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Review

Lipids - two sides of the same coin in lung fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is characterized by progressive extracellular matrix deposition in the lung parenchyma leading to the destruction of lung structure, respiratory failure and premature death. Recent studies revealed that the pathogenesis of IPF is associated with alterations in the synthesis and the activity of lipids, lipid regulating proteins and cell membrane lipid transporters and receptors in different lung cells. Furthermore, deregulated lipid metabolism was found to contribute to the profibrotic phenotypes of lung fibroblasts and alveolar epithelial cells. Consequently, several pharmacological agents, targeting lipids, lipid mediators, and lipoprotein receptors, was successfully tested in the animal models of lung fibrosis and entered early phase clinical trials. In this review, we highlight new therapeutic options to counteract disturbed lipid hemostasis in the maladaptive lung remodeling.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a severe disease characterized by chronic inflammation, myofibroblast accumulation, excessive extracellular matrix deposition in the lung tissue resulting in the destruction of the pulmonary architecture and respiratory failure [1]. Despite extensive studies of recent years, the key etiological factors and molecular mechanisms leading to the disease development remained unidentified. Nevertheless, various abnormalities in the signaling pathways have been described [2] and some of the them have been targeted in the preclinical and early phase clinical studies [3–6]. Recent reports highlighted disturbed lipid metabolism as one of the factors determining progression of several lung disorders including chronic obstructive pulmonary disease (COPD), asthma, acute respiratory distress syndrome (ARDS), lung cancer, pulmonary arterial hypertension (PAH) and lung fibrosis [7–9]. The molecular mechanisms, by which altered lipid metabolism contributes to the progression of lung diseases, remained, however, elusive. The association between impaired lipid homeostasis and lung fibrogenesis is currently an area of extensive research. In this review, we provide recent insights into the role of the disturbed lipid metabolism in lung inflammation and fibrosis and, in addition, we highlight new therapeutic options to counteract these abnormalities.

Abbreviations: AC, adenylyl cyclase; ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; ACAT, acyl-coenzyme A (CoA):cholesterol acyltransferase; Akt, protein kinase B; Apo A1, apolipoprotein A1; Apo E, apolipoprotein E; ATII, alveolar type II cell; BALF, bronchoalveolar lavage fluid; cAMP, cyclic adenosine monophosphate; Cer, ceramide; CERase, ceramidase; COX-1/2, cyclooxygenase-1/2; cPLA2, cytosolic phospholipases A2; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; GPCR, G-protein coupled receptor; HDL, high-density lipoprotein; IL, interleukin; IDL, intermediate-density lipoprotein; IP3, inositol trisphosphate; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; 5-LOX, 5-lipoxygenase; LPA, lysophosphatidic acid; LPA_{1-5}, lysophosphatidic acid receptor 1–5; LPP, lipid phosphate phosphatase; LRP1, low-density lipoprotein receptor-related protein 1; LT, leukotriene; MAG, monoacylglycerol; MMP, matrix metalloprotease; NCEH, neutral cholesterol ester hydrolase; PI3K, phosphatidylinositol 3-kinase; PLC-β, phosphoinositide phospholipase C-β; PG, prostaglandin; RTC, reverse cholesterol transport; SMase, sphingomyelinase; Sph, sphingosine; S1P, sphingosine 1-phosphate; Shpk 1/2, sphingosine kinase 1/2; PLA1/2, phospholipases A1/2; $S1P_{1-4}$, sphingosine 1-phosphate receptor 1–4; Spns2, spinster homolog 2 transporter; TXA2, thromboxane A2; TGF-β, fransforming growth factor-β; TNF-α, tumor necrosis factor-α; VLDL, very low-density lipoprotein

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2. Lipid metabolism

Lipids are defined as a group of organic compounds that are insoluble in water but soluble in organic solvents [10]. A range of molecules, which belong to the lipid family, plays key biological roles, including energy storage, components of cellular membrane, steroid hormones, bile acids, vitamins and signal transduction molecules. Due to their hydrophobicity, lipids are transported in the plasma bound to albumin (free fatty acids) or incorporated into lipoproteins (triacylglycerol, cholesterol esters, cholesterol and phospholipids).

Triglycerides are supplied from a diet or *de novo* synthesized in the liver and, to a lesser extent, in other organs. Initially, dietary triglycerides are digested into fatty acids and sn-2-monoacylglycerols by pancreatic lipase in the small intestines and then absorbed by enterocytes [11]. In the erythrocytes, triglycerides are rebuilt and packed together with cholesterol and apolipoprotein (Apo) B-48 into chylomicron particles. Chylomicron particles formed in the enterocytes are secreted into the lymphatic system and subsequently *via* the superior vena cava to the systemic circulation. In the adipose tissue which captures the majority of chylomicron particles, triglycerides are hydrolyzed by lipoprotein lipase (LPL) into free fatty acids. Mechanistically, LPL, attached to the proteoglycans at the luminal side of the capillary endothelial cells, interacts with triglyceride-rich chylomicron particles [12,13] and in the presence Apo C2, hydrolyzes triglycerides [14]. Newly formed free fatty acids are taken up by local cells and used as an energy source.

Similarly to triglyceride, cholesterol is also supplied from a diet or *de novo* produced by the cells in the pathway regulated by hydroxymethyl-glutaryl coenzyme A reductase (HMGCR) [15]. Cholesterol molecules, accumulated in the hepatocytes, are assembled with Apo B into very low-density lipoprotein (VLDL) particles in order to enter the systemic circulation. In blood, VLDL are metabolized into low density lipoprotein (LDL) particles, which then carry cholesterol to the cells of peripheral tissues. LDL particles are taken up by the cells through low-density lipoprotein receptors (LDLR) or scavenger receptors. In the peripheral tissues, the cholesterol levels are regulated by the expression of LDLR and HMGCR as well as by the 'reverse cholesterol transport' (RCT) system. RTC removes excess cholesterol from the cells and delivers it back to the liver in the form of high density lipoprotein (HDL) particles [16].

In the cells, cholesterol plays diverse biological activities not only serving as a structural component of the cell membrane but also as a modulator of the activities of the cell membrane proteins. In addition, cholesterol plays a unique role in the lung tissue, where it serves as one of the components of the surfactant system [17]. In rats > 80% of pulmonary cholesterol is taken up from the circulation and the rest is produced by the resident lung cells [18]. Half of the pulmonary cholesterol uptake is mediated by the specific lipoprotein receptors while another half is endocytosed through a receptor-independent mechanism [19]. Lipoprotein receptors of pulmonary endothelial cells bind circulating LDL particles and mediate their endocytosis. Following endocytosis, the LDL particles are degraded in lysosomes and the released cholesterol is esterified by acyl-coenzyme A:cholesterol acyltransferase (ACAT) and stored in the cytosol in the cholesteryl ester-rich lipid droplets [20]. When necessary, the cholesteryl esters in the lipid droplets are hydrolyzed by neutral cholesteryl ester hydrolase (NCEH) or by lysosomal acid lipase to free cholesterol [20]. Cellular free cholesterol moves to the plasma membrane where it is available for efflux. The four cholesterol efflux pathways have been identified. The two passive processes involve simple diffusion (an aqueous diffusion pathway) and scavenger receptor B1-mediated facilitated diffusion. The two active processes relay on the members of the ATP-binding cassette (ABC) family of transmembrane transporters, namely ABCA1 and ABCG1 [20–22]. In the following sections, we will provide evidence for the role of lipids and their metabolites in lung diseases, in particular, in lung fibrosis.

3. Apolipoproteins

3.1. Apolipoprotein A1

Apolipoprotein A1 (Apo A1) is the most abundant protein of HDL [23]. It is primarily produced in the liver and small intestines and then excreted to the circulation [24]. Interestingly, Apo A1 may be also synthetized in the lung tissue by alveolar macrophages and epithelial cells [25]. The primary function of Apo A1 in the lung is to remove excess lipids from the cells in order to prevent their lipid overload. ABCA1 promotes efflux of unesterified cholesterol and phospholipids to Apo A1 to form a discoidal nascent HDL [23]. Following esterification by lecithin-cholesterol acyltransferase (LCAT), cholesterol is transported into the center of the particle and a spheroidal HDL is generated. Then, the spheroidal HDL becomes able to take additional cholesterol and phospholipids effluxed from peripheral cells *via* scavenger receptor B type I or ABCG1 [26]. Interestingly, HDL not only interacts with ABCA1 to take up cholesterol but also directly induces ABCA1 expression in alveolar type II (ATII) cells [27]. Besides removing excess lipids from the lung, HDL also transports some essential molecules to this organ. For example, HDL delivers vitamin E to ATII cells [28] thus partially contributing to the activity of the antioxidant system in the lung. Furthermore, it transports to the lung α-antitrypsin [29], which inhibits inflammatory cell-derived proteases thus protecting ECM from destruction. The protein-cargo property of HDL was recently proven in a study, in which the concomitant administration of HDL and α-antitrypsin prevented lung injury in a mouse model of elastase-induced emphysema [30]. In addition, HDL Apo A1 stabilizes prostaglandin I2 (PGI2) [31] leading to the inhibition of platelet activation and to the suppression of the release of pro-fibrotic agents from these cells and thereby to the attenuation of lung fibrosis (Fig. 1) [32]. Finally, HDL was reported to support survival and proliferation of ATII cells, to decrease expression of inflammatory mediators by these cells, and to maintain (along with LDL) surfactant homeostasis [27,33,34].

