Mechanistic insights and therapeutic potential of sphingosine-1-phosphate in the development of pulmonary fibrosis (Review)

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Received November 17, 2025; Accepted February 13, 2026

DOI: 10.3892/mmr.2026.13847

Abstract. Pulmonary fibrosis represents a group of chronic, progressive lung disorders arising from diverse etiological factors. Its defining pathological feature is the excessive deposition of collagen, which ultimately results in irreversible distortion of the lung parenchyma. Current therapeutic strategies can slow disease progression but are insufficient to halt it completely. Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid metabolite that binds to sphingosine-1-phosphate receptors (S1PRs) to regulate numerous vital intracellular metabolic pathways associated with cell proliferation, survival and apoptosis. The present reviewsummarizedthe molecular network through which S1P contributes to the pathogenesis of pulmonary fibrosis, outlines existing pharmacological modulators of the S1P pathway anddiscussedtheir potential therapeutic value in treating this condition.

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Abbreviations: ABC, ATP-binding cassette; BALF, bronchoalveolar lavage fluid; Cer, ceramide; Dpr1, Dapper1; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; ERK1/2, extracellular signal-regulated kinase 1/2; FMT, fibroblast-to-myofibroblast transition; HDAC, histone deacetylase; IL-1β, interleukin-1beta; IL-6, interleukin-6; IPF, idiopathic pulmonary fibrosis; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MS, multiple sclerosis; mtROS, mitochondrial reactive oxygen species; NF-κB, nuclear factor kappa-B; NLRP3, NOD-like receptor family pyrin domain-containing 3; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; RAC1, Ras-related C3 botulinum toxin substrate 1; RhoA/ROCK1, Ras homolog family member A/Rho-associated coiled-coil containing protein kinase 1; ROS, reactive oxygen species; Sph, sphingosine; S1P, SPh1-phosphate; S1PL, S1P lyase; S1PRs, S1P receptors; SphK1, Sph kinase 1; Spns2, spinster homolog 2; SPP, S1P phosphatase; STAT3, signal transducer and activator of transcription 3; TAZ, transcriptional coactivator with PDZ-binding motif; TGF-β1, transforming growth factor β1; TNF-α, tumor necrosis factor α; YAP, Yes-associated protein

Key words: sphingosine-1-phosphate, pulmonary fibrosis, mechanism, signaling pathway, treatment

Contents

1. Introduction

Pulmonary fibrosis, a common end-stage manifestation of various interstitial lung diseases, arises from incompletely elucidated etiologies involving diverse risk factors such as environmental exposures, smoking, genetic predisposition and autoimmune disorders. This etiological complexity hinders the identification of viable therapeutic targets (1). Idiopathic pulmonary fibrosis (IPF) refers to pulmonary fibrosis of unknown cause. Its pathological core involves excessive deposition of extracellular matrix (ECM), which disrupts alveolar architecture, leading to the formation of extensive fibrotic scars and ultimately irreversible loss of lung function. As the most prevalent interstitial lung disease, IPF predominantly affects middle-aged and elderly individuals and carries a poor prognosis. Data indicate that untreated IPF patients have a median survival of only 2-6 years following diagnosis (2,3). Epidemiological studies as of 2020 report a global IPF incidence ranging from 1-13 per 100,000 person-years and a prevalence of 3 to 45 per 100,000 population. The highest incidence and prevalence rates of IPF are observed in three regions: Korea, Canada and the US (4). A meta-analysis of global studies estimated 3- and 5-year cumulative survival rates for IPF patients at 61.8 and 45.6%, respectively (5). Therefore, developing precise and effective treatments for pulmonary fibrosis is imperative.

In recent years, the therapeutic focus for IPF has shifted from anti-inflammatory strategies to antifibrotic agents and comorbidity management (6). However, no reliable cure exists. Current pharmacologic options for IPF are limited. Although nintedanib and pirfenidone are US FDA-approved for IPF and can modestly slow disease progression (7). Moreover, a significant proportion of patients on long-term treatment with these drugs experience severe gastrointestinal adverse effects. Lung transplantation remains the only curative intervention, but it is not widely accessible due to limitations in donor organ availability, economic constraints and challenges in postoperative care. Consequently, there is a pressing need to develop novel, low-toxicity and high-efficiency antifibrotic therapies to alleviate symptoms and improve survival.

S1P signaling has been extensively investigated in the context of lung diseases. Previous reviews by Ebenezer *et al* (8) and Mohammed and Harikumar *et al* (9) summarize the roles of S1P signaling across a broad spectrum of pulmonary disorders, with a primary focus on immune regulation, inflammatory responses and vascular-related functions. By contrast, the present review focusedon pulmonary fibrosis and provides a mechanism-oriented synthesis of recent advances regarding the roles of S1P signaling ininflammation, fibroblast-to-myofibroblast transition (FMT), epithelial-to-mesenchymal transition (EMT), autophagy and oxidative stress, with the aim of clarifying its functional relevance and potential therapeutic implications in pulmonary fibrosis.

2. Overview of S1P

S1P is a bioactive lipid mediator, primarily synthesized and secreted into the circulation by erythrocytes and platelets. As a critical intercellular signaling molecule, S1P regulates essential physiological processes, such as cell proliferation, survival, migration, apoptosis, angiogenesis and inflammation. Through the modulation of these core cellular functions, S1P plays a significant role in complex pathophysiological conditions, including immune response, angiogenesis and fibrosis (10,11). S1P is synthesized through a stepwise enzymatic pathway. Sphingomyelin is first hydrolyzed to ceramide (Cer) by sphingomyelinase. Cer is then converted to sphingosine (Sph) by ceramidase. Finally, Sph is phosphorylated by Sph kinases (SphKs) to generate S1P (12). This intracellular synthesis primarily depends on two key rate-limiting enzymes, SphK1 and SphK2. Although SphK1 and SphK2 share high sequence homology, they exhibit distinct differences in subcellular localization, tissue distribution and biological functions (13,14). SphK1 is predominantly cytosolic but can translocate to the plasma membrane or nucleus to exert its catalytic activity, thereby promoting cell proliferation and survival (15,16). By contrast, SphK2 is primarily localized within organelles such as the nucleus and endoplasmic reticulum and is more closely associated with inhibiting DNA synthesis and inducing apoptosis (17).

Cellular S1P levels are maintained by a tightly regulated dynamic balance between its synthesis and degradation. S1P degradation proceeds via two principal pathways: Reversible dephosphorylation back to Sph by S1P phosphatases (SPP) and irreversible catabolization to hexadecenal and phosphor-ethanolamine by S1P lyase (S1PL) (18-20). In tissues, low S1P concentrations are maintained due to efficient degradation by S1PL. By contrast, erythrocytes and platelets lack S1PL, resulting in the high S1P concentration characteristic of blood. S1P mediates signaling through both intracellular and extracellular mechanisms. While its extracellular signaling is well-established, its intracellular roles remain less defined. Intracellularly, S1P can function as a second messenger, directly targeting proteins such as histone deacetylase (HDAC) to influence Ca^{2+} homeostasis, gene transcription and protein modification (21). S1P can act via autocrine mechanisms or be exported to the extracellular milieu by transporters, including specific ATP-binding cassette (ABC) transporters and spinster homolog 2 (Spns2) transporters. Once extracellular, S1P binds to five S1PRs on the target cell surface, initiating diverse downstream signaling cascades (22-24).

