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Review Article

Lysophosphatidic acid (LPA) signaling through LPA₁ in organ fibrosis: A pathway with pleiotropic pro-fibrotic effects

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Fibrosis characterizes many chronic diseases that result in end-stage organ failure, causing major morbidity and mortality. Fibrosis in many of these diseases appears to result from aberrant or over-exuberant wound-healing responses to chronic injury, producing excessive accumulation of fibroblasts and extracellular matrix that disrupt normal tissue homeostasis. The potent bioactive lipid lysophosphatidic acid (LPA), signaling through one of its receptors LPA₁, mediates numerous fundamental cell behaviors involved in wound healing responses, including cell contraction, migration, survival, proliferation, and gene expression. Recent studies indicate that the LPA-LPA₁ pathway regulates many of the aberrant wound-healing responses that have been implicated in fibrotic diseases. This pathway has been shown to exert pro-fibrotic effects on multiple cell types: LPA-LPA₁ signaling promotes epithelial cell apoptosis and fibroblast migration, proliferation and resistance to apoptosis, and impairs endothelial cell barrier function. Consistent with its broad pro-fibrotic activities, inhibition of the LPA-LPA₁ pathway has recently been demonstrated to have profound anti-fibrotic effects. Targeting LPA-LPA₁ signaling has been demonstrated to be an effective therapeutic strategy in mouse models of fibrotic diseases affecting multiple different organs, including the lung, kidney, skin and peritoneum. The breadth of these effects suggest that LPA and LPA₁ represent a core pathway in fibrosis, and make these molecules attractive targets for the development of new therapies with the potential to be effective for multiple human fibrotic diseases.

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Introduction

Fibrosis is a pathological hallmark of many chronic diseases that produce end-stage organ failure, and conse-

quently is associated with very substantial morbidity and mortality. The pathogenesis of fibrosis in many of these diseases is thought to involve aberrant or over-exuberant

Fig.1 Chemical structure of LPA

LPA is the common name for a family of 1-acyl-2-hydroxy-sn-glycerol-3-phosphate and 1-hydroxy-2-acyl-sn-glycerol-3-phosphate species, all of which consist of a glycerol phosphate backbone esterified with a single fatty acid, and differ from each other in the identity and the position of their fatty acid moieties.

wound-healing processes initiated to protect the host from injurious stimuli¹). In response to noxious stimuli of many different types, dysregulated repair processes can result in excessive accumulation of fibroblasts/myofibroblasts, and excessive deposition of extracellular matrix, that disrupt normal tissue homeostasis. The molecular mediators driving these aberrant repair processes have not yet been fully identified, however, and their recognition will hopefully lead to discovery of new therapeutic targets for fibrotic diseases, most of which are refractory to currently available therapies.

Lysophosphatidic acid (LPA) is a bioactive lipid that signals through interactions with specific G protein-coupled receptors (GPCRs), of which at least six have been definitively identified and designated LPA₁₋₆²⁻³). By signaling through these LPA receptors, LPA mediates many fundamental cell behaviors, including cell contraction, migration, survival, proliferation, and gene expression⁴⁻⁶). Following tissue injury, LPA signaling specifically through LPA₁ mediates pro-fibrotic responses of multiple cell types, including fibroblasts, endothelial cells and epithelial cells⁷⁻⁹). We and others have recently demonstrated that LPA-LPA₁ signaling is required for the development of fibrosis in mouse models of fibrotic diseases affecting multiple organs, including the lung, peritoneum, kidney and skin⁸⁻¹⁴). In this review, we describe the important roles of LPA and LPA₁ that have been identified so far in the pathogenesis of organ fibrosis.

LPA structure

There are many different species of LPA molecules, which are either 1-acyl-2-hydroxy-sn-glycerol-3-phosphates, or 1-hydroxy-2-acyl-sn-glycerol-3-phosphates. As demonstrated

in Figure 1, the structure of these molecules consists of a glycerol phosphate backbone esterified with a single fatty acid^{2, 15}). The different species of LPA molecules differ from each other in the identity and the position of their fatty acid moieties.