The important insights into the role of Apo A1 in lung pathologies have been gained from the studies which employed genetically modified animals. While, Apo $A1^{-/-}$ mice displayed signs of increased airway hyperresponsiveness, inflammation, oxidative stress and alveolar septal thickening [35], animals overexpressing human Apo A1 in ATII cells developed attenuated pulmonary fibrosis along with reduced inflammatory reactions in response to silica [36]. In addition, mice overexpressing human Apo A1 in ATII cells were protected from cigarette smoke-induced lung injury and remodeling [37]. In line with these studies, intratracheal instillation of human Apo A1 attenuated lung inflammation and fibrosis following bleomycin administration [38].

The beneficial role of Apo A1 has been also proven in the Multi-Ethnic Study of Atherosclerosis (MESA). In this multi-center, prospective cohort study of 6814 adults, the association of greater HDL-C and Apo A1 levels with lower high attenuation areas (a quantitative CT-measure of subclinical lung inflammation and extracellular matrix remodeling) was shown. [39]. Similarly, in asthma patients higher levels of circulating Apo A1 and HDL positively correlated with lesser degree of airway obstruction [40].

Taken together, an increasing body of evidence indicates that the protective role of Apo A1 in lung injury and fibrosis may be partially explained by its ability to prevent lipid overload of pulmonary cells and to dampen inflammation and oxidative stress. However, the exact molecular mechanisms, by which Apo A1 exerts these effects, remain unknown and need to be deciphered in future studies.

3.2. Apolipoprotein E

Apolipoprotein E (Apo E) is one of several apolipoproteins of very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL) and chylomicrons. Although, Apo E expression is observed in

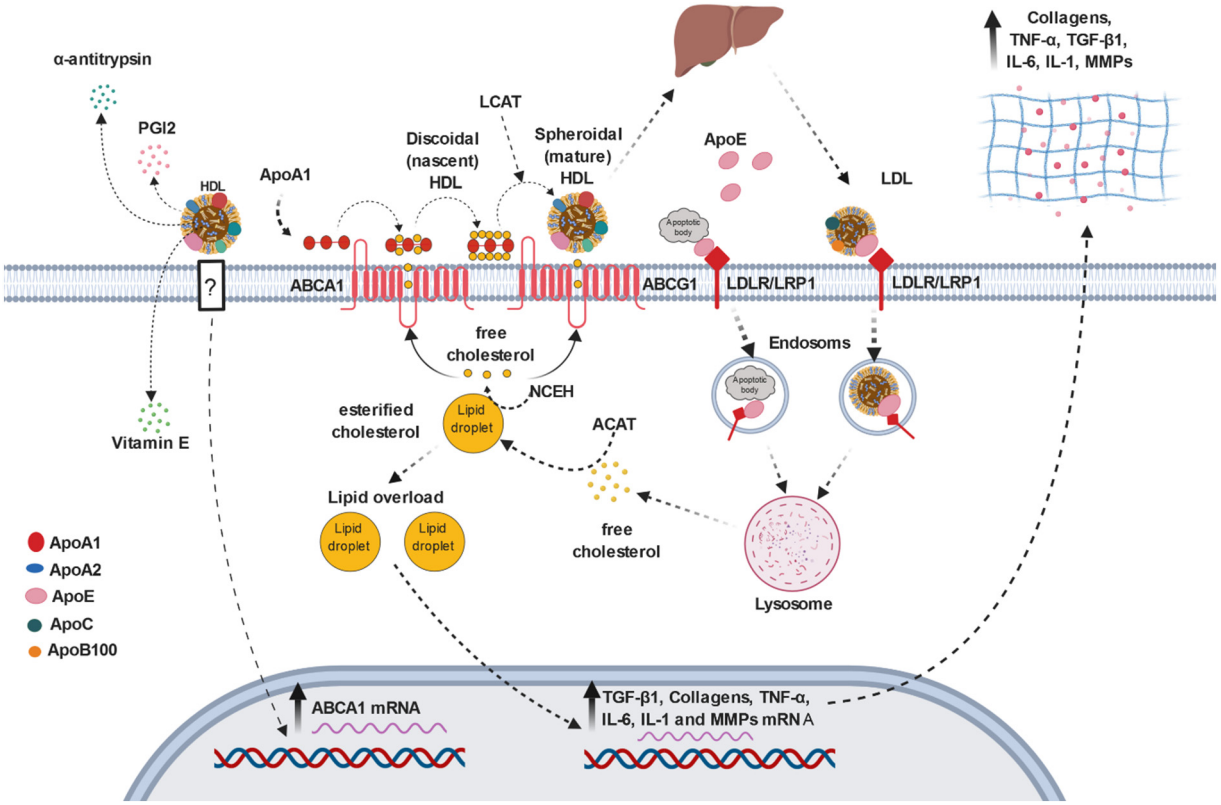

Fig. 1. Lipoprotein-triggered cellular activities in the lung. Low-density lipoprotein (LDL) particles deliver cholesterol along with other lipid molecules such as fatty acids and phospholipids to the pulmonary cells. In the lung tissue, LDL particles are captured and internalized by low-density lipoprotein receptor (LDLR) and low-density lipoprotein receptor-related protein 1 (LRP1) to endosomes resulting in formation of lysosomes which release free cholesterol into the cytoplasm. Cytoplasmic free cholesterol is esterified with acyl-coenzyme A (CoA):cholesterol acyltransferase (ACAT) and stored in lipid droplets. Overabundant accumulation of lipid droplets in the lung cells induces expression of collagens, transforming growth factor-β1 (TGF-β1), tumor necrosis factor-α (TNF-α), interleukins (ILs) and matrix metalloproteinases (MMPs) resulting in lung inflammation and fibrosis. Excess cholesterol from lipid droplets is converted to free cholesterol by neutral cholesterol ester hydrolase (NCEH). Subsequently, free cholesterol is transported across the cell membrane to the circulating Apo A1 by ATP-binding cassette transporter A1 (ABCA1) resulting in the formation of a nascent HDL particle. In the nascent HDL particle, free cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT) and moved into the core of the particle giving rise to an unsaturated HDL particle. This HDL particle is further saturated with cholesterols exported *via* ATP-binding cassette transporter G1 (ABCG1) forming a mature spheroidal HDL. The mature spheroidal HDL is transported to the liver. Besides, circulating HDL particles may induce ABCA1 expression in pulmonary cells and transport prostaglandin I2 (PGI2), α-antitrypsin and vitamin E to the lung. Apoptotic bodies formed during lung injury and inflammation are captured by Apo E and cleared from the extracellular space *via* LDLR and LRP1.
The graphic artwork was created using Biorender software.

several organs including lung, brain, spleen, adrenal, ovary and kidney, the main source of circulating Apo E are hepatocytes and macrophages residing in different tissues [41–43]. The main cell type responsible for the local synthesis of Apo E in the lung is ATII cell [43]. Apo E mediates uptake of cholesterol-rich lipoproteins by binding to LDLRs (Fig. 1) [44]. In plasma, the receptor-mediated uptake and endocytosis of Apo E-containing lipoproteins contribute to the overall decrease of circulating lipoproteins [45]. Like Apo A1, Apo E also plays a crucial role in maintaining pulmonary lipid homeostasis and exerts anti-inflammatory and anti-fibrotic functions. For example, it was shown that genetic ablation of Apo E increases inflammation and oxidative stress in the lung and accelerates lung stiffening in older age [46]. In addition, Apo $E^{-/-}$ mice fed a cholate-containing high-fat diet developed pulmonary granulomatous inflammation that mimicked pulmonary sarcoidosis and proceeded to fibrosis with age [47]. These features could be partially explained by the accumulation of cholesterol and oxidized LDL particles in the alveolar compartment of Apo $E^{-/-}$ mice [48–50]. Besides, it has been demonstrated that Apo E enhances efferocytosis (Fig. 1) [51] and inhibits the classical complement cascade by the direct binding to C1q [52]. Defective efferocytosis as well as overactivation of the complement system have been associated with many chronic lung diseases, including lung fibrosis [53,54]. This further supports the role of Apo E in the modulation of lung inflammation and remodeling.

Clinically, it was shown that variants of Apo E gene alleles may cause subtle pulmonary phenotypes. For instance, > 70 years old female carriers of Apo E ε4 allele were found to display reduced FEV_1/FVC (forced expiratory volume in one second divided by the forced vital capacity) values [55] suggesting a link between the Apo E ε4 allele, female sex, and a reduction of lung function in older individuals. In Taiwanese adults, however, no association between Apo E genotype and measures of a physical and a pulmonary function was reported [56]. This indicates that further studies providing new insight into how the polymorphic Apo E alleles might influence human lung physiology in specific gender and ethnic groups during aging are needed.