Extracellular S1P signaling via S1PRs has been extensively characterized.S1PRs are expressed on nearly all cell types, with particularly high levels found on immune cells such as neutrophils, dendritic cells, natural killer cells and macrophages (11). S1PR1, highly expressed on endothelial and immune cells, promotes cell proliferation, migration, angiogenesis and immune regulation through pathways including mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and extracellular signal-regulated kinase 1/2 (ERK1/2) (25). S1PR2 and S1PR3 are predominantly expressed on fibroblasts and epithelial cells, where they regulate cell proliferation and extracellular matrix synthesis. S1PR4 is found in hematopoietic and lymphoid tissues, as well as the lung and is implicated in immune regulation and tumor suppression. S1PR5 is primarily expressed in the central nervous system and is involved in neuromodulation. To date, research on S1PRs in fibrotic diseases has largely focused on S1PR1-3, with the roles of S1PR4 and S1PR5 being less explored (Fig. 1).

3. Molecular mechanisms of S1P in pulmonary fibrosis

Massive fibroblast proliferation and ECM accumulation constitute the fundamental pathological hallmarks of pulmonary fibrosis (26). Repeated injury to alveolar epithelial cells initiates an inflammatory response that recruits inflammatory cells to the site of damage. These infiltrating inflammatory cells subsequently generate and secrete abundant pro-fibrotic factors, thereby stimulating fibroblast proliferation, promoting their differentiation into myofibroblasts and ultimately leading to excessive ECM deposition (27). Disruption of the balance between tissue injury and repair results in lung scarring and progressive architectural distortion, which impairs gas exchange and manifests as overt pulmonary fibrosis.

S1P is a crucial bioactive sphingolipid metabolite that functions as both an extracellular and intracellular signaling mediator. It has been shown to regulate physiological and pathophysiological processes in a variety of diseases. For instance, in malignancies, S1P accelerates disease progression by remodeling the tumor microenvironment and promoting angiogenesis, invasion and metastasis (28,29). In brain injury pathology, S1P participates in modulating neuroinflammatory responses and neuronal survival (30). Similarly, in cardiovascular and pulmonary diseases, S1P is recognized as a key molecular driver of disease progression (31,32). In

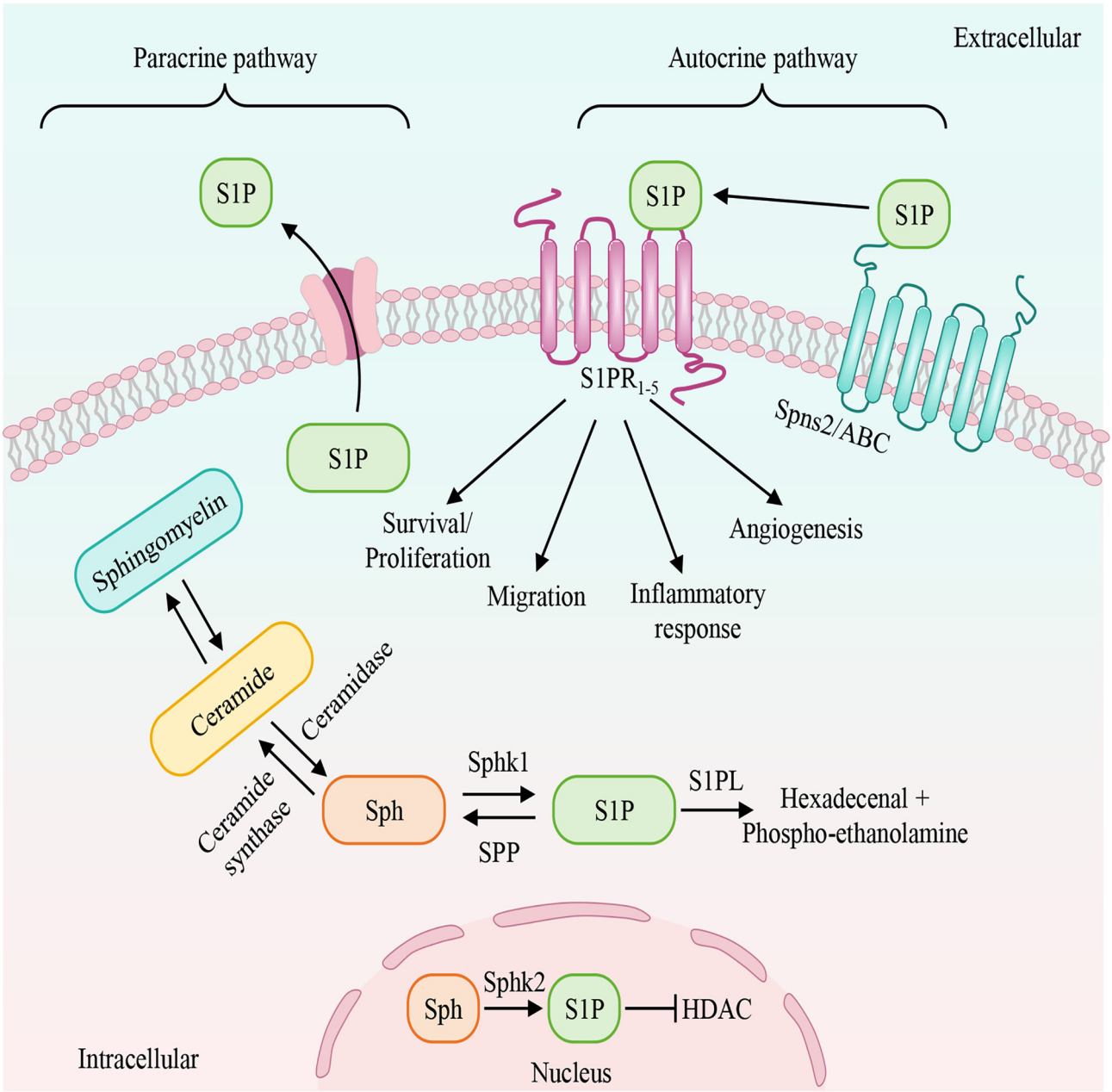

Figure 1. Synthesis, degradation and transport of S1P. This figure depicts the intracellular synthesis, degradation and transport of S1P, leading to extracellular signaling. Sphingomyelinases catalyzes the conversion of sphingomyelin to produce Cer, which is then converted into Sph by ceramidase. S1P can be generated by SphK1 and SphK2, while S1P produced by SphK2 in the nucleus inhibits HDAC activity. Following S1P generation, SPL degrades it into phosphor-ethanolamine and hexadecenal, or it is exported out of the cell by Spns2 and ABC, acting on extracellular S1PRs via autocrine or paracrine mechanisms. By binding to different receptors, S1P regulates numerous physiological and pathological processes. '→' represents 'activation'; '—l' represents 'inhibition'.S1P, sphingosine-1-phosphate; Sph, sphingosine; SphK1, sphingosine kinase 1; SphK2 sphingosine kinase 2; HDAC, histone deacetylase; S1PRs, sphingosine-1-phosphate receptors; Spns2, spinster homolog 2; ABC, ATP-binding cassette.

recent years, attention on the role of S1P in fibrotic diseases has steadily increased. Accumulating evidence indicates that S1P plays a central pro-fibrotic role in the fibrosis of multiple tissues and organs, including the lung, liver and kidney (33-35). The SphK1/S1P/S1PRs signaling axis has been identified as a critical pathway mediating pathological injury in various diseases, including tissue fibrosis (36), thereby offering important insights for mechanistic studies and therapeutic target discovery in fibrotic diseases.