LPA metabolism

LPA has been noted to be produced in response to injury in numerous tissues, including the lung, kidney, cornea and skin^{8, 12, 16-17}). In addition to LPA's role in pathological fibrosis, in at least some of these tissues, it has been noted to promote normal wound healing¹⁸⁻²⁰). There are at least two major pathways of LPA production²¹): cleavage of lysophospholipids such as lysophosphatidylcholine by the lysophospholipase D activity of autotaxin (ATX), and hydrolysis of phosphatidic acid (PA) by phospholipase A₁ or A₂, as shown in Figure 2. Of these, the ATX pathway appears to be responsible for the majority of extracellular LPA produced *in vivo*, since plasma LPA levels in mice heterozygous for an ATX-null allele are one half of those present in wild-type mice²²⁻²³). LPA levels may also be regulated by its degradation. LPA degradation can also be mediated by several different enzymatic pathways, including those involving lipid phosphate phosphatases (LPPs), LPA acyltransferase (LPAAT) or lysophospholipases²⁴⁻²⁵). Of these, hydrolysis of LPA by LPPs appears to be the major pathway responsible for LPA degradation *in vivo*²⁶).

LPA receptors

The six definitively identified LPA receptors, LPA₁₋₆, are all type 1 rhodopsin-like GPCRs with seven-transmembrane alpha helices^{2-3, 5-6, 27}). Of these receptors, LPA₁₋₃ belong to

Fig.2 Major pathways of LPA synthesis

LPA species are synthesized through two major pathways. As shown on the left, phospholipids such as phosphatidylcholine (PC) can be converted to lysophospholipids such as lysophosphatidylcholine (LPC) by members of the phospholipase A₂ (PLA₂) families of enzymes. These lysophospholipids can then be converted to LPA by the lysophospholipase D activity of autotaxin (ATX). Alternatively, as shown on the right, PLA₂ enzymes can produce LPA directly by hydrolysis of phosphatidic acid (PA). PLA₁ enzymes can also participate in LPA synthesis. The 2-acyl LPA species that they produce can also be converted to 1-acyl LPA species by acyl chain migration to the thermodynamically favored sn-1 position.

Table 1 LPA receptors and their biological functions

Receptors	G protein coupling [ref 80]	Biological functions	References
EDG family			
LPA ₁	Gα _{i1} , Gα _q , Gα _{12/13}	Fibroblast migration, resistance to apoptosis and pro-fibrotic gene expression Epithelial cell apoptosis Vascular barrier disruption and vascular smooth muscle cell migration after injury Inhibition of adipogenesis Brain and bone development Neuroprogenitor cell survival and differentiation Neuron survival, synaptic regulation and release of neurotransmitters Neuropathic pain Cancer cell invasion and metastasis	8, 51-52, 81 9 8, 82 83 84-85 86 84, 87-88 89 90, 91
LPA ₂	Gα _{i1} , Gα _q , Gα _{12/13}	Activation of latent TGF-β Vascular smooth muscle cell migration after injury Inhibition of dendritic cell activation Neuroprogenitor cell survival and differentiation Colon carcinogenesis Ovarian and endometrial cancer cell proliferation, migration, and invasion	77-78 82 92 86 93-94 95-96
LPA ₃	Gα _{i1} , Gα _q	Timing and spacing of embryo implantation Spermatogenesis Chemotaxis of immature dendritic cells Neuropathic pain	97 98 99 100
P2Y family			
LPA ₄	Gα _{s1} , Gα _{i1} , Gα _q , Gα _{12/13}	Blood and lymphatic vessel development Suppression of LPA ₁ -driven cell migration and invasion	101 102
LPA ₅	Gα _q , Gα _{12/13}	Neuropathic pain	103
LPA ₆	Gα _{s1} , Gα _{i1} , Gα _{12/13}	Vascular barrier disruption Hair growth	79 28, 104-105

the endothelial differentiation gene (EDG) family, and share substantial sequence homology. In contrast, LPA₄₋₆ all belong to the P2Y receptor family, whose ligands are typically nucleotides rather than lysophospholipids, and comprise a second subgroup of LPA receptors²⁸⁻²⁹. The LPA receptors consequently have evolved through at least two distinct lineages in the GPCR family.