4. Lysophospholipids

Lysophospholipids (LP) are small bioactive lipid molecules derived from phospholipids in which one of the acyl derivatives has been removed by hydrolysis [57]. Two members of LPs, lysophosphatidic acid (LPA) derived from glycerophospholipids and sphingosine 1-phosphate (S1P) derived from sphingophospholipids, were reported to drive diverse cellular processes, including cell proliferation, apoptosis, migration, cytokine and chemokine secretion, platelet aggregation, smooth muscle cell contraction, by employing G protein-coupled receptors (GPCRs) (Fig. 2) [57,58]. In the following sections, we will mainly focus

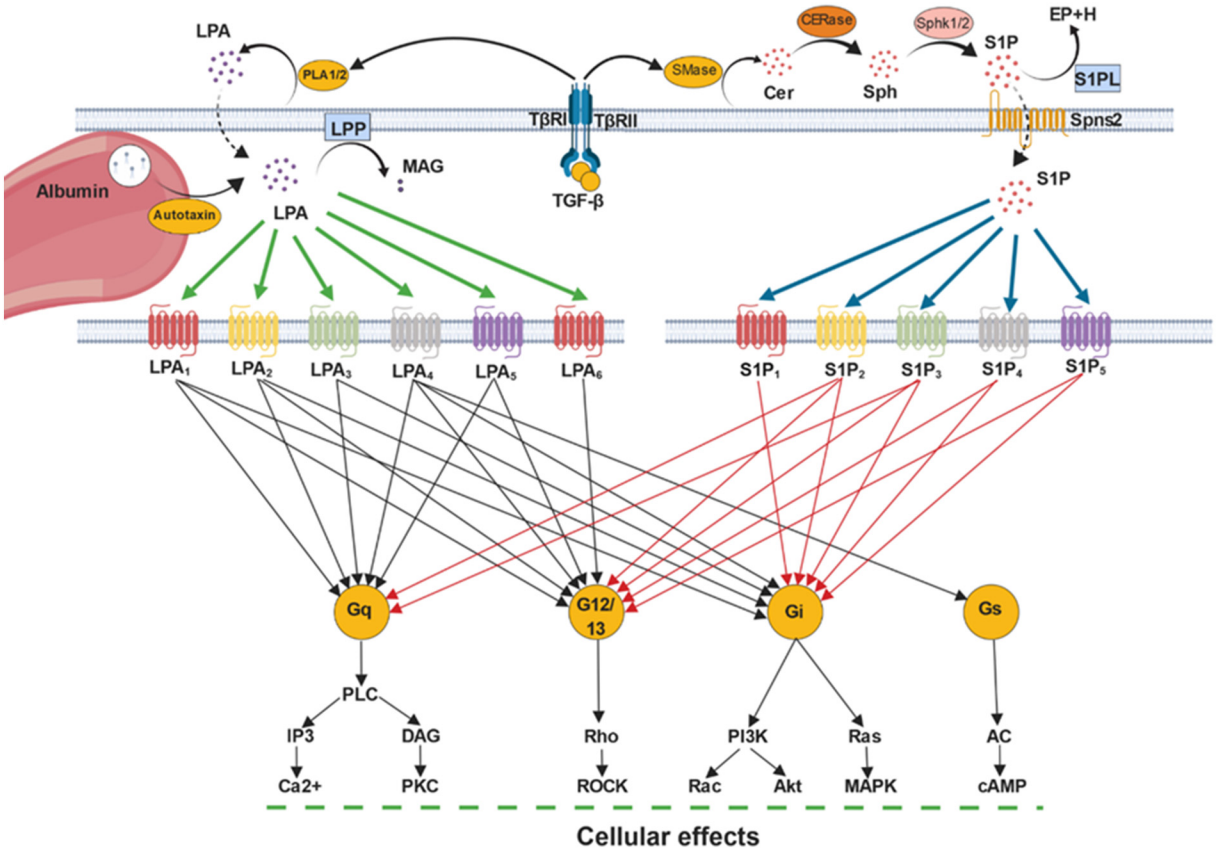

Fig. 2. Lysophospholipids as signaling molecules. Intracellular lysophosphatidic acid (LPA) is generated by phospholipase A1/2 (PLA1/2), whereas extracellular LPA is produced by autotaxin which metabolizes lysophospholipids bound to albumin in plasma. Extracellular LPA can be also metabolized to monoacylglycerol (MAG) by lipid phosphate phosphatases (LPP). LPA causes a broad range of biological effects on target cells by employing six GPCRs: LPA_1, LPA_2, LPA_3, LPA_4, LPA_5 and LPA_6. Sphingomyelinase (SMase) catalyzes the formation of ceramide (Cer) from membrane glycerophospholipids. Cer is then metabolized by ceramidase (CERase) to sphingosine (Sph). Sph itself is phosphorylated by sphingosine kinase 1/2 (Sphk1/2) leading to S1P production. Intracellular S1P is trafficked to the extracellular space by the spinster homolog 2 (Spns2) transporter. Intracellularly, S1P is degraded to ethanolamine phosphate (EP) and hexadecenal (H) by sphingosine-1-phosphate lyase (S1PL). S1P mediates its cellular effects through GPCRs: $S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$ and $S1P_5$. LPA and S1P receptors are coupled to heterotrimeric G proteins (Gs, Gi, Gq and G12/13 alpha subunits) and can initiate several cellular responses following activation. The expression of PLA1/2 and SMase can be regulated by transforming growth factor-β (TGF-β). PLC, phospholipase C; IP3, inositol trisphosphate; DAG, diacylglycerol; PKC, protein kinase C; ROCK, Rho-associated protein kinase; PI3K, phosphatidylinositol 3-kinase; Rac, Ras-related C3 botulinum toxin substrate; Akt, protein kinase B; MAPK, mitogen-activated protein kinase; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate.
The graphic artwork was created using Biorender software.

on the role of LPA and S1P in lung fibrosis.

4.1. Lysophosphatidic acid

Two enzymatic systems are responsible for lysophosphatidic acid (LPA) production. Whereas the intracellular LPA is generated by phospholipase A1 and A2 (PLA1 and PLA2)-mediated hydrolysis of membrane phosphatidic acids (PAs), the extracellular LPA is produced in the plasma by the lysophospholipase D activity of autotaxin which metabolizes albumin-bound lysophospholipids (LPLs), lysophosphatidylcholine (LPC) and lysophosphatidylserine (LPS) to LPA (Fig. 2) [59,60]. LPA can be found in almost all tissue types of the body [61]. It is a small-sized lipid molecule, which possesses a glycerol backbone with a phosphate head group and one fatty acid chain (usually unsaturated) at the sn-1 (or sn-2) position [62]. The most abundant fatty acid moieties in LPA species are: stearoyl (18:0), palmitoyl (16:0), oleoyl (18:1), linoleoyl (18:2), arachidonoyl (20:4) acyl chains [62]. In plasma, LPA is bound to both lipoproteins and albumin and its levels do not depend on the circadian rhythm and fasting condition in healthy subjects [63]. The circulating LPA levels, however, positively correlate with the concentrations of autotaxin [64], thus indicating that autotaxin is a key enzyme responsible for the synthesis of this lipid mediator in plasma. Genetic ablation of autotaxin in mice is not compatible with life [65,66], pointing towards a pivotal role of this protein in embryonic survival.

In IPF patients and bleomycin challenged mice, the levels of autotaxin in the lung tissue are elevated [67]. Accordingly, mice with bronchial epithelial cell- or macrophage-specific deletion of autotaxin or mice following injection with an autotaxin inhibitor, GWJ-A-23, exhibit attenuated lung fibrosis in response to bleomycin [67]. The last observation was not confirmed in the study employing another autotaxin inhibitor, PAT-048 [68], thus suggesting that an alternative pathway responsible for the synthesis of extracellular LPA may exist. Nevertheless, the beneficial effects of autotaxin inhibitors in preclinical studies led to the initiation of a clinical trial testing the safety and efficacy of an autotaxin blocker in IPF patients. In the FLORA phase 2a study, GLPG1690, a small molecule autotaxin inhibitor, showed stabilization of the disease over the 12-week period *versus* disease progression in the placebo arm [69]. Initiated in 2018, phase 3 studies, ISABELA 1 (NCT03711162) and ISABELA 2 (NCT03733444), will demonstrate whether GLPG1690 has potential to enter the clinic.

LPA causes a broad range of biological effects by employing at least six distinct GPCRs including LPA_1- LPA_6 [70]. Among them, LPA_1 is predominantly expressed in mouse and human pulmonary fibroblasts

[71]. LPA_1 is coupled to heterotrimeric G proteins (G_i, G_q, and $G_{12/13}$ alpha subunits) and can initiate several cellular responses following LPA stimulation (Fig. 2) [72]. IPF patients and bleomycin challenge mice exhibit high LPA levels in bronchoalveolar lavage fluid (BALF) [71]. Genetic deficiency of LPA_1 or pharmacological inhibition of this receptor with Ki16425 or VPC12249 result in the reduction of lung fibroblast migration, but not proliferation, in response to LPA [71]. In addition, LPA_1 blockage suppresses the trans-differentiation of bone marrow derived stem cells to myofibroblast and the secretion of ECM components upon exposure to LPA [73]. Consequently, LPA_1 deficient mice and mice treated with LPA_1 antagonist, antalpa1, display attenuated lung fibrosis in response to bleomycin [71,73]. Interestingly, Cai et al. reported that another LPA_1 antagonist, AM966, disrupts lung microvascular barrier integrity [74], thus suggesting that LPA_1 agonists and antagonists share the same intracellular signaling pathways and detailed evaluation of LPA_1 antagonists in the preclinical studies is essential for the development of new therapeutic approaches. Apart from LPA_1, LPA_2 was also demonstrated to be involved in the development of pulmonary fibrosis, namely $LPA_2^{-/-}$ mice were found to be protected against bleomycin induced lung injury as manifested by decreased expression of ECM proteins and diminished levels of TGF-β1 and IL-6 in BALF [75].

Taken together, the autotaxin-LPA-LPA_1 axis seems to play a role in the development and progression of lung fibrosis, however, further studies are needed to fully clarify whether interference with any of the components of this system holds potential for combating tissue damage in lung fibrosis.