The dysregulated role of S1P in IPF, a clinically refractory form of pulmonary fibrosis, has been preliminarily established. Clinical study reveals that S1P levels are such as elevated in bronchoalveolar lavage fluid (BALF) and lung tissues from IPF patients compared with healthy controls and its expression correlates inversely with key pulmonary function parameters; specifically, diffusion capacity for carbon monoxide, expiratory volume and lung volumes (37). Investigations using clinical specimens and animal models further confirm that S1P concentrations are markedly increased in plasma, lung tissue and BALF from pulmonary fibrosis patients and bleomycin-induced mice, with this upregulation closely linked to the severity of lung function impairment. Notably, SphK1

expression is also upregulated in fibrotic lungs; selective silencing of SphK1 not only effectively reduces endogenous S1P levels but also such as attenuates the severity of bleomycin-induced pulmonary fibrosis and decreases mortality in mice (38).

Although current studies suggest a potential pivotal role for S1P in the pathogenesis of pulmonary fibrosis, the precise molecular mechanism through which S1P regulates fibrotic progression remains incompletely understood. The present reviewsynthesizedrecent advances in the understanding of S1P in IPF development, to provide a theoretical foundation for further elucidating the pathological mechanisms of pulmonary fibrosis and facilitating the development of targeted therapeutic strategies (Fig. 2; Table I).

Inflammation. Inflammation is a critical defense mechanism for maintaining organismal homeostasis, primarily functioning to eliminate harmful stimuli and initiate tissue repair. The classical inflammatory response comprises four core components: The inflammatory trigger, the corresponding receptor, the release of inflammatory mediators and the resulting response in target tissues (39). Under physiological conditions,the inflammatory response is rapidly activated upon tissue injury to initiate repair.However, if dysregulated and sustained, it can progress into a chronic state, thereby promoting the development of various chronic inflammatory diseases (40). At the molecular level, immune cells secrete multiple pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6 and tumor necrosis factor-alpha (TNF-α), upon inflammatory initiation. These cytokines regulate the expression and function of inflammation-related genes by binding to receptors on target cells and activating multiple intracellular signaling pathways, including nuclear factor κB (NF-κB) (41,42). A distinct phase transition in inflammation occurs during pulmonary fibrosis progression, characterized by a persistent inflammatory response and abnormal fibrous tissue proliferation. This phase features the substantial release of various inflammatory factors and chemokines, which damage alveolar epithelial and endothelial cells. The resulting increase in vascular permeability triggers extensive exudation of inflammatory mediators (43). These mediators further amplify the local inflammatory response and activate the inflammatory cascade, ultimately stimulating the excessive proliferation of fibroblasts and myofibroblasts. This leads to disproportionate ECM deposition, thereby disrupting alveolar architecture and normal physiological functions (44).

S1P is a key regulator of inflammatory responses and exhibits context-dependent bidirectional effects, exerting either pro-inflammatory or anti-inflammatory actions depending on specific S1PR binding profiles and the tissue environment. This dual nature has made S1P a central focus in research on various inflammation-related diseases (45-47). Increased vascular permeability is a critical early step in inflammation. Restoring S1P-S1PR1 signaling enhances vascular barrier integrity, limiting the extravasation of inflammatory cells and cytokines and thereby attenuates tissue inflammation and injury in pulmonary fibrosis. Therefore, modulating vascular permeabilityrepresents a promising therapeutic strategy for treating and halting pulmonary fibrosis progression. Among S1PRs, S1PR1 is the predominant receptor expressed on pulmonary endothelial cells. Studies show that S1PR1-knockout mice display severe impairment of the pulmonary endothelial barriers, which aggravates pulmonary fibrosis. Conversely, augmenting S1PR1 expression restores endothelial tight junctions, suppresses inflammatory cell infiltration andmarkedly reduces collagen deposition. Mechanistically, S1PR1 activation inhibits transforming growth factor-β1 (TGF-β1)-mediated activation of Smad 2/3 and Ras homolog family member A (RhoA)/Rho-associated coiled-coil containing protein kinase 1 (ROCK1) signaling pathways, thereby preserving pulmonary vascular endothelial barrier integrity and limiting fibrotic progression (48). Another study further indicates that the loss of S1PR1 expression and function after acute injury impedes tissue repair, ultimately promoting chronic inflammation and fibrosis (49), underscoring the protective role of S1PR1 in maintaining lung tissue integrity. S1P also modulates fibrotic processes by regulating inflammatory effector cells such as macrophages. For example, S1P can promote the synthesis of pro-inflammatory and pro-fibrotic mediators, including IL-1β and TGF-β (50). In bleomycin-induced pulmonary fibrosis models, macrophages show elevated S1PR3 expression. Knockdown of S1PR3 inhibits M2-type macrophage polarization via the PI3K/Akt-signal transducer and activator of transcription 3 (STAT3) pathway. Since M2 macrophages secrete various growth factors and cytokines such as TGF-β, which stimulate fibroblast proliferation and collagen synthesis, reduced M2 polarization alleviates pulmonary fibrosis (51). The dual pro- and anti-inflammatory roles of S1P highlight its complex regulation in pulmonary fibrosis. Sobel *et al* (52) found that in pulmonary fibroblasts, S1P receptor agonists activate Smad-independent PI3K/Akt and ERK1/2 pathways via S1PR2/S1PR3, stimulating extracellular matrix synthesis and exerting a pro-fibrotic effect. By contrast, specific knockout of S1PR1 in pulmonary vascular endothelial cells disrupts tight junctions, increases vascular permeability and exacerbates bleomycin-induced pulmonary fibrosis (53), indicating that S1P actions depend on cell type and receptor subtype. Furthermore, S1P concentration and exposure duration critically shape its effects. At low concentrations (<1 μM or 85 μg/kg), S1P protects the endothelium from inflammatory damage, whereas high levels (>5-10 μM) can disrupt the endothelial barrier *in vitro*, probably via S1PRs other than S1PR1 (54). Similarly, short-term administration of S1P1 agonists prevents vascular leakage in acute lung injury models, but prolonged exposure leads to functional antagonism at S1PR1 and worsens post-injury vascular leakage (55). These findings underscore that the influence of S1P on pulmonary inflammation is both concentration- and time-dependent.

The NF-κB signaling pathway constitutes a key target through which S1P mediates cross-regulation between inflammation and fibrosis. In a cigarette smoke-induced mouse model of chronic obstructive pulmonary disease, deletion of SphK2 reduced S1P production, enhanced cystic fibrosis transmembrane conductance regulator activity and indirectly suppressed the expression and nuclear translocation of NF-κBsubunit p65 (56). Together, these changes alleviated small airway fibrosis and inflammatory responses. Moreover, S1P can promote the priming and activation of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome. In a liver fibrosis model, S1P activated the NLRP3 inflammasome in a