LPA₁, the first high-affinity LPA receptor to be identified, was initially noted to be expressed in neurogenic regions of the developing cerebral cortex, and was subsequently found to be widely expressed throughout the body³⁰. LPA₄ and LPA₅ have also been found to be broadly expressed, whereas tissues with high expression of LPA₂, LPA₃ and LPA₆ appear to be more limited. LPA₂ is highly expressed in immune organs such as thymus and spleen³¹, LPA₃ is highly expressed in reproductive organs such as testis and uterus³², and LPA₆ is highly expressed in hair follicles, where it has been identified as an important mediator of hair growth²⁸.

The different LPA receptors couple to different extents with heterotrimeric G-proteins containing different G α subunits, including G α_i , G α_s , G α_q and G $\alpha_{12/13}$ ³³. These different G-protein coupling patterns of LPA's receptors, along with their different patterns of tissue expression, allow LPA to produce varied effects in different tissues and organs³⁴. LPA₁ and LPA₂ couple to G α_i -containing G-proteins, through which these receptors suppress cAMP levels and activate Ras, Rac and ERK^{27, 30, 35}. LPA₁ and LPA₂ also couple to G $\alpha_{12/13}$ -containing G-proteins to induce actin cytoskeleton rearrangements through activation of the small GTPase RhoA³⁵. Each of the EDG subfamily of LPA receptors, LPA₁, LPA₂ and LPA₃, couple to G α_q -containing G-proteins, which activate phospholipase C^{32, 36}. The P2Y subfamily of LPA receptors also appear to couple with different subtypes of G-proteins, including G α_q - and G $\alpha_{12/13}$ -containing G-proteins^{2, 27}. The G-protein coupling and biological effects of the identified LPA receptors are summarized in Table 1.

LPA-LPA₁ signaling and fibrosis

Recent studies have demonstrated the importance of LPA as a pro-fibrotic mediator in multiple organs. The development of fibrosis in a wide variety of mouse fibrotic disease models requires LPA signaling mainly through LPA₁, leading to the recognition of LPA₁ as a promising new target for anti-fibrotic therapies. In the mouse model of pulmonary

fibrosis induced by bleomycin, LPA levels in bronchoalveolar lavage (BAL) fluid increase after bleomycin challenge, and LPA₁-deficient mice are dramatically protected from fibrosis and mortality⁸. Administration of an LPA₁-specific antagonist also suppresses the development of pulmonary fibrosis induced by bleomycin¹⁰. Similarly, in the mouse model of renal fibrosis induced by unilateral ureteral obstruction (UUO), LPA levels in media conditioned by kidney explants increase after obstruction, and genetic deletion or pharmacological inhibition of LPA₁ attenuates the extent of fibrosis produced¹²⁻¹³. Further, genetic deletion or pharmacological inhibition of LPA₁ also significantly suppresses the development of fibrosis in the mouse model of scleroderma dermal fibrosis induced by bleomycin, and the mouse model of peritoneal dialysis-associated peritoneal fibrosis induced by chlorhexidine gluconate^{11, 14}. In addition to these studies demonstrating anti-fibrotic effects of LPA₁ deletion or inhibition, targeting LPA synthesis has recently also been shown to mitigate fibrosis: the development of pulmonary fibrosis in the bleomycin mouse model was significantly attenuated by pharmacological inhibition of ATX, or by deletion of this LPA-synthesizing enzyme specifically from bronchial epithelial cells, or from macrophages and neutrophils³⁷.