4.2. Sphingosine 1-phosphate

Generation of S1P is initiated by the formation of ceramide from membrane sphingophospholipids by lysosomal enzymes sphingomyelinase (SMase) [76]. Ceramide is further metabolized by ceramidase (CERase) to sphingosine (Sph) [76], which is then phosphorylated by sphingosine kinase 1 or 2 (Sphk1 or Sphk2) leading to S1P formation [76,77]. Cytosolic S1P levels are controlled by sphingosine-1-phosphate lyase (S1PL) which degrades S1P to ethanolamine phosphate (EP) and hexadecenal (H) [78]. Intracellular S1P is trafficked to the extracellular space by the spinster homolog 2 (Spns2) transporter [79]. S1P mediates its effects through GPCRs, named $S1P_{1–5,}$ on S1P-producing or -neighboring cells thereby signaling in an autocrine or a paracrine fashion, respectively [80]. In addition, locally synthesized S1P can bind to the HDL particles and reach tissues placed further away [81]. S1P receptors are coupled to heterotrimeric G proteins (G_i, G_q and $G_{12/13}$ alpha subunits) and mediate several cellular responses following S1P binding (Fig. 2). Although some studies demonstrated that S1P can also function as an intracellular second messenger [82,83], it is widely accepted that the majority of S1P-mediated effects are performed *via* its binding to GPCRs on the cell membrane [84,85].

Dysregulation of S1P signaling/metabolism has been observed in many lung diseases including asthma, COPD, ARDS, IPF, lung cancer and cystic fibrosis [86,87]. In the fibrotic lungs, all essential enzymes involved in the synthesis of S1P, such as SMase, CERase, Sphk1 and Sphk2, are upregulated [88–90] and produced virtually by all lung cells [88]. S1P may induce inflammatory cell recruitment *via* upregulation of ICAM-1 expression in ATII cells and trigger epithelial-to-mesenchymal transition (EMT) through $S1P_2$ and $S1P_3$ [88,91]. Increased reactive oxygen species (ROS) production and elevated TGF-β1 expression were found to mediate S1P-iduced EMT [88]. Interestingly, TGF-β1, through the induction of Sphk1 synthesis, can accelerate S1P generation in lung fibroblasts, thus suggesting that this self-perpetuating condition may well aggravate lung tissue damage [90,92]. *In vitro*, knockdown of Sphk1 in lung fibroblasts reduces TGF-β1-induced expression of α-SMA and fibronectin [93], while activation of S1P receptors with FTY720-P, ponesimod, and SEW2871 increases ECM synthesis. Since the response to FTY720-P - a non-selective S1P receptor agonist - was stronger than to ponesimod and SEW2871 - which are selective $S1P_1$ agonists - it was concluded that S1P receptor agonist-induced ECM production is mediated by $S1P_2$ and $S1P_3$ [94]. *In vivo*, prolonged administration of FTY720 worsens bleomycin-triggered lung injury as manifested by increased pulmonary capillary leak and mortality. Although, the underlying molecular mechanism was not investigated in detail, it was suggested that FTY720 can either result in functional antagonism of $S1P_1$ on endothelial cells or in activation of $S1P_2$ and $S1P_3$ [95]. The former is supported by a study demonstrating how a pharmacologic inhibition of $S1P_1$ [96] causes increased vascular permeability in response to tissue injury, whereas the latter by a report showing inhibition of H_2O_2-induced permeability in the rat lung perfused model following $S1P_2$ antagonist administration [97]. The importance of $S1P_2$ and $S1P_3$ in the response of the lung to injury is further supported by the reduction of inflammation and fibrosis in $S1P_2^{-/-}$ and $S1P_3^{-/-}$ mice in response to bleomycin challenge [98–100]. Nevertheless, further studies applying highly selective S1P receptor agonists and antagonists are needed to fully decipher the role of the S1P-S1P receptor systems in acute and chronic lung diseases.

Next to the role of S1P receptors, also the contribution of enzymes involved in S1P production and degradation to the pathogenesis of lung fibrosis has been investigated. In this regard, it has been reported that genetic ablation of SMase increases resistance to pulmonary fibrosis in response to bleomycin [89]. Similarly, knockout of Sphk1 increased survival and attenuated lung damage in this animal model [101]. Accordingly, pharmacological inhibition of Sphk1 conferred protection against lung injury induced by bleomycin [102]. In addition, partial deletion of S1PL ($Sgpl1^{+/-}$) augmented bleomycin-triggered lung fibrosis as manifested by increased TGF-β1, collagen, fibronectin and α-SMA levels and decreased expression of autophagy markers, LC3 II and beclin-1 [103]. These results support an idea of potential significance of insufficient autophagy in IPF and highlight the role of S1P in the regulation of autophagosome formation.

In IPF patients the levels of S1P were reported to be increased in BALF and serum and inversely correlated with diffusing capacity of the lung for carbon monoxide (DLCO), forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). Concurrently, elevated expression of Sphk1 in alveolar macrophages and lung tissue of IPF patients was reported [88]. Increased expression of S1PL in peripheral blood mononuclear cells (PBMCs) of IPF patients was described as well [103]. Low levels of S1PL in PBMCs were associated with higher severity of fibrosis and lower survival rate.

Altogether, these findings suggest that disturbed S1P metabolism is mechanistically linked to the pathogenesis of IPF and may be considered as a promising target for therapeutic innervations.

5. Eicosanoid metabolites

Arachidonic acid is the initial substrate used for the generation of prostaglandins and leukotrienes. Prostaglandins (PG) and leukotrienes (LT) are collectively known as eicosanoids because they consist of a chain of 20 carbon atoms (in Greek eikosi means twenty). In the following sections we will highlight eicosanoids' activities in lung fibrosis.

5.1. Prostaglandins

Cyclooxygenase (COX) catalyzes arachidonic acid to prostaglandin G2 (PGG2), which is further converted to prostaglandin H2 (PGH2) by the peroxidase activity of the enzyme. Then, PGH2 serves as a precursor for all prostanoids, including prostaglandin D2 (PGD2), E2 (PGE2), F2α (PGF2α), I2 (PGI2) and thromboxane A2 (TXA2) (Fig. 3). Once formed in the cytoplasm, they are exported to the extracellular space by C type of ATP-binding cassette (ABC) exporters, namely ABCC1, ABCC2 and ABCC4 [104]. Prostanoids exert their effects through GPCRs, $DP_{1–2}$, $EP_{1–4}$, FP, IP, and TP, [105]. The IP, DP_1, EP_2 and EP_4 receptors mediate signal transduction through Gs proteins resulting in the increased

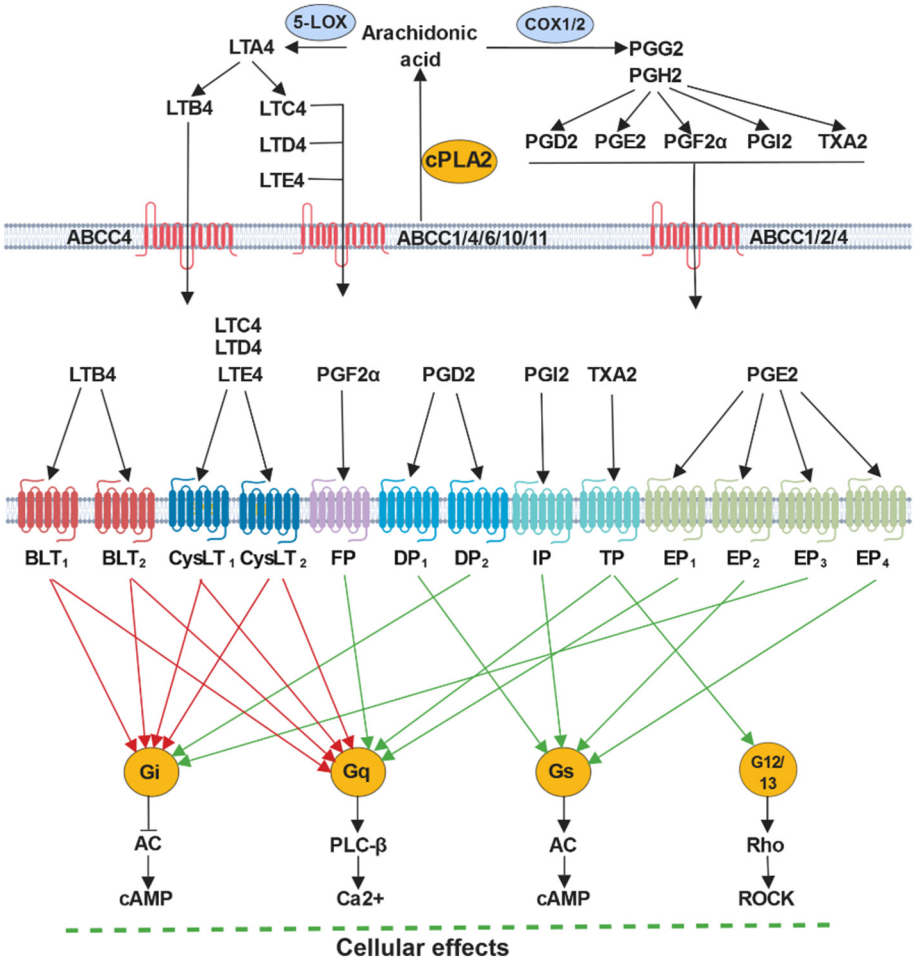

Fig. 3. Eicosanoids as signaling mediators. Initially, cytosolic phospholipase A2 (cPLA2) metabolizes membrane phospholipids to arachidonic acid which can be further metabolized by cyclooxygenase 1/2 (COX1/2) or 5-lipoxygenase (5-LOX) to prostaglandins (PGs) or leukotrienes (LTs), respectively. COX1/2 leads to the formation of PGG2, which is then converted to PGH2 and subsequently to PGD2, PGE2, PGF2α and PGI2 and to thromboxane A2 (TXA2). Once formed in the cytosol, PGs are exported to the extracellular space by multidrug ABCC subfamily of the ATP binding cassette (ABC) exporters. 5-LOX metabolizes arachidonic acid into LTA4, which is further converted to LTB4, LTC4, LTD4 and LTE4. LTs are also exported to the extracellular space through ABCC exporters. PGs and LTs mediate their cellular effects by binding to their cognate G protein-coupled receptors (GPCRs). PG and LT receptors are coupled to heterotrimeric G proteins (Gs, Gi, Gq and G12/13 alpha subunits) and can initiate several cellular responses upon stimulation. AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; PLC-β, phospholipase C-β; ROCK, Rho-associated protein kinase.
The graphic artwork was created using Biorender software.

intracellular levels of cyclic adenosine monophosphate (cAMP). EP_3 and DP_2 receptors engage Gi proteins to reduce the intracellular levels of cAMP, while EP_1, FP and TP receptors signal through Gq to induce calcium mobilization. G12/13 proteins control the Rho-Rho-associated protein kinase (ROCK) signaling pathway upon TP activation [106] (Fig. 3). In the following subsections, we will describe each prostaglandin metabolite separately.