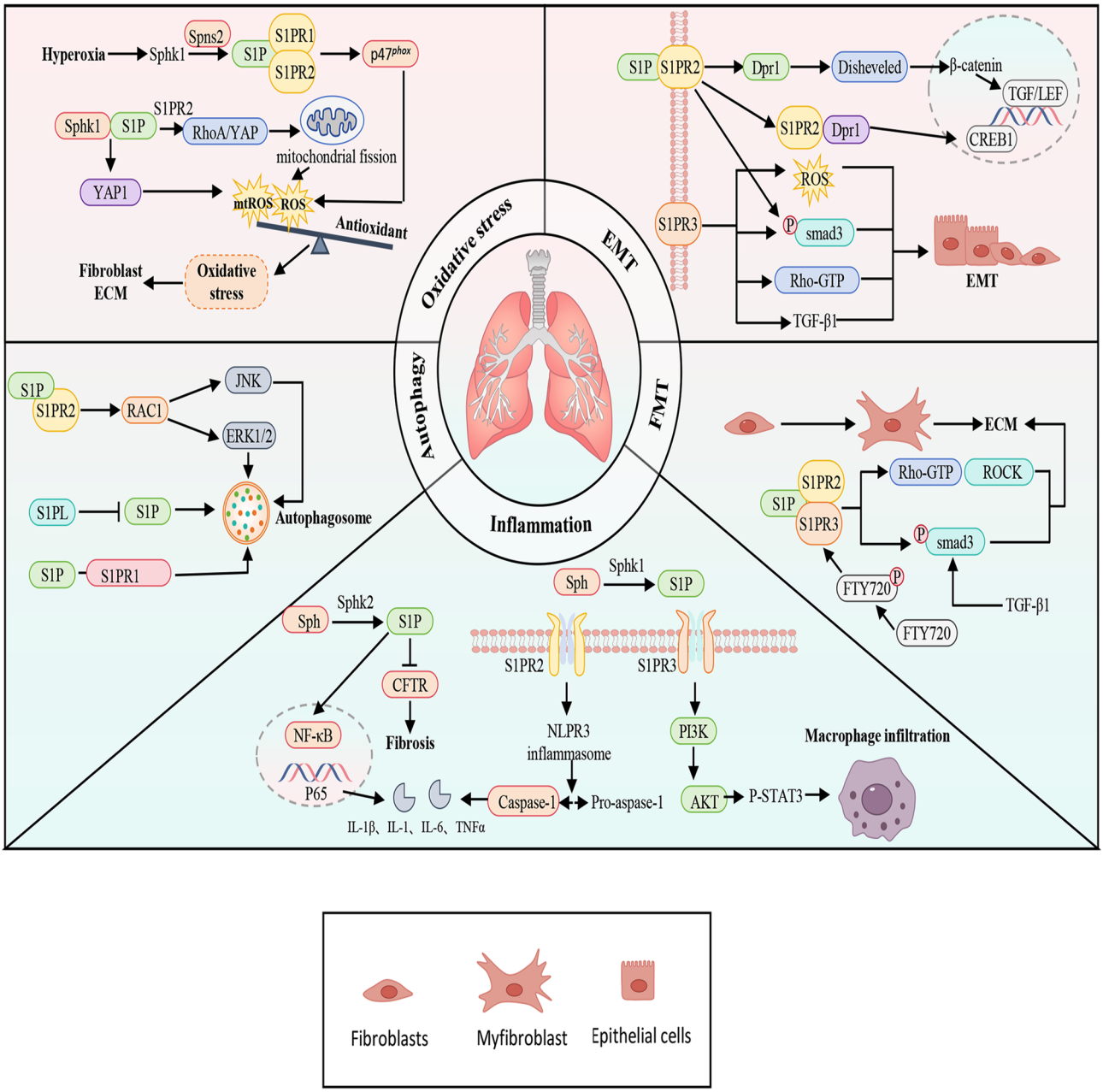

Figure 2. Mechanisms of S1P in Pulmonary Fibrosis. S1P drives the progression of pulmonary fibrosis by regulating multiple key pathological processes, including inflammatory responses, FMT, EMT, autophagy and oxidative stress. '→' represents 'activation'; '—|' represents 'inhibition'. S1P, Sph1-phosphate; Sph, sphingosine; SphK1, Sph kinase 1; CFTR, cystic fibrosis transmembrane conductance regulator; NF-κB, nuclear factor κB; NLRP3, NOD-like receptor family pyrin domain-containing 3; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor α; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; STAT3, signal transducer and activator of transcription 3; FMT, fibroblast-to-myofibroblast transition; ECM, extracellular matrix; ROCK1, Rho-associated coiled-coil containing protein kinase ; TGF-β1, transforming growth factor-beta 1; EMT, epithelial-to-mesenchymal transition; Dpr1, Dapper1; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; CREB1, cyclic AMP-responsive element-binding protein 1; ROS, reactive oxygen species; mtROS, Mitochondrial reactive oxygen species: JNK, c-Jun N-terminal kinase; RhoA, Ras homolog family member A; YAP, Yes-associated protein.

concentration-dependent manner and stimulated the secretion of IL-1β and IL-18. By contrast, specific knockdown of S1PR2 markedly inhibited NLRP3 inflammasome activation, thereby delaying hepatic inflammation and fibrosis progression (57), suggesting that the S1P-NLRP3 axis may play a similar pro-inflammatory role in pulmonary fibrosis. In summary, by engaging receptors such as S1PR1/2/3, S1P activates critical signaling pathways including PI3K/Akt-STAT3, NF-κB and the NLRP3 inflammasome. These pathways modulate the secretion of pro-inflammatory mediators and the infiltration of inflammatory cells, thereby driving fibrotic progression. Different S1PRs mediate distinct downstream cascades, eliciting varied cellular responses at the tissue level; together, these integrated effects ultimately shape the pathological outcome of fibrosis. Importantly, the seemingly contradictory profibrotic and antifibrotic effects of S1P reported across different experimental models can be explained by differences in target cell types, S1P receptor subtype specificity, ligand concentration and disease stage or exposure timing and therefore do not represent true inconsistencies.

Table I. List of molecular mechanism of S1P regulating pulmonary fibrosis.

First author/s, year	Phenotype	Molecular	Target	Experimental model	(Refs.)
Xiong *et al*, 2023	Inflammation	S1PR1	Smad2 Smad3 RhoA/ROCK1	Mice HPMECs	(48)
Qiu *et al*, 2024		S1PR3	PI3K/Akt-	Mice, Mouse	(51)
Chen *et al*, 2023		SphK2	STAT3 CFTR, NF-κB-p65	BMDMs Mice, -	(56)
Urata *et al*, 2005	FMT	S1PR2/3	RhoA/ROCK	Mice, WI-38	(64)
Sobel *et al*, 2013, Keller *et al*, 2007		S1PR2/3	Smad3	Mice, Human lung fibroblasts	(52,67)
Milara *et al*, 2012	EMT	S1PR2/3	Smad3, RhoA-GTP	-, ATII, A549	(37)
Mu *et al*, 2025		S1PR2	Dpr1, CREB1	Mice, BEAS-2B, A549	(74)
Huang and Natarajan, 2015	Autophagy	S1PL	-	Mice, Human lung fibroblasts	(82)
Goel *et al*, 2021		S1PR1	-	Mice, HLMVECs	(83)
Liu *et al*, 2021		S1PR2	RAC1/JNK, RAC1/ERK1/2	Mice, MLE-12	(84)
Milara *et al*, 2012	Oxidative stress	S1PR2/3	RhoA-GTP	-, ATII, A549	(37)
Harijith *et al*, 2016		SphK1	p47phox	Mice, HLMVECs	(95)
Zhou *et al*, 2023		S1PR2	RhoA/YAP Fis1, Drp1	Mice, MLE-12	(96)
Huang *et al*, 2020		SphK1	Hippo/YAP	Mice, Mouse primary fibroblasts	(98)

Sph, sphingosine; S1P, Sph1-phosphate; SMAD2, SMAD family member 2; HPMECs, human pulmonary microvascular endothelial cells; RhoA/ROCK1, Ras homolog family member A/Rho-associated coiled-coil containing protein kinase 1; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; STAT3, signal transducer and activator of transcription 3; BMDMs, bone marrow-derived macrophages; CFTR, cystic fibrosis transmembrane conductance regulator; NF-κB, nuclear factor κB; FMT, fibroblast-to-myofibroblast transition; WI-38, human lung fibroblast cell line; EMT, epithelial-to-mesenchymal transition; BEAS-2B, human bronchial epithelial cell line; A549, human lung adenocarcinoma epithelial cell line; Dpr1, Dapper1; CREB1, cyclic AMP-responsive element binding protein 1; S1PL, S1P lyase; RAC1, Ras-related C3 botulinum toxin substrate 1; JNK, c-Jun N-terminal kinase; ERK1/2, extracellular signal-regulated kinase 1/2; HUVECs, human umbilical vein endothelial cells; MLE-12, type 2 alveolar epithelial cells; ATII, human alveolar type II cells; SphK1, Sph kinase 1; p47phox, neutrophil cytosolic factor 1; HLMVECs, human lung microvascular endothelial cells; YAP, Yes associated protein; Fis1, fission 1; Drp1, dynamin-related protein 1; RhoA-GTP, GTP-bound Ras homolog family member A.