Molecules such as LPA and LPA₁ that are important in mouse models of fibrosis of multiple different organs have recently been suggested to be part of 'core' pathways in fibrosis, i.e. pathways essential to lead from an initial stimulus to the development of fibrosis³⁸. Since the evolution of organs predated the evolution of mammalian species, the differences between organs may consequently be more substantial than the differences between mammals within a specific organ³⁹. Pathways such as LPA-LPA₁ signaling that contribute to the development of fibrosis in multiple organs in mice therefore may be more likely to be shared by mice and humans than pathways found to be important in fibrosis of only one organ system, and targeting such core pathways may have greater potential to be effective in humans than would targeting tissue-specific pathways³⁸.

LPA-LPA₁ signaling can mediate several of the wound-healing responses to tissue injury that are now thought to lead to fibrosis rather than repair when they are aberrantly or excessively activated. The hallmarks of pathological fibrosis are the accumulation of fibroblasts and myofibroblasts, and the extracellular matrix that these cells produce, in amounts that disrupt normal tissue homeostasis³⁹. Patho-

logic accumulation of fibroblasts may result from a combination of increased fibroblast recruitment and proliferation, and decreased fibroblast apoptosis; following tissue injury all three of these fibroblast behaviors can be promoted by LPA and LPA₁. LPA-LPA₁ signaling may also contribute to pro-fibrotic behaviors induced in epithelial and endothelial cells by tissue injury, including increased epithelial cell apoptosis, and decreased endothelial cell barrier function. In the sections that follow, we review the multiple mechanisms through which LPA-LPA₁ signaling in fibroblasts, epithelial cells and endothelial cells may contribute to the pathogenesis of fibrosis.

1) LPA-LPA₁ signaling and fibroblast migration

Fibroblast migration into the provisional fibrin matrix of the wound clot was classically described during granulation tissue formation following cutaneous injury⁴⁰⁻⁴¹. In patients with idiopathic pulmonary fibrosis (IPF), lung fibroblasts are thought to analogously migrate into the fibrin-rich exudates that develop in the airspaces after lung injury⁴². Fibroblast chemoattractant activity is generated in the airspaces in IPF, and is present in BAL fluid recovered from these patients. The extent of BAL fibroblast chemoattractant activity, i.e. the extent to which BAL fluid from an IPF patient induces fibroblast migration, correlates with his or her disease severity⁴³. A pathogenic role for fibroblast migration in IPF is further suggested by studies of patients with an accelerated variant of this disease: genes associated with cell migration are upregulated in the lungs of such “rapid progressor” patients, and fibroblast chemoattractant activity is greater in BAL samples from these rapid progressors than is present in BAL from slow progressors⁴⁴. Evidence of a pathogenic contribution of fibroblast migration to pulmonary fibrosis has also come from mouse models, in which inhibition of fibroblast migration attenuates the development of pulmonary fibrosis, and the promotion of fibroblast migration exaggerates fibrosis⁴⁵⁻⁴⁶.

LPA potently induces the migration of multiple cell types, including fibroblasts⁴⁷. As noted above, LPA levels in BAL samples recovered from mice increase after bleomycin challenge. As is the case with BAL from IPF patients, BAL samples recovered from mice developing pulmonary fibrosis post-bleomycin injury induce fibroblast migration, whereas BAL from uninjured mice do not. We demonstrated that the increased levels of LPA present in post-bleomycin challenge BAL fluid are responsible for the majority of the fibroblast

chemoattractant activity present in these samples⁸), suggesting that LPA-LPA₁ signaling is predominantly responsible for fibroblast recruitment to sites of lung injury in the bleomycin mouse model of lung fibrosis. Consistent with this hypothesis, LPA₁-deficient mice demonstrated diminished fibroblast accumulation in their lungs after bleomycin challenge⁸. We found analogous evidence that LPA-LPA₁ signaling is predominantly responsible for fibroblast recruitment to sites of lung injury in the lungs of IPF patients: LPA levels were increased in BAL samples from IPF patients, LPA₁ was highly expressed by fibroblasts recovered from these samples, and inhibition of LPA₁ markedly reduced fibroblast responses to the chemotactic activity of those BAL samples⁸.