5.1.1. Prostaglandin E

Being synthesized by all cell types of the lung [107,108], PGE2 plays an important role in the protective and reparative processes occurring in this organ. PGE2 inhibits cell proliferation and TGF-β1-triggered collagen secretion in lung fibroblasts [109]. Among all PGE2 receptors, EP_2 and EP_4 are the most abundantly expressed in human and mouse lung fibroblasts [110]. EP_2 agonists were reported to decrease lung fibroblast proliferation by suppressing the expression of protease-activated receptors and by activating rap guanine nucleotide exchange factor 1 (Epac1) [110,111]. Strikingly, it seems that the activation of different PGE2 receptors results in opposite biological effects. Li et al. showed that EP_1 and EP_3 activation leads to the increased migration of lung fibroblasts, while EP_2 and EP_4 stimulation inhibits the motility of these cells [112]. Similar findings were reported by White *et al*, who demonstrated that PGE2 potentates IL-1β induced proliferation of lung fibroblasts through EP_3 receptor but blocks this effect *via* EP_2 [113]. Diverse effects of PGE2 receptors were also observed in airway epithelial cells undergoing EMT. Following EMT, EP_2 and EP_4 agonists decreased cell migration, whereas EP_1 and EP_3 agonists did not have any effect [114]. In addition, PGE2 activities were found to be cell type dependent as PGE2 promoted FasL-induced apoptosis in lung fibroblasts and inhibited FasL-triggered cell death in ATII cells [115].

In IPF patients, the levels of PGE2 are decreased in both lung tissue and isolated lung fibroblasts [116]. PGE2 administration prevents lung function decline and pulmonary fibrosis in bleomycin treated mice [117]. Similarly, intratracheal instillation of nanostructured lipid carriers containing PGE2 alone or in combination with siRNAs targeting matrix metallopeptidase (MMP)-3, CC-chemokine ligand (CCL) 12, and hypoxia-inducible factor 1α (HIF1α) markedly attenuates lung fibrosis and improves survival of bleomycin challenged mice [118,119]. Likewise, the beneficial effects of PGE2 synthetic analogue, 16,16-dimethyl prostaglandin E2, are observed [120]. The exacerbated lung fibrosis in response to bleomycin was reported in mice with genetic ablation of COX2 and EP_2, but not in mice lacking EP_1 and EP_3. $EP_1^{-/-}$ and $EP_3^{-/-}$ mice exhibited similar fibrotic changes in the lung as did WT littermates [121,122]. Other studies, however, did not confirm more severe fibrosis in $EP_2^{-/-}$ animals, thus highlighting the need for further research on the role of PGE2 receptors in the regulation of profibrotic processes [123,124].

Circulating PGE2 is taken up by the cells and further degraded in the cytoplasm by 15-hydroxyprostaglandin dehydrogenase (15-PGDH) [125]. Slco2a1, a solute carrier organic anion transporter family member 2A1, is responsible for the uptake and clearance of PGE2 in the lung [126–128] and is predominantly expressed in airway and alveolar epithelial cells [129–132]. Mice lacking Slco2a1 develop more severe pulmonary fibrosis in response to bleomycin as compared to WT animals. The aggravated lung fibrosis in $Slco2a1^{-/-}$ mice is manifested by the retention of PGE2 in alveolar lumen thus indicating the critical role of Slco2a1 in the transport of PGE2 from the alveolar to the interstitial space of the lung [133]. The unique role of Slco2a1 in the lung was

Table 1
Summary of studies evaluating the effects of lipid targeting agents in animal models of lung fibrosis.

Agent	Mechanism of action	Strategy	Disease model	Agent application	Main effects	Ref.
PBI-4050	GPR40 agonist and GPR84 antagonist	Curative	Bleomycin, mice (21 days)	Oral gavage, 200 mg/kg/day (days 7–20)	- reduced lung fibrosis (↓fibrotic lesions)	Gagnon 2018 [164]
Liposomes	"empty" liposomes composed of PC and cholesterol	Preventive	Bleomycin, mice (22 days)	Oropharyngeal aspiration, 100 μL (days 0, 4, 8, 12, and 16)	- decreased lung fibrosis (↓lung hydroxyproline content, ↓fibrosis index) - iminished lung inflammation (↓inflammation score) - prevented lung function decline (↑dynamic and static lung compliance)	Gwinn 2011 [176]
Liposomes	"empty" liposomes composed of PE	Preventive	Bleomycin, mice (21 days)	Aerosol, 0.75 mg/mL, every second day (days 1–21)	- reduced lung fibrosis (↓fibrosis index, ↓total lung collagen content)	Vazquez-de-Lara 2018 [178]
PF-8380	Autotaxin inhibitor	Preventive	Bleomycin. mice (14 days)	Oral gavage, 60 or 120 mg/kg, twice a day (days 1–14)	- reduced lung fibrosis (↓Ashcroft score, ↓collagen expression) - reduced lung inflammation (↓ BALF protein content) - decreased mortality	Ninou 2018 [179]
PF-8380	Autotaxin inhibitor	Curative	Bleomycin, mice (7 days)	Oral gavage, 30 or 100 mg/kg, twice a day (days 3–7)	- reduced lung fibrosis (↓lung hydroxyproline content) - reduced lung inflammation (↓BALF cells)	Ninou 2018 [179]
GWJ-A-23	Autotaxin inhibitor	Preventive	Bleomycin, mice (14 days)	Injection (i.p.), 10 mg/kg, every second day (days 1–14)	- decreased lung fibrosis (↓lung and BALF collagen content, ↓lung destruction ↓BALF TGF-β1 levels) - decreased lung inflammation (↓BLAF protein and cellular content)	Oikon-omou 2012 [67]
PAT-048	Autotaxin inhibitor	Preventive	Bleomycin, mice (14 days)	Oral gavage, 20 mg/kg/day (days 1–14)	- did not prevent lung inflammation (↔ BALF protein content) - did not prevent lung fibrosis (↔ lung hydroxyproline content) - decreased BALF and plasma autotaxin activity	Black 2016 [68]
AMIRA095	LPA_1 antagonist	Preventive	Bleomycin, mice (14 days)	Oral gavage, 200 mg/kg, twice a day (days 1–14)	- decreased lung fibrosis (↓BALF and lung collagen content, - diminished lung inflammation (↓BALF cells)	Ninou 2018 [179]
Antalpa1	LPA_1 antagonist	Preventive	Bleomycin, SCID/Beige mice (14 days)	Injection (s.c.), 20 mg/kg/day (days 1–14)	- decreased fibroblast differentiation (↓α-SMA^+ cells) - reduced lung fibrosis (↓lung collagen content)	Tang 2013 [73]
VPC12249	$LPA_{1/3}$ antagonist	Preventive	Irradiation, mice (6 months)	Injection (i.p.), 1 mg/kg, twice a week (6 months)	- reduced lung fibrosis (↓lung hydroxyproline content)	Gan 2011 [180]
AM966	LPA_1 antagonist	Preventive	Bleomycin, mice (14 days)	Oral gavage, 30 mg/kg, twice a day (days 1–14)	- decreased lung fibrosis (↓fibrosis score, ↓BALF collagen content) - diminished lung inflammation (↓BALF protein content) - reduced mortality	Swaney 2010 [181]
Myriocin	SPTLC1 inhibitor	Preventive	Radiation, mice (18 weeks)	Oral gavage, 0.375 mg/kg, 3× per week (18 weeks)	- reduced mortality - reduced lung inflammation (↓BLAF protein and cellular content) - decreased lung fibrosis (↓ lung collagen content, ↓α-SMA expression)	Gorshkova 2012 [182]
SKI-II	Sphk1 inhibitor	Preventive	Bleomycin, mice (21 days)	Injection (i.p.), 5 mg/kg, every second day (days 7–20)	- reduced mortality - reduced lung fibrosis (↓Ashcroft score, ↓lung collagen content)	Shuang Huang 2013 [101]

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Table 1 (*continued*)