FMT. FMTrepresents a central pathological event in pulmonary fibrosis development. Under the synergistic influence of inflammatory factors and growth factors, fibroblasts initiate a phenotypic transformation program and differentiate into myofibroblasts, which in turn drive aberrant synthesis and deposition of ECM (58,59). It is now widely accepted that FMT constitutes the primary route for myofibroblast accumulation in lung tissue; The canonical myofibroblast marker α-smooth muscle actin (α-SMA) is routinely used to distinguish these cells from untransformed fibroblasts (60,61). As the main effector cells responsible for excessive ECM deposition, myofibroblasts can be activated across diverse pathological microenvironments, making FMT a key therapeutic target in anti-fibrotic interventions (62).

In recent years, the regulatory role of S1P in FMT has attracted increasing research attention, with multiple studies confirming its involvement through diverse molecular mechanisms (63). Specifically, S1P can selectively bind to S1PR2 and S1PR3 on the cell membrane, triggering Rho-GTPase-mediated signaling (64). This initiates a Rho-kinase-mediated cascade that ultimately alters lung fibroblast morphology and function, conferring myofibroblast-like characteristics. Evidence indicates that S1P induces fibroblasts to adopt a myofibroblast phenotype via trans-activation of the TGF-β1 signaling

pathway, wherein SphK1 serves as a molecular bridge linking TGF-β1 and S1P signaling (65). One study showed that TGF-β1 stimulation markedly upregulates SphK1 expression in lung fibroblasts; activated SphK1 then translocates from the cytoplasm to the plasma membrane, where it catalyzes sphingosine phosphorylation to generate S1P. The newly synthesized S1P binds to S1PR2 and S1PR3, activates Rho/Rho kinase pathways and accelerates fibroblast-to-myofibroblast differentiation (66). Furthermore, studies on fingolimod (FTY720) support S1P's role in regulating FMT. FTY720 is phosphorylated intracellularly to its active form FTY720-P, which binds to S1PR2/S1PR3, activates the downstream Smad3 signaling pathway andultimately induces FMT (52,67,68). Notably, the Smad3 pathway operates as a downstream branch of S1P receptors, parallel to the aforementioned Rho kinase pathway, with both being regulated by upstream TGF-β1 signals. Collectively, the S1P signaling axis regulates FMT, which subsequently contributes to the pathological progression of pulmonary fibrosis.

Epithelial-to-mesenchymal transition (EMT). EMTis a pivotal process in tissue repair and a critical mechanism in the pathogenesis of pulmonary fibrosis. As a reversible biological process, EMT involves the loss of epithelial polarity and the acquisition of a mesenchymal phenotype. This transition is characterized by downregulation of epithelial markers such as E-cadherin and upregulation of mesenchymal markers, including N-cadherin and vimentin (69,70). EMT has been consistently observed in lung tissues, both *in vitro* using lung epithelial cell models and *in vivo* in animal studies (71). Notably, S1P levels show a significant positive correlation with EMT in pulmonary fibrosis (72,73), suggesting that S1P may contribute to fibrosis by modulating EMT. *In vitro* experiments conducted by Milara *et al* (37) using A549 cells demonstrated that S1P drives EMT primarily through its specific receptors S1PR2 and S1PR3. Receptor activation triggers multiple downstream signaling events, including SMAD3 phosphorylation, RhoA-GTP activation, increased oxidative stress and elevated production and release of TGF-β1. The same study further indicated that TGF-β1-induced EMT was partly mediated via the S1P/SPHK1 axis, pointing to functional crosstalk between the TGF-β1 signaling pathway and the S1P/SPHK1 axis. This crosstalk mechanism indicates that S1P not only directly induces EMT, but also further amplifies the pro-fibrotic effects of TGF-β1 itself by promoting its release. In another study, stimulation of A549 cells with either TGF-β or S1P induced similar fibroblast-like morphological changes, accompanied by increased expression of the mesenchymal marker cluster of differentiation 90 and decreased expression of the epithelial marker epithelial cell adhesion molecule. Immunofluorescence confirmed EMT induction, implying that S1P and TGF-β exert comparable effects in this process. Importantly, treatment with the TGF-β receptor inhibitor LY2109761, namely the antagonists of TGF-β Type I and Type II, markedly attenuated S1P-induced EMT, suggesting that S1P-dependent EMT requires TGF-β signaling downstream (72). These findings collectively indicate that targeting the S1P/TGF-β axis may offer a promising therapeutic strategy for EMT-associated pulmonary fibrosis. Further elucidating the mechanism, Mu *et al* (74) reported that S1PR2 agonists strongly promote EMT in human bronchial epithelial cells. S1PR2 appears to modulate EMT through two parallel pathways: i) By interacting with Dapper1 (Dpr1) to inhibit Dishevelled degradation, leading to β-catenin nuclear accumulation and activation of T-cell factor/lymphoid enhancer-binding factor-dependent transcription of EMT-related genes; and ii) by forming and S1PR2-Dpr1 complex that translocates to the nucleus and binds to and activates cyclic AMP-responsive element-binding protein 1, thereby enhancing the expression of EMT-associated transcription factors (74). Although this mechanism has been established *in vitro*, its relevance *in vivo*, particularly its clinical implications, requires further investigation. In summary, current evidence supports the hypothesisthat S1P contributes to the pathological progression of pulmonary fibrosis, at least in part, through the regulation of EMT.

Autophagy. Autophagy is a highly conserved catabolic process in eukaryotic cells, primarily involving the lysosome-mediated degradation of abnormal proteins, damaged organelles and other dysfunctional cellular components, thereby maintaining intracellular homeostasis (75). S1P and its receptors are known to interfere with multiple stages of autophagy, including initiation, nucleation, elongation, maturation, membrane fusion and substrate degradation and ultimately modulate autophagic activity through various signaling and metabolic pathways (76).

As research on the pathogenesis of pulmonary fibrosis advances, dysregulated autophagy has been recognized as one of its key pathological features (77). In the fibrotic lung microenvironment, autophagic activity is typically suppressed. This is evidenced by decreased expression of autophagic markers LC3 and Beclin-1, alongside a significant reduction in autophagosome numbers observed by transmission electron microscopy (78). Such inhibition of autophagy can accelerate pulmonary fibrosis by aggravating alveolar epithelial cell injury, promoting myofibroblast activation and enhancing abnormal ECM deposition (79,80).