2) LPA-LPA₁ signaling and fibroblast proliferation

In addition to fibroblast recruitment to sites of tissue injury, the proliferation of resident fibroblasts within injured tissues is central to the accumulation of these cells⁴⁸. LPA itself can induce fibroblast proliferation⁴⁹, through mitogen-activated protein kinase activation⁵⁰. In addition, LPA-induced fibroblast proliferation *in vitro* is at least partly mediated by LPA inducing these cells to express the potent fibroblast mitogen connective tissue growth factor (CTGF)⁵¹, which can then drive fibroblast proliferation in an autocrine fashion⁵². Experiments with fibroblasts from LPA₁-deficient, LPA₂-deficient, and LPA₁-LPA₂-doubly deficient mice have suggested that LPA-induced fibroblast proliferation *in vitro* can be mediated by either LPA₁ or LPA₂³⁵), although LPA-induced fibroblast proliferation was recently demonstrated to be inhibited in a dose-dependent manner by an LPA₁-selective antagonist⁵³.

We have recently demonstrated a specific requirement for LPA₁ for fibroblast proliferation *in vivo*, in the chlorhexidine gluconate mouse model of peritoneal dialysis-associated peritoneal fibrosis¹¹. Genetic deletion or selective pharmacological antagonism of LPA₁ significantly attenuated peritoneal fibroblast proliferation, as well as the development of peritoneal fibrosis, induced by chlorhexidine¹¹. We found evidence that as fibrosis develops in this model, LPA-LPA₁ signaling is at the center of a pro-fibrotic collaboration between peritoneal mesothelial cells and fibroblasts, in which LPA-LPA₁ signaling drives mesothelial cell CTGF expression, and this mesothelial CTGF in turn drives fibroblast proliferation in a paracrine fashion. Such a pro-fibrotic collaboration between mesothelial cells and fibroblasts is con-

sistent with accumulating evidence that paracrine interactions between multiple cell types are central to the development of pathological fibrosis⁵⁴). Although LPA has been noted to induce CTGF expression by fibroblasts themselves *in vitro*, we found robust expression of CTGF protein in peritoneal mesothelial cells rather than peritoneal interstitial cells after chlorhexidine challenge *in vivo*. This peritoneal CTGF expression was dramatically diminished by genetic deletion or pharmacological inhibition of LPA₁. LPA activation of LPA₁ on primary peritoneal mesothelial cells induced robust CTGF expression by these cells *in vitro*, through a novel G $\alpha_{12/13}$ — RhoA — myocardin-related transcription factor (MRTF)-A and -B — serum response factor (SRF) pathway¹¹). By mechanistically linking the pro-fibrotic activities of LPA and CTGF, this novel signaling pathway connects two important mediators that are currently being evaluated independently as therapeutic targets in patients with fibrotic diseases.

3) LPA-LPA₁ signaling and fibroblast resistance to apoptosis

In the course of wound-healing, apoptosis of fibroblasts is thought to help to terminate the fibroproliferative response⁵⁵). In contrast, the development of fibroblast resistance to apoptosis is thought to contribute to excessive fibroblast accumulation during the development of pathological fibrosis. Dermal fibroblasts explanted from patients with scleroderma-associated skin fibrosis are resistant to apoptosis induced *ex vivo*⁵⁶⁻⁵⁷), as are normal dermal fibroblasts that have been chronically exposed to the major pro-fibrotic cytokine transforming growth factor (TGF)- β ⁵⁸). Compared with lung fibroblasts from control subjects, lung fibroblasts isolated from patients with IPF are also resistant to apoptosis induced *ex vivo*⁵⁹). Our laboratory demonstrated that LPA signaling specifically through LPA₁ can completely suppress primary mouse lung fibroblast apoptosis induced by serum deprivation⁹), suggesting that promotion of fibroblast resistance to apoptosis is another mechanism through which LPA-LPA₁ signaling may promote fibroblast accumulation during the development of fibrosis.