Agent	Mechanism of action	Strategy	Disease model	Agent application	Main effects	Ref.
FTY720-P	$S1P_{1,3-5}$ agonist	Preventive	Bleomycin, mice (7 or 14 days)	Injection (i.p.), 5 mg/kg or 0.5 mg/kg, 3× per week	- increased lung injury - elevated lung inflammation (↑BLAF protein content and cellularity) - aggravated lung fibrosis (↑lung hydroxyproline content) - increased mortality	Shea 2010 [95]
AUY954	$S1P_1$ agonist	Preventive	Bleomycin, mice (7 or 14 days)	Injection (i.p.), 5 mg/kg, once daily	- increased lung fibrosis (↑lung hydroxyproline content)	Shea 2010 [95]
S1PR2i	$S1P_2$ antagonist	Preventive	Bleomycin, mice (33 days)	Powder diet (days −3-33)	- reduced lung fibrosis (↓fibrotic area, ↓BALF collagen content)	Zhao 2018 [183]
Montelukast	$CysLT_1$ antagonist	Curative	Bleomycin, rats (35 days)	Oral gavage, 1 mg/kg/day (days 14–35)	- reduced lung fibrosis (↓lung collagen deposition, ↓αSMA^+ cells)	Shaker 2010 [158]
Montelukast	$CysLT_1$ antagonist	Preventive	Bleomycin, mice (7 or 14 days)	Injection (s.c), 1.0 mg/kg, on days 1–5 of each week for 2 weeks	- decreased lung fibrosis (↓Ashcroft score, ↓lung hydroxyproline content) - reduced lung inflammation (↓BALF cells)	Izumo 2007 [157]
Montelukast	$CysLT_1$ antagonist	Preventive	Bleomycin, rats (4 or 15 days)	Injection (i.p.), 10 mg/kg/day (days −5-4 or 15)	- reduced lung fibrosis (↓lung collagen content) - decreased lung inflammation (↓BALF cells)	Topaloğlu 2018 [184]
Montelukast	$CysLT_1$ antagonist	Preventive	Bleomycin, mice (14 days)	Oral gavage, 10 mg/kg/day, once a day (days −4-14)	- reduced lung fibrosis (↓lung fibrosis score, ↓lung hydroxyproline content) - decreased lung inflammation (↓BALF cells)	Shimbori 2011 [185]
Montelukast	$CysLT_1$ antagonist	Preventive	Radiation, rats (7 days)	Injection (i.p.), 10 mg/kg/day (days −3-7)	- reduced lung fibrosis (↓lung fibrosis score, ↓lung hydroxyproline content) - decreased lung inflammation (↓BALF cells)	Osman Tokat 2018 [186]
MK-571	$CysLT_1$ antagonist	Preventive	Bleomycin, mice (7 days)	Osmotic minipump, 0.5 μL/h (days 1–7)	- decreased lung fibrosis (↓fibrosis score) - reduced lung inflammation (↓BALF cells) - reduced mortality	Failla 2006 [187]
KP-496	LTD4 and TP antagonist	Preventive	Bleomycin, mice (21 days)	Aerosol, 30 min morning and evening (days 1–21)	- reduced lung fibrosis (↓fibrosis score) - decreased lung inflammation (↓inflammatory score)	Kurokawa 2010 [156]
Zileuton	5-LOX inhibitor	Preventive	Bleomycin, mice (7 days)	Oral gavage, 50 mg/kg/day (days 1–7)	- reduced lung fibrosis (↓fibrosis score) - decreased lung inflammation (↓BALF cells) - reduced mortality	Failla 2006 [187]
U75302	BLT_1 antagonist	Preventive	Bleomycin, mice (21 days)	Intratracheal instillation, 5 μg/mouse, days 0, 3, 6 and 9	- reduced lung fibrosis (↓Ashcroft score, ↓lung collagen content) - reduced lung inflammation (↓BALF cells)	Lv 2017 [188]
U75302	BLT_1 antagonist	Curative	Bleomycin, mice (21 days)	Intratracheal instillation, 5 μg/mouse, days 10, 13, 16 and 19	- no effect on lung fibrosis (↔Ashcroft score, ↔lung collagen content) - no effect on lung inflammation (↔BALF cells)	Lv 2017 [188]
ONO-4057	LTB4 antagonist	Preventive	Bleomycin, mice (21 days)	Injection (i.p.), 1 mg/kg, days 1–5of each week (3 weeks)	- reduced lung fibrosis (↓Ashcroft score, ↓lung hydroxyproline content) - reduced lung inflammation (↓BALF cells)	Izumo 2009 [189]
DP-1904	TBXAS1 inhibitor	Preventive	Bleomycin, mice (21 days)	Osmotic minipump, 20 mg/kg/day (days 1–21)	- decreased lung fibrosis (↓ lung collagen content)	Sato 2004 [190]
ONO-1301	IP agonist with TBXAS1 inhibitory activity	Preventive	Bleomycin, mice (21 days)	Injection (s.c.), 6 mg/kg, twice a day (1–3 or − 7 or − 21 days)	- reduced lung fibrosis (↓Ashcroft score, ↓lung hydroxyproline content) - decreased lung inflammation (↓BALF cells) - increased survival	Murakami 2005 [138]
Iloprost	PGI2 analogue	Preventive	Bleomycin, rats (16 days)	Injection (i.p.), 200 kg/kg/day (days −2-16)	- reduced lung fibrosis (↓Ashcroft score, ↓lung hydroxyproline content)	Aytemur 2012 [137]

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Table 1 (*continued*)

Agent	Mechanism of action	Strategy	Disease model	Agent application	Main effects	Ref.
PGE2 + siRNAs	Liposomal PGE2 with siRNAs targeting MMP3, CCL12, and HIF1α	Preventive	Bleomycin, mice (21 days)	Nebulization, twice a week (days 1–21)	- reduced lung fibrosis (↓lung hydroxyproline content) - reduced mortality	Garbuze-nko 2017 [118]
PGE2	Liposomal PGE2	Preventive	Bleomycin, mice (21 days)	Nebulization, twice a week (days 1–21)	- reduced lung fibrosis (↓lung hydroxyproline content) - decreased mortality	Ivanova 2012 [119]
PGE2	PGE2	Preventive	Bleomycin, mice (7 or 21 days)	Osmotic minipumps, (days −7-14)	- reduced lung function decline (↑static compliance) - reduced lung fibrosis (↓Ashcroft score, ↓lung collagen content)	Dackor 2011 [117]
Iloprost	PGI2 analogue	Preventive	Bleomycin, mice (7 or 21 days)	Osmotic minipumps, (days −7-14)	- reduced lung function decline (↑static compliance) - decreased lung fibrosis (↓Ashcroft score, ↓lung collagen content)	Dackor 2011 [117]
Iloprost	PGI2 analogue	Preventive	Bleomycin, mice (21 days)	Injection (i.p.), 200 μg/kg, single injection	- reduced lung fibrosis (↓Ashcroft score, ↓lung hydroxyproline content) - reduced lung inflammation (↓BALF cells) - reduced lung function decline (↑lung compliance)	Zhu 2010 [136]
INS1009 (liposomal treprostinil)	PGI2 analogue	Curative	Bleomycin, rats (21 days)	Inhalation, 10, 30, or 100 μg/kg/day (days 10–27)	- decreased lung fibrosis (↓lung hydroxyproline content)	Corboz 2018 [191]

BALF, bronchoalveolar lavage fluid; GPR40, G-protein-coupled receptor 40; GPR84, G-protein-coupled receptor 84; LPA, lysophosphatidic acid; S1P, sphingosine-1-phosphate; SPTLC1, serine palmitoyltransferase 1; PC, phosphatidylcholine; PE, phosphatidylethanolamine; Sphk1, sphingosine kinase 1; $CysLT_1$, cysteinyl leukotriene receptor 1; 5-LOX, 5-lipoxygenase; PGE2, prostaglandin E2; PGI2, prostaglandin I2; TP, thromboxane A2 receptor; IP, prostaglandin I2 receptor; EP, prostaglandin E2 receptor; TBXAS1, thromboxane A synthase 1; s.c., subcutaneous; i.p., intraperitoneal; MMP3, matrix metallopeptidase 3; CCL12, CC-chemokine ligand (CCL) 12; HIF-1α, hypoxia-inducible factor-1α; siRNA, small interfering ribonucleic acid.

Table 2
Summary of clinical trials evaluating agents targeting lipids in IPF patients.

Trial registry number	Phase	Agent	Mechanism of action	Sample size	Duration	Primary endpoint	Status	Outcome	Report in the form of publication
NCT 00262405	2	Zileuton	inhibitor of 5-LOX	$n = 44$	26 weeks	LTB4 levels in BALF	Completed	NA	NA
NCT 02503657	2	Tipelukast (MN-001)	inhibitor of LT receptors, PDEs and 5-LOX	$n = 15$	26 weeks	decline in FVC	Completed	NA	NA
NCT 01766817	2	BMS-986020	LPA_1 antagonist	$n = 108$	26 weeks	decline in FVC	Completed, terminated earlier	primary endpoint met, terminated due to safety issues	Palmer 2018 [192]
FLORA NCT 02738801	2a	GLPG1690	inhibitor of autotaxin	$n = 23$	12 weeks	safety, tolerability, pharmaco-kinetics, pharmaco-dynamics	Completed	primary endpoint met, a trend towards reduction in the FVC decline	Maher 2018 [69]
NCT 02538536	2	PBI-4050	GPR40 agonist and GPR84 antagonist	$n = 41$	12 weeks	safety tolerability, pharmaco-kinetics, pharmaco-dynamics	Completed	primary endpoint met, maintained FVC when applied alone or in combination with nintedanib, reduced FVC when applied in combination with pirfenidone	Khalil 2019 [193]
ISABELA1 NCT 03711162	3	GLPG1690	inhibitor of autotaxin	$n = 750$ (estimated)	52 weeks	decline in FVC	Expected to be completed in 2021		
ISABELA2 NCT 03733444	3	GLPG1690	inhibitor of autotaxin	n = 750 (estimated)	52 weeks	decline in FVC	Expected to be completed in 2021		

5- LOX, 5-lipoxygenase; LT, leukotriene; PDE, phosphodiesterase; LPA_1, lysophosphatidic acid receptor 1; BALF, bronchoalveolar lavage fluid; FVC, forced vital capacity; NA, not available.

recently underscored in a study by Nakanishi et al., which demonstrated Slco2a1-mediated apical-to-basal transport of PGE2 in alveolar type I (ATI) cells [134].