Emerging evidence indicates that S1P-mediated regulation of autophagy represents a critical pathway in fibrogenesis (81). S1PL is a central enzyme controlling S1P synthesis and degradation. Notably, S1PL expression is upregulated in lung tissues from patients with IPF and in bleomycin-induced pulmonary fibrosis models. Mechanistically, S1PL overexpression enhances autophagy by increasing LC3 and Beclin-1 expression while reducing TGF-β-induced intracellular S1P accumulation in lung fibroblasts. Conversely, S1PL knockdown exacerbates bleomycin-induced pulmonary fibrosis in mice. These findings collectively suggest that enhancing S1PL activity to downregulate S1P signaling may offer a therapeutic strategy for pulmonary fibrosis (82). Further supporting this hypothesis, studies in human lung microvascular endothelial cells from smokers showed reduced expression of both S1PR1 and autophagy-related proteins. Knockdown of S1PL elevates intracellular S1P levels and promotes autophagy, whereas inhibition of S1PR1 suppresses autophagic activity (83). Together, these results highlight S1PR1 as a key nodal molecule in S1P-mediated regulation of autophagy.

However, the role of S1P in autophagy is not unidirectional. Although most evidence suggests that S1P promotes

disease progression by suppressing autophagy, it can also exert opposite effects in specific contexts. In a murine asthma model (84), S1P binding to S1PR2 was found to activate autophagy, whereas S1PR2 antagonism suppressed autophagic activity in lung tissue. This inhibitory effect could be reversed by a Ras-related C3 botulinum toxin substrate 1 (RAC1) inhibitor. Furthermore, alterations in c-Jun N-terminal kinase (JNK) and ERK1/2 pathway activity was associatedwith changes in autophagy-related protein levels, indicating that the S1P-S1PR2 axis activates downstream JNK and ERK1/2 pathways via RAC1 stimulation, thereby promoting autophagy (84). Thus, the bidirectional regulation of autophagy by S1P likely depends on receptor subtypes, target cell types and the specific tissue microenvironment. For instance, in lung microvascular endothelial cells from chronic smokers, decreased S1PR1 expression positively correlated with reduced levels of autophagic markers. suggesting that S1P1 downregulation inhibits the autophagy pathway. Knockdown of S1PR1 suppressed S1P-induced autophagy, suggesting that S1P-mediated positive regulation of autophagy requires S1PR1 (83). In pulmonary epithelial cells, S1P/S1PR3 signaling has been shown to help prevent sepsis by activating the ERK1/2 and p38 pathways; a mechanism thought to restrain excessive autophagy and thereby preserve pulmonary epithelial barrier integrity (85). The precise molecular mechanisms through which S1P regulates autophagy in pulmonary fibrosis remain incompletely understood and warrant further targeted investigation.

Overall, these observations suggest that the apparently bidirectional effects of S1P on autophagy arise from context-dependent S1PR signaling, particularly differences in receptor subtype engagement, target cell identity and local pulmonary microenvironment, rather than true inconsistencies among studies.

Oxidative stress. Oxidative stress plays a critical role in the pathogenesis of pulmonary fibrosis and correlates strongly with disease severity. Reactive oxygen species (ROS) serve as the central effector molecules driving fibrosis-related cytopathological events (86). Oxidative stress occurs when ROS production exceeds the capacity of the endogenous antioxidant defense system. This oxidation-antioxidation imbalance leads to cellular structural and functional abnormalities. In mammalian cells, ROS are primarily generated through cellular oxidative metabolism, with the NADPH oxidase (NOX) family and mitochondria constituting the two major sources (87). Elevated ROS levels directly damage alveolar epithelial cells and compromise alveolar barrier integrity. Moreover, ROS act as signaling molecules that trigger FMT and ECM deposition (88,89). Clinical evidence further supports the involvement of oxidative stress in IPF. Markers of oxidative stress are markedly elevated in exhaled breath condensate, bronchoalveolar lavage fluid and diseased lung tissue from IPF patients, directly linking oxidative stress to IPF pathogenesis (90,91).

S1P modulates oxidative stress through multiple molecular mechanisms, thereby acting as a key signaling node linking redox imbalance to pulmonary fibrosis. Studies have shown that oxidative stress signals can activate SphK1, leading to increased intracellular S1P levels and establishing a positive feedback loop termed the 'oxidative stress-SphK1-S1P' axis (92-94). Evidence from a hyperoxia-induced lung injury model demonstrates that S1P regulates NOX-mediated ROS generation. Hyperoxia markedly upregulates SphK1 expression in lung tissue, thereby elevating S1P production. Mechanistically, S1P is exported via the Spns2 transporter and subsequently activates endothelial S1PR1/2. This receptor activation modulates the activity of the NOX subunit p47phox, driving substantial ROS production. Notably, SphK1 knockout such as reduced ROS levels and attenuated lung injury (95). At the receptor level, Zhou *et al* (96) reported that knockdown of S1pr2 inhibits S1P binding of S1P to S1PR2, thereby regulating the RHOA/YAP pathway. This in turn influences the expression of downstream mediators such as connective tissue growth factor and cysteine-rich angiogenic inducer 61 and remodels mitochondrial dynamics by promoting mitochondrial fusion and mitofusin expression while suppressing fission. Concomitantly, it downregulates phosphorylation of fission 1 and dynamin-related protein 1, reduces mitochondrial ROS production and alleviates pulmonary fibrosis.

The production of mitochondrial ROS (mtROS) is a critical contributor to pulmonary fibrosis (97). SphK1/S1P regulation of mtROS has been shown to involve the Hippo signaling pathway. Specifically, S1P activates the transcriptional co-activator YAP1, which undergoes dephosphorylation and nuclear translocation, directly initiating transcription of genes involved in mtROS synthesis and leading to mtROS overproduction. Inhibition of SphK1 attenuated YAP1 nuclear translocation and mtROS generation (98). Furthermore, ROS accumulation can amplify fibrotic responses via crosstalk with the TGF-β1 pathway. Milara *et al* (37) demonstrated that S1P directly promotes ROS production through S1PR2/3 activation. The elevated ROS then further stimulates TGF-β1 signaling, ultimately inducing EMT and driving fibrosis. In summary, S1P contributes to pulmonary fibrosis by regulating NOX-derived and mitochondrial ROS production and by participating in ROS-TGF-β1 crosstalk. These mechanisms provide new insights into the central role of S1P in fibrotic pathogenesis. Notably, most mechanistic insights into S1P-mediated regulation of oxidative stress in pulmonary fibrosis are derived from animal models and *in vitro* experiments; therefore, their relevance to human pulmonary fibrosis requires further clinical validation.

4. Therapeutic strategies for targeting S1P in pulmonary fibrosis

Given the established role of S1P-related signaling as a potential therapeutic target, the development of specific inhibitors has become a major focus in pharmacological and pharmaceutical research. A variety of natural and synthetic compounds have been shown to modulate S1P. Among these, the polyphenolic flavonoid quercetin is considered one of the most potent SphK1 inhibitors. Zhang *et al* (99) reported that quercetin blocks S1P-mediated pro-fibrotic signaling by inhibiting SphK1 expression. Conversely, upregulation of SphK1 attenuates quercetin's anti-fibrotic effects, further confirming that its action depends on the SphK1/S1P axis. Myricetin targets serine palmitoyltransferase to inhibit de novo sphingolipid biosynthesis and suppresses SphK1

activation, thereby alleviating radiation-induced pulmonary fibrosis (100). Moreover, fenugreek alkaloid (trigonelline), a natural plant-derived alkaloid with diverse pharmacological properties, reduces SphK1 activity and S1P production, blocks phosphorylation and nuclear translocation of YAP/transcriptional coactivator with PDZ-binding motif (TAZ) in the Hippo signaling pathway and consequently suppresses cell proliferation and matrix deposition, ultimately mitigating pulmonary fibrosis (101).