4) LPA-LPA₁ signaling and epithelial cell apoptosis

Increased epithelial cell apoptosis in response to tissue injury is now believed to be a critical step in the pathogenesis of multiple fibrotic diseases. Increased numbers of apoptotic cells have been observed in the alveolar and bron-

chial epithelia of patients with IPF⁶⁰⁻⁶¹), and alveolar and bronchial epithelial cell apoptosis is also prominent in the bleomycin model of pulmonary fibrosis⁶²). Induction of pulmonary epithelial cell apoptosis in mice by anti-Fas antibody or transgenic overexpression of TGF- β results in the development of fibrosis⁶³⁻⁶⁵), as does targeted injury of alveolar epithelial cells⁶⁶). Similarly, evidence has accumulated that increased apoptosis of renal tubular epithelial cells is involved in the pathogenesis of renal fibrosis. The extent of renal fibrosis that develops in the UUO model correlates with the extent of tubular apoptosis produced⁶⁷), and inhibition of tubular apoptosis in rodent models attenuates fibrosis and/or progressive renal dysfunction⁶⁸⁻⁶⁹). Finally, targeted injury of renal epithelial cells has recently been demonstrated to induce renal fibrosis⁷⁰), as is the case with targeted injury of alveolar epithelial cells leading to pulmonary fibrosis.

We found evidence that LPA-LPA₁ signaling contributes to epithelial apoptosis during the development of pulmonary fibrosis in the bleomycin mouse model⁹). The number of apoptotic cells present in the alveolar and bronchial epithelia of LPA₁-deficient mice was significantly reduced compared with wild-type mice post-bleomycin challenge, suggesting that LPA-LPA₁ signaling promotes epithelial apoptosis after injury⁹). Consistent with these *in vivo* results, we found that LPA signaling through LPA₁ induced apoptosis in cultured bronchial and alveolar epithelial cells⁹). In these *in vitro* studies, LPA-LPA₁ signaling appeared to specifically mediate anoikis, the apoptosis of anchorage-dependent cells induced by their detachment⁷¹).

LPA-LPA₁ signaling therefore has distinct effects on the apoptotic behaviors of epithelial cells and fibroblasts, promoting apoptosis in the former but suppressing apoptosis in the latter. These results are consistent with previous studies of LPA's effects on apoptosis, which showed them to be cell-specific, promoting apoptosis of certain cell types but inhibiting apoptosis of others⁷²). Divergent susceptibilities of epithelial cells and fibroblasts to apoptosis in IPF has been referred to as an "apoptosis paradox", in which increased apoptosis of epithelial cells is present simultaneously with increased fibroblast resistance to apoptosis⁵⁹). The molecular pathways responsible for the divergent susceptibilities of epithelial cells and fibroblasts to apoptosis in IPF have yet to be fully identified, but increased LPA levels, by signaling through LPA₁, may contribute both to the increased epithelial apoptosis and the fibroblast resis-

tance to apoptosis present in the lungs in this disease.