Taken together, an accumulating body of evidence suggests that PGE2 works in concert with multiple signaling pathways to protect the lung against damage and maladaptive remodeling.

5.1.2. Prostaglandin I2

Prostaglandin I2 (PGI2), also called prostacyclin, is one of the metabolites of arachidonic acid with different biological functions in the body. Although, PGI2 is well-known for its beneficial effects in PAH [135], its role in lung fibrosis is still evolving. Lovgren et al. demonstrated that aggravated bleomycin-induced lung fibrosis in $COX2^{-/-}$ mice is associated with the decreased levels of PGI2 [123]. Accordingly, mice lacking PGI2 receptor (IP) were prone to bleomycin-triggered pulmonary fibrosis [123]. Another study, however, did not confirm this finding and showed that IP deficient mice display similar degree of lung fibrosis in response to bleomycin as WT littermates [124].

PGI2 is secreted by ATII cells and exerts anti-fibrotic and anti-inflammatory effects on lung fibroblasts. Iloprost, a synthetic prostacyclin analog, was found to attenuate bleomycin-induced pulmonary fibrosis by upregulating the expression of anti-fibrotic cytokines (interferon-γ and C-X-C motif chemokine (CXCL) 10) and by downregulating the expression of pro-inflammatory and pro-fibrotic mediators (tumor necrosis factor (TNF)-α, interleukin (IL)-6, and TGF-β1) [136]. Moreover, iloprost was more effective in decreasing bleomycin-triggered fibrotic changes as compared to methyl-prednisolone, a corticosteroid used to suppress the immune system [137]. The reduction of bleomycin-triggered pulmonary fibrosis was also observed following administration of ONO-1301, a novel long-acting prostacyclin agonist with thromboxane A synthase 1 (TBXAS1) inhibitory activity. Mice treated with ONO-1301 had reduced total cell and neutrophil counts as well as total protein levels in BALF. Moreover, they exhibited the decreased levels of TXB2 in BALF and the increased levels of cAMP in plasma [138]. Despite these promising preclinical studies, the beneficial effects of inhaled iloprost were not confirmed in a double-blind, multicenter, short duration (12 week) trial in IPF patients with elevated pulmonary arterial pressures (PAP) [139].

5.1.3. Prostaglandin F2α

The expression of PGF2α is regulated by IL-1β in a COX2 dependent manner in IPF, but not donor lung fibroblasts [140]. PGF2α stimulates lung fibroblast proliferation and collagen production *via* FP receptor. These effects were found to be independent of the TGF-β signaling pathway [124]. FP deficient mice exhibit attenuated bleomycin-induced pulmonary fibrosis, while maintaining similar levels of alveolar inflammation and TGF-β activation [124].

The levels of PGF2α were reported to be increased in BALF and plasma of IPF patients [124,141]. In plasma, the elevated levels of PGF2α negatively correlated with FEV_1, FVC, DLCO and six-minute walk distance (6MWD). In addition, IPF patients with higher plasma PGF2α levels had increased risk of mortality after adjusting for disease severity indices represented by the composite physiologic index [141]. These findings suggest the potential role of PGF2α in the pathogenesis of IPF and strongly encourage further research on the role of this prostaglandin in pathologic remodeling of lung tissue.

5.1.4. Prostaglandin D2

PGD2 and its analogue BW245C inhibited collagen secretion in lung fibroblasts in response to TGF-β1 [109] an reduced lung fibroblast migration induced by fibronectin [142]. In addition, Kohyama et al., showed that PGD2 stimulates lung fibroblast-mediated collagen gel contraction and thereby regulates adaptive as well as maladaptive tissue repair processes [143]. Correspondingly, hematopoietic prostaglandin D synthase (H-PGDS) deficient mice developed more severe pulmonary inflammation and fibrosis as compared to WT littermates in

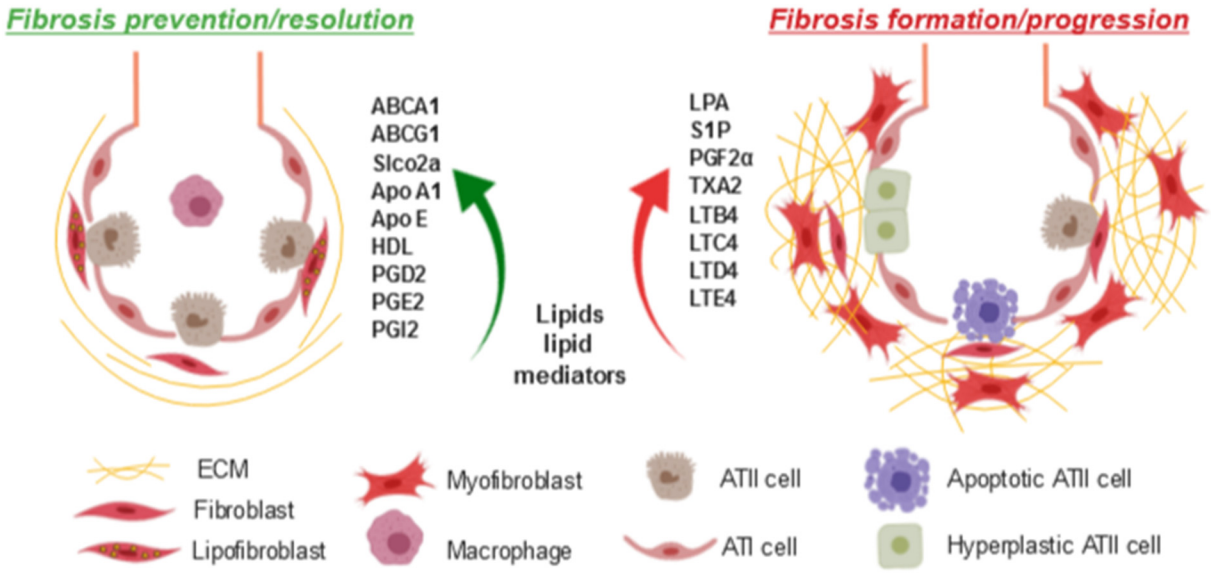

Fig. 4. Diverse activities of lipids and lipid regulators in lung fibrosis. While ATP-binding cassette transporter (ABC) A1, ABCG1, solute carrier organic anion transporter family member 2a1 (Slco2a1), apolipoprotein (Apo) A1, Apo E, high-density lipoprotein (HDL), and prostaglandins (PG) D2, E2 and I2 contribute to the maintenance of normal lung structure and function, increased levels of lysophosphatidic acid (LPA), sphingosine 1-phosphate (S1P), PGF2, thromboxane A2 (TXA2) and leukotriens (LT) B4, C4, D4, and E4 lead to lung malfunction and fibrosis.
The graphic artwork was created using Biorender software.

response to bleomycin. The enhanced fibrotic response, observed in H-PGDS$^{-/-}$ animals, was accompanied by increased vascular permeability, enhanced infiltration of neutrophils and macrophages into the lung, and elevated expression of inflammatory mediators (TNFα, monocyte chemoattractant protein-1, COX2), thus suggesting the prominent role of hematopoietic PGD2 in the regulation of inflammatory reactions [144]. Similarly, genetic ablation of chemoattractant receptor-homologous with T-helper cell type 2 cells (CRTH2), a receptor for PGD2, aggravated bleomycin induced lung fibrosis as manifested by enhanced accumulation of inflammatory cells, reduced pulmonary compliance, and increased levels of collagen in the lung, pointing towards an important role of CRTH2-expresssing γδT cells in fibrotic lung remodeling [145]. In line with these findings, intravenous administration of PGD2 synthase expressing fibroblasts attenuated lung injury and fibrosis along with improved survival of bleomycin-treated mice [146]. Interestingly, the levels of PGD2 in plasma of IPF patients were found to be comparable to those observed in sarcoidosis patients [124] implying that alterations in PGD2 levels may be a result of a general response of the lung to injury.

To sum up, it seems that PGD2 is an important mediator of anti-inflammatory responses in the lung, however, to exclusively delineate its anti-fibrotic properties further *in vivo* studies employing non-inflammatory models of lung fibrosis are needed.

5.2. Leukotrienes

5-lipoxygenase (5-LOX) metabolizes arachidonic acid to the labile 5-hydroperoxyeicosatetraenoic acid, which is then converted to 5-hydroxyeicosatetraenoic acid and leukotriene A4 (LTA4). LTA4 serves as the precursor for leukotriene B4 (LTB4) and the cysteinyl-leukotrienes (leukotriene C4 (LTC4), leukotriene D4 (LTD4), and leukotriene E4 (LTE4)). Intracellularly formed leukotrienes are exported to the extracellular space by C type of ABC exporters including ABCC1, ABCC4, ABCC6, ABCC10 and ABCC11 [104]. Leukotrienes play diverse biological functions *via* GPCR receptors, BLT_1, BLT_2, $CysLT_1$ and $CysLT_2$. Whereas LTB4 binds to BLT_1 and BLT_2, cysteinyl-leukotrienes interact with $CysLT_1$ and $CysLT_2$ (Fig. 3) [147]. In general, leukotrienes were found to regulate fibroblasts and epithelial cell activities [148,149]. For example, LTD4 potentiated fibronectin-induced human lung fibroblast migration through the $CysLT_1$-Gi/o signaling pathway [150] and enhanced human lung fibroblast collagen synthesis in response to TGF-β1 [151]. Increased collagen production was also observed in rat lung fibroblasts following exposure to LTD4 [149]. Medina et al. reported LTC4-triggered collagenase expression in lung fibroblasts derived from donors and IPF patients thus suggesting that LTC4 not only elevates collagen synthesis but also controls remodeling of ECM [152]. Finally, LTC4 was reported to induce TGF-β1 expression in airway epithelial cells *via* the p38 mitogen-activated protein kinase (MAPK) signaling pathway [153].