In a similar vein, Huang *et al* (98) observed that PF543 inhibits SphK1 activation and thereby prevents nuclear translocation of YAP1. This reduces co-localization between YAP1 and ferroptosis suppressor protein 1in fibroblasts, attenuates fibroblast activation and alleviates pulmonary fibrosis. Notably, the SphK1 inhibitor (SKI-349) suppresses SphK1 activity, downregulates S1P levels and attenuates fibroblast aggregation and neutrophil infiltration, leading to amelioration of pulmonary fibrosis (102). Additionally, the S1PR1 agonist IMMH002 helps maintain endothelial barrier integrity, thereby reducing inflammatory responses and collagen accumulation, which effectively mitigates fibrotic progression (49). Inhibitors targeting S1PR2 (such as GLPG2938, S118, JTE-013) and S1PR3 (such as TY-52156, CAY10444) can modulate inflammatory responses and EMT by antagonizing their respective receptors, thus intervening in pulmonary fibrosis development (53,74,96,103). Collectively, these studies provide experimental support for developing combined therapeutic regimens that pair S1P-pathway inhibitors with anti-fibrotic natural products (Table II). Although the pathogenic role of S1P in pulmonary fibrosis is well documented, a key translational challenge remains: how to precisely harness its regulatory potential and tune its activity to achieve optimal therapeutic outcomes.

A comprehensive understanding of the upstream regulatory mechanisms governing S1P is critical for elucidating its roles in physiological and pathological contexts, as well as for developing targeted therapeutic strategies. S1P expression is regulated at multiple levels, with microRNAs (miRNAs) emerging as important modulators. Dysregulation of specific miRNAs can offer valuable insights into diseases associated with aberrant S1P signaling. For example, miR124, miR125b, miR133b and miR130a can downregulate key components of the S1P pathway, including SphK1, SGPL1, S1PR1 and S1PR2, by directly targeting their respective genes (104). In cancer, miR-495-3p inhibits tumor proliferation by acting on SphK1 (105); similarly, miR-92a (106), miR302-367 (107) and miR363 (108) have been shown to target and suppress S1PR1 expression; while miR-148a targets S1PR1 to suppress hepatocyte metastasis (109). These miRNA-mediated regulations not only affect the transcription and translation of S1P-associated molecules but also modulate their functions in metabolism, inflammation and fibrosis. Further investigation of these mechanisms will provide a stronger theoretical foundation for developing targeted S1P therapies and enhance their translational potential.

5. Clinical application of S1P signaling

Given the critical involvement of the SphK-S1P signaling axis in various diseases, SphK inhibitors and S1P receptor antagonists represent promising therapeutic candidates for pulmonary fibrosis. A review of clinical trial databases, including PubMed, ClinicalTrials.gov andthe WHO international clinical trials registry platform, reveals that most registered trials targeting S1P have focused on neurological autoimmune and inflammatory conditions; particularly multiple sclerosis (MS), ulcerative colitis and Crohn's disease. Nevertheless, modulators of S1P receptors have achieved notable clinical success, with several agents already approved and in clinical use. FTY720 (fingolimod) stands out as the first approved non-selective S1P receptor modulator for multiple sclerosis treatment. It is a structural analogue of endogenous S1P that, after oral administration, is phosphorylated *in vivo* to FTY720 phosphate. This active metabolite acts as an agonist at S1PR1, S1PR3, S1PR4 and S1PR5 but exhibits low affinity for S1PR2. Its binding to S1PR1 induces receptor internalization and degradation, resulting in functional antagonism that inhibits lymphocyte egress and attenuates inflammatory responses (110). Phase III trial demonstrated that FTY720 markedly reduces the annualized relapse rate and delays disability progression in patients with MS (111,112). Due to its S1PR1-targeted activity, FTY720 has also been explored as a potential therapeutic for IPF. Preclinical studies indicate its ability to ameliorate fibrosis in cardiac, renal and hepatic tissues (113-115). Though limited to animal model studies, findings regarding its effect on pulmonary fibrosis are conflicting. One study indicated that FTY720 reduces pulmonary fibrosis by inhibiting the TGF-β1/TGF-β-activated kinase 1/P38MAPK pathway and promoting autophagy (116). Conversely, long-term administration of FTY720 was shown to exacerbate bleomycin-induced pulmonary fibrosis and vascular leakage in mice andthe effect is potentially mediated through S1PR3 activation (55). This discrepancy appears to be dose- and regimen-dependent. Short-term, low-dose FTY720 predominantly activates S1PR1, thereby enhancing endothelial barrier function and attenuating pulmonary edema and fibrosis (117). By contrast, prolonged or high-dose exposure leads to S1PR1 desensitization, shifting the dominant signaling toward the S1PR3-mediated pathway (118). This latter promotes vascular permeability, inflammatory cell infiltration and fibrotic responses. Thus, the net effects of FTY720 in pulmonary fibrosis depend critically on the dosing strategy and the resulting receptor-activation profile. Taken together, the divergent effects of FTY720 on pulmonary fibrosis are best explained by dose- and duration-dependent shifts in S1PR signaling, particularly the balance between S1PR1 and S1PR3, rather than indicating genuine disagreement in the literature.

MS serves as a prototypical autoimmune disorder, characterized by T cell-driven aberrant immune attacks (119). FTY720 achieves its therapeutic effect in MS primarily by modulating lymphocyte trafficking, thereby inhibiting immune cell infiltration into the central nervous system (110). However, it also induces a pronounced reduction in peripheral CD4+ T cells, which may exacerbate immunosuppression (120), a potentially serious risk for patients with pre-existing immune compromise or chronic infections. By contrast, IPF is not solely an immune-mediated condition. Beyond its immunomodulatory properties, the clinical use of FTY720 in IPF is complicated by the patient population profile: IPF predominantly affects middle-aged and elderly

Table II. List of the therapeutic effects of S1P pathway-targeting drugs in pulmonary fibrosis.

First author/s, year	Compound	Target	Mechanism of action	Therapeutic effect	(Refs.)
Hao *et al*, 2023	IMMH002	S1PR1	Activate S1PR1 to protect the integrity of the endothelial barrier	Reducing inflammatory responses and collagen deposition to improve pulmonary fibrosis	(49)
Qiu *et al*, 2024	TY-52156 CAY10444	S1PR3	Antagonizes S1PR3, inhibiting activation of the PI3K/AKT-STAT3 signaling pathway	Reducing TGF-β1 release, decrease collagen deposition	(51)
Mu *et al*, 2025	S118	S1PR2	Inhibits binding to Dpr1, reduces β-catenin accumulation, and blocks nuclear translocation of the S1PR2	Suppressing inflammatory responses and EMT formation	(74)
Zhou *et al*, 2023	JTE-013	S1PR2	Antagonizes S1PR2, inhibits mitochondrial membrane potential elevation, reactive oxygen species production, and apoptosis, and suppresses the expression of collagen	Reducinglung inflammation and fibrosis	(96)
Huang *et al*, 2020	PF543	SphK1	Inhibiting SphK1 suppresses YAP1 nuclear translocation, reduces mtROS, and decreases the expression of fibronectin and α-SMA.	Reducing the colocalization of YAP1 and FSP1 in fibroblasts, thereby decreasing fibroblast activation	(98)
Zhang *et al*, 2018	Quercetin	SphK1	Inhibition of SphK1/S1P signaling	Reducing collagen deposition	(99)
Gorshkova *et al*, 2012	Myristicin	SphK1	Inhibition of SphK1 activation	Alleviating radiation-induced pulmonary fibrosis	(100)
Zeyada *et al*, 2024	Fenugreek alkaloid	SphK1	Reducing SphK1 activity decreases S1P production, thereby inhibiting the phosphorylation and nuclear translocation of YAP/TAZ	Inhibiting cell proliferation and matrix deposition alleviates pulmonary fibrosis	(101)
Lu *et al*, 2025	SKI-349	SphK1	Inhibit SphK1 to downregulate S1P expression	Reducingfibroblast accumulation and neutrophil infiltration	(102)
Mammoliti *et al*, 2021	GLPG2938	S1PR2	Antagonizes S1PR2, preventing S1P from interacting with its receptor	Reducing inflammatory response and mitigate lung tissue damage	(103)

