRF-mediated transcription of profibrotic genes, myofibroblast activation, and ECM accumulation also remain unclear. A detailed analysis of whether SRF cooperates with other pathways in response to ezetimibe treatment could help identify new antifibrotic mechanisms. Moreover, preclinical studies should include more animal models with established fibrosis, and clinical trials should monitor biomarkers of autophagy (such as LC3-II), cholesterol metabolism, and SRF activity in IPF patients. Metformin in combination with simvastatin has previously been studied in glioma progression via metabolic modulation, although through mechanisms distinct from antifibrosis (Qiao et al., 2024). Nevertheless, it is possible to treat IPF with multidrug combinations or by adding new agents to classical antifibrotic therapies. For example, a recent study demonstrated that metformin enhances the antifibrotic effects of pirfenidone, potentially through mechanisms involving oxidative stress reduction and NOX4 inhibition(Liu et al., 2024). These findings have greatly broadened the understanding of novel therapeutic strategies for IPF.

6. Conclusions

In summary, mounting evidence suggests that the AMPK-mTORC1 signaling axis is a core regulatory node in metabolic reprogramming in idiopathic pulmonary fibrosis. Dysregulation of this axis leads to persistent fibroblast activation, enhanced collagen biosynthesis, and impaired autophagy turnover.

Therapeutic strategies that restore AMPK activity, selectively inhibit mTORC1-dependent translation, or modulate lysosomal nutrient sensing offer mechanistically evidence-based approaches to halting fibrosis progression. Among current drug candidates, approved drugs such as metformin and ezetimibe offer practical opportunities for translation due to their established safety profiles, while selective mTORC1 inhibitors highlight the importance of targeting collagen synthesis at the level of translational control.

Future advancements in the treatment of idiopathic pulmonary fibrosis (IPF) may require fine-tuning of the AMPK-mTORC1 axis rather than broad metabolic inhibition, focusing on long-term

tolerability, pathway-specific biomarkers, and rational combination therapy strategies. Continuing to integrate mechanistic insights with translational research is crucial for developing more effective and sustainable treatments for IPF.

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