In vivo studies demonstrated that LTC4 synthase or 5-LOX deficient mice develop attenuated lung fibrosis in response to bleomycin [154,155]. Furthermore, inhaled KP-496, a novel dual antagonist of cysteinyl-leukotrienes and TXA2 receptors, diminished fibrotic changes in the same experimental model [156]. Similarly, montelukast, a $CysLT_1$ antagonist, decreased lung fibrosis by suppressing TGF-β1 expression [157] and by reducing the number of α-SMA positive myofibroblasts [158] in bleomycin-challenged mice and rats, respectively. $CysLT_1$ knockout mice, however, exhibited aggravated lung fibrosis in response to bleomycin, thus implying that other cysteinyl-leukotriene receptors may compensate for the loss of $CysLT_1$ following tissue injury [154]. Indeed, further *in vivo* experiments revealed that $CysLT_2$ possesses superior profibrotic activities over $CysLT_1$ [159].

Clinically, the BALF levels of LTB4 and LTE4 were found to be elevated in systemic sclerosis patients with lung diseases as compared to those without lung diseases and healthy controls. In addition, the levels of both leukotrienes correlated positively with the total number of cells in the BALF and correlated negatively with FVC [160,161]. The levels of LTB4 and LTC4 were also reported to be increased in IPF lung homogenates and to associate with histologic indices of both inflammation and fibrosis [162]. Moreover, IPF alveolar macrophages were proposed to be the main source of LTB4 and LTC4 in the fibrotic lung. [162]. A long list of profibrotic activities of leukotrienes encourage further efforts to scale up the work on the role of these lipid mediators in fibrotic lung diseases.

6. Lipid transporters and receptors

6.1. Lipid receptors

One of the main functions of free fatty acids (FFA) is regulation of cellular and systemic metabolism through GPCRs [163]. Among GPCRs responding to lipids, GPR40 and GPR48 were found to be involved in regulation of the fibrotic processes [164]. Whereas, GPR40 is activated by both medium- and long-chain FFAs and is coupled to Gq or Gi/o proteins, GPR84 is responsive to medium-chain FFAs only and exclusively activates pertussis toxin-sensitive Gi/o signaling pathways [165–167]. In addition, GPR40 and GPR84 exhibit distinct tissue distribution profiles. GPR40 is mainly detectable in kidney, intestine, skin and in monocytes, while GPR84 is abundantly found in brain, heart, muscle, colon, thymus, spleen, kidney, liver, intestine, placenta, lung, and leukocytes. Furthermore, the expression of GPR84 in normal human dermal fibroblasts is upregulated following stimulation with TGF-β [164]. Studies on the role of GPR40 and GPR84 in experimental lung fibrosis are largely missing with one report documenting the beneficial effects of PBI-4050 (GPR40 agonist and GPR84 antagonist) administration in the bleomycin model of lung injury [164].

6.2. Lipid transporters

Membrane lipid transporters play an important role in the regulation of intracellular and extracellular lipid homeostasis [168]. In the bleomycin model of lung fibrosis, decreased expression of fatty acid transport protein (FATP) 1, 3, 4 and CD36, also known as a fatty acid translocase, was observed. Concomitantly, the levels of oleic and linoleic acids in the lung tissue were found to be suppressed suggesting the impaired surfactant synthesis and secretion [169]. Alterations in the expression of ABCA1, a cholesterol and phospholipid exporter, were described in a cigarette smoke exposure-induced model of emphysema in mice. In this model, enhanced pulmonary inflammation was associated with decreased expression of ABCA1 [170]. Genetic ablation of ABCA1 was manifested by respiratory distress, alveolar proteinosis, and cholesterol enrichment in lung tissue, surfactants, and macrophages [171]. A study by McNeish et al. confirmed these findings accentuating the presence of foci of foamy ATII cells and cholesterol clefts in the lungs of ABCA1$^{-/-}$ mice [172]. In addition, ABCA1 deficient mice exhibited increased pulmonary inflammation characterized by accumulation of inflammatory cells and increased expression of inflammatory mediators in the lung [173]. Similar abnormalities were reported in mice lacking another cholesterol exporter, ABCG1 [174]. Accordingly, overexpression of ABCA1 in endothelial cells attenuated airway epithelial remodeling in a murine ovalbumin-induced model of asthma [175]. Collectively, these findings provide the basis for additional experiments to elucidate the role of lipid transporters and foamy cells in the pathogenesis of lung diseases.

7. Lipids as therapeutic targets

The efficacy of pharmacological agents targeting lipids/lipid metabolism has been studied in preclinical models of lung fibrosis (for the details please refer to Table 1). It seems that, not only pharmacological agents interfering with lipids/lipid metabolism, but also intratracheally delivered lipids hold potential for the treatment of lung injury and fibrosis. Several preclinical studies demonstrated that blockage of certain lipid receptors, like GPR84 (PBI-4050), LPA_1 (Antalpa1, VPC12249), or $CysLT_1$ (Montelukast, MK-571), and activation of others, including GPR40 (PBI-4050), provides protection against lung fibrosis. The same was observed for some lipid mediators. While inhibition of LPA (PF-8380, GWJ-A-23) or S1P (SKI-II) production was found to be beneficial in animal models of lung fibrosis, interference with prostacyclin activities turned out to be rather detrimental. Fine-tuned lipid requirements of the lung were underscored by the studies focusing on the administration of “empty” liposomes of well-defined lipid composition directly to the lung. In this regard, Gwinn et al. demonstrated that locally delivered liposomes consisting of L-α-phosphatidylcholine and cholesterol exhibited protective effects in the bleomycin-induced lung injury in mice [176]. Supporting this finding, Kornilova et al. showed that local application of phosphatidylcholine liposomes displays wound-healing properties in a surgical lung injury model in guinea pigs [177]. All these studies indicate that different lipid molecules are required for the proper functioning of the lung and that lipid diversity in this organ is strictly controlled by complex signaling networks. In repose to injury, series of biological processes, including increased vascular permeability, inflammatory cell recruitment, fibroblast activation, and re-epithelialization, are initiated. In all these processes, lipid mediators play an important role. If their temporal profiles are appropriate, the injury culminates in restoration of normal lung structure and function, however, if any of these profiles gets exacerbated or diminished progressive lung dysfunction ensues. Keeping lipid profiles in balance in the right place at the right time still remains a challenge.

Nevertheless, the promising results of preclinical studies led to the initiation of several clinical trials evaluating safety and efficacy of agents targeting lipid mediators/receptors in IPF patients. These include: a clinical trial NCT00262405 testing Zileuton (a 5-LOX inhibitor), a clinical trial NCT02503657 evaluating MN-001 (a LT receptor antagonist and an inhibitor of phosphodiesterases and 5-LOX), a clinical trial NCT01766817 examining BMS-986020 (a LPA_1 antagonist), a clinical trial NCT02538536 testing PBI-4050 (a GPR40 agonist and GPR84 antagonist) and clinical trials NCT02738801, NCT03711162, NCT03733444, all evaluating GLPG1690 (an autotaxin inhibitor) (for the details please refer to Table 2). BMS-986020 was tested in a phase 2, parallel-arm, multicenter, randomized, double-blind, placebo-controlled trial. Despite markedly reduced the decline rate of FVC in IPF patients treated for 26 weeks with BMS-986020, this study was terminated earlier as off-target, drug-specific effects leading to the development of cholecystitis in some patients were observed. PBI-4050 was evaluated in a 12-week phase 2 single-arm open-label study, which demonstrated encouraging results for lung function and no safety concerns for PBI-4050 alone and in combination with nintedanib. GLPG1690 was successfully tested in the FLORA phase 2a clinical trial and went to the phase III clinical trials called ISABELA1 (NCT03711162) and ISABELA2 (NCT03733444). These studies plan to recruit 1500 IPF patients until 2021. In addition, clinical trials evaluating safety and efficacy of a synthetic PGI2 analogue (Treprostinil) are ongoing in patients with pulmonary hypertension (PH) due to interstitial lung diseases (NCT02630316 and NCT02633293). The future will show whether agents currently tested in aforementioned clinical trials have the chance to enter the clinic.

8. Conclusions

A growing body of evidence suggests that balanced lipid profiles are crucial in maintaining healthy lung function and structure and that initiation/progression of lung fibrosis is associated with the alterations in these profiles. Since lipids and their regulators have diverse biological functions, some of them prevent and/or repair lung injury including ABCA1, ABCG1, Slco2a1, Apo A1, Apo E, HDL, PGD2, PGE2 and PGI2, while others induce and/or promote lung scarring like LPA, S1P, TXA2, LTB4, LTC4, LTD4, and LTE4 (Fig. 4), the challenge remains to keep them all in balance. Understanding good and bad sides of lipids will open new avenues in the treatment of lung diseases characterized by maladaptive remodeling of the tissue.

Conflicts of interest

The authors declare no conflict of interest.

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