Sph, sphingosine; SphK1, Sph kinase 1; S1P, Sph1-phosphate; YAP, Yes associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; FSP1, ferroptosis suppressor protein 1; Dpr1, Dapper1; EMT, epithelial-to-mesenchymal transition; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; STAT3, signal transducer and activator of transcription 3; S1PR, S1P receptor; TGF-β1, transforming growth factor-β1.

individuals, who often have cardiovascular comorbidities (such as hypertension, coronary heart disease) and exhibit pulmonary vascular remodeling and right ventricular dysfunction (121,122). These factors may amplify the risk of adverse reactions to S1P-targeting agents. FTY720 is known to induce bradycardia (123), which could worsen pre-existing cardiac output limitations in IPF patients and thereby trigger or aggravate dyspnea. Consequently, despite its potential anti-fibrotic

benefits, the clinical translation of FTY720 for IPF remains markedly constrained by cardiovascular safety concerns.

Second-generation selective S1PR modulators, such as siponimod, ozanimod and ponesimod, have been developed to improve safety profiles while maintaining therapeutic efficacy through optimized receptor selectivity (124,125). Ozanimod acts as a potent agonist of S1PR1 and S1PR5; siponimod is an antagonist of both receptors; and ponesimod functions as a selective S1PR1 antagonist (126). Ozanimod is clinically approved for reducing immune-mediated inflammation in MS andmoderate-to-severe ulcerative colitis (127) and is under investigation for Crohn's disease (128), systemic lupus erythematosus (129) and coronavirus disease 2019 (COVID-19) (130). In an *in vitro* study using TGF-β1-stimulated human lung fibroblasts to investigate S1PR agonist-mediated fibrotic responses, ponesimod induced less extracellular matrix synthesis than FTY720, likely due to its weaker activation of S1PR3. This suggests that receptor-specific modulators such as ozanimod, siponimod and ponesimod may offer a therapeutic advantage over FTY720 in pulmonary fibrosis. Nevertheless, these agents also carry risks. Although higher receptor selectivity may reduce cardiovascular side effects, ozanimod is associated with potential hepatotoxicity, mainly reflected in elevated transaminases (131); a particular concern for IPF patients who may have concurrent liver impairment (132). Moreover, in clinical trials for colitis and MS, ozanimod administration was linked to measurable declines in lung function (133). Consequently, caution should be exercised when prescribing ozanimod to patients with severe respiratory disorders or pulmonary fibrosis. Similarly, siponimod and ponesimod have been reported to reduce forced expiratory volume in early-stage MS trials (134), which could further burden respiration in IPF patients. Therefore, future clinical applications must involve careful patient stratification based on cardiovascular and hepatic function, as well as concurrent medications. Priority should be given to agents with higher receptor selectivity to minimize off-target effects. Throughout treatment, rigorous monitoring of heart rate, cardiac and hepatic function and pulmonary parameters is essential to ensure patient safety.

Several other S1PR1 modulators are currently under clinical investigation, including ceralifimod (ONO-4641), cenerimod (ACT-334441), etrasimod (APD334), amiselimod (MT-1303), VPC01091 and VPC23019a (135). These agents primarily exert immunosuppressive effects through receptor antagonism. Although clinically effective, they are often associated with adverse reactions such as bradycardia and impaired endothelial barrier function. Targeting S1P transport may offer an alternative therapeutic approach. Spns2 transport inhibitors can such as lower extracellular S1P levels by blocking its export. For example, the Spns2 inhibitor (SLF1081851) attenuated inflammation and improved fibrosis in a renal fibrosis model (136). Moreover, the Spns2 inhibitor (SLF80821178) was reported not to induce bradycardia or impair pulmonary endothelial barrier function, while exerting only a mild effect on lymphocytes (95,137). These findings highlight Spns2 as a promising alternative target for pulmonary fibrosis therapy.

To date, only a limited number of inhibitors targeting S1P-metabolic enzymes (such as SphKs and SPL) and S1P receptor agonists/antagonists have been developed, with most studies still confined to preclinical stages. In the future, combination strategies that pair S1P-pathway inhibitors with existing first-line anti-fibrotic agents (such as nintedanib, pirfenidone), natural compounds, signaling-pathway inhibitors (such as NF-κB, YAP/TAZ, ROCK or TGF-β receptor inhibitors), antioxidants, or anti-inflammatory drugs hold considerable promise. Such multi-targeted approaches could overcome the limitations of monotherapy and provide more effective, precise treatment options for pulmonary fibrosis. Importantly, the translation of S1P-based combination therapies into human trials requires careful consideration of drug safety and toxicity, disparities between animal models and human pathophysiology and interindividual variability in treatment responses. Clinical trial designs should therefore account for these potential factors and incorporate rigorous safety and toxicity assessments to minimize potential harm to healthy tissues.

6. Conclusion and outlook

S1P is a bioactive sphingolipid that plays a broad role in fundamental cellular processes, including cell proliferation, differentiation, migration and inflammation. S1P exerts a central pro-fibrotic function in IPF by modulating key pathological pathways such as inflammatory responses, EMT, FMT, autophagy and oxidative stress. Although substantial evidence has elucidated the contribution of S1P to pulmonary fibrosis, translating this knowledge into effective S1P-targeted therapies remains challenging. Several important questions remain unresolved. The cell type-specific functions of different S1P receptor subtypes, as well as their potential interactions, are not fully understood, with S1PR2 and S1PR3 being of special interest. Clarifying these issues will require the generation of cell-specific knockout mouse models to determine how the loss of S1P signaling from distinct cellular compartments affects the development and progression of pulmonary fibrosis. Moreover, the role of S1P export mediated by the transporter Spns2 in lung fibrosis has yet to be elucidated. It remains unclear which cell types are responsible for Spns2-dependent S1P release in the lung and how this transport process contributes to the regulation of the local fibrotic microenvironment. Single-cell transcriptomic approaches could be used to identify Spns2-expressing cell populations, followed by the establishment of cell-type-specific Spns2 knockout mice to further dissect the underlying molecular mechanisms. The present review has summarized the involvement of S1P signaling in pulmonary fibrosis, systematically analyzed its underlying mechanisms and discussed current therapeutic strategies aimed at the S1P pathway and its associated molecules. These insights provide a valuable foundation for identifying novel therapeutic targets and developing new treatment approaches for IPF.

In the future, therapeutic strategies may evolve from single-target modulation toward integrated and multi-pathway interventions that concurrently address several core mechanisms of pulmonary fibrosis. For instance, combining single-cell sequencing with S1P signaling analysis could elucidate its cell-type-specific distribution and activity, thereby revealing precise cellular targets for intervention. Further investigation is warranted to uncover new mechanistic insights and translate them into innovative treatment strategies for S1P-driven pulmonary fibrosis.

Acknowledgements

Not applicable.

Funding

The present review was supported by the Guangxi Science and Technology Base and Talent Project (grant no. Guike AD22035221).

Availability of data and materials

Not applicable.

Authors' contributions

YQ and CT conceived the study and drafted the manuscript. GL and ST provided critical revision and supervised the work. Data authentication is not applicable. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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