5) LPA-LPA₁ signaling and vascular permeability

“Vascular leak” is another hallmark of tissue injury^{40, 44}, and impaired endothelial cell barrier function resulting in increased vascular permeability has been found to characterize fibrotic diseases resulting from chronic tissue injury. For example, increased alveolar-capillary permeability has been demonstrated to be present in the lungs of IPF patients and to predict worse outcomes⁷³⁻⁷⁴. Tissue injury can directly disrupt blood vessels, but it also results in the production of bioactive mediators that cause an increase in vascular permeability that persists throughout the early phases of tissue repair⁷⁵. In the lung, LPA appears to be one of the mediators that contribute to persistent vascular leak after injury. LPA is known to disrupt endothelial monolayers *in vitro* through activation of RhoA and Rho kinase within endothelial cells, which results in the formation of intracellular actin stress fibers and the opening of paracellular gaps⁷⁶. This process also appears to be mediated by LPA₁, as we have found that LPA-induced endothelial barrier disruption *in vitro* is inhibited by a selective LPA₁ receptor antagonist (AM095¹⁴, and unpublished data). LPA₁-deficient mice exhibit decreased vascular leak after bleomycin lung injury, indicating that LPA-LPA₁ signaling contributes to endothelial barrier dysfunction induced by lung injury *in vivo*⁸. The LPA-LPA₁ pathway therefore may also contribute to pathological fibrosis by increasing vascular permeability after injury.

Other LPA receptors in fibrosis

Several studies have implicated other LPA receptors in addition to LPA₁ in the development of organ fibrosis. LPA signaling through LPA₂ may contribute to TGF- β activation in the development of both pulmonary and renal fibrosis. LPA induces activation of latent TGF- β by the α v β 6 integrin through signaling pathways shown to involve LPA₂, G α _q, RhoA and Rho kinase in cultured human lung epithelial cells and renal proximal tubule cells⁷⁷⁻⁷⁸. Expression levels of both LPA₂ and the α v β 6 integrin were upregulated during the development of bleomycin-induced pulmonary fibrosis in mice, and both proteins co-localized in the fibrotic lung epithelium in this model⁷⁷. LPA₂ and β 6 integrin expression were similarly increased in a rat model of renal fibrosis induced by ischemic reperfusion injury⁷⁸. In contrast, LPA₂-deficient mice were not protected from

bleomycin-induced dermal fibrosis in a mouse model of scleroderma¹⁴, suggesting that the involvement of LPA₂ in the development of fibrosis might vary in different organs and in fibrosis produced by different causes. Expression of LPA₃ is elevated in addition to that of LPA₁ in a mouse model of radiation-induced pulmonary fibrosis⁵¹. Finally, although as discussed above we demonstrated that LPA-LPA₁ signaling contributes to endothelial barrier dysfunction induced by lung injury in the bleomycin mouse model of pulmonary fibrosis *in vivo*⁸, recent evidence suggests that LPA₆ mediates barrier dysfunction induced by LPA in human pulmonary artery endothelial cell monolayers *in vitro*⁷⁹. Thus multiple LPA receptors in addition to LPA₁ may contribute to LPA's effects in organ fibrosis.

Conclusions

LPA mediates a wide spectrum of basic cell behaviors, including cell contraction, migration, survival, proliferation, and gene expression, many of which are fundamentally involved in wound-healing responses to injury. Recent studies indicate that LPA signaling specifically through LPA₁ regulates several of the aberrant or excessive wound-healing responses implicated in the pathogenesis of fibrotic diseases. LPA-LPA₁ signaling has pro-fibrotic effects on multiple cell types, including the promotion of fibroblast migration, proliferation and resistance to apoptosis, the promotion of epithelial cell apoptosis, and the impairment of endothelial cell barrier function. Consistent with these broad pro-fibrotic activities of LPA-LPA₁ signaling, inhibition of this pathway has been demonstrated to have broad anti-fibrotic effects. Targeting the LPA-LPA₁ pathway has been demonstrated to be an effective therapeutic strategy in multiple mouse models of fibrotic diseases, affecting multiple different organs. The breadth of these effects suggests that LPA signaling through LPA₁ represents a core pathway in the development of fibrosis that has likely been conserved across mammalian species, and underscores the rationale for clinical trials of LPA-LPA₁ pathway inhibitors in human fibrotic diseases.

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Conflict of interest

The authors have no conflicting financial interests.

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