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Review Article

Lysophosphatidic acid (LPA) signaling through LPA_1 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 LPA_1, 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-LPA_1 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-LPA_1 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-LPA_1 pathway has recently been demonstrated to have profound anti-fibrotic effects. Targeting LPA-LPA_1 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 LPA_1 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 consequently 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

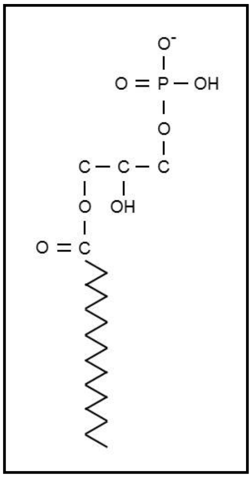

Fig.1 Chemical structure of LPA

LPA is the common name for a family of 1-acyl-2-hydroxy-sn-glycero-3-phosphate and 1-hydroxy-2-acyl-sn-glycero-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 $LPA_{1\text{-}6}$2-3). 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 LPA_1 mediates pro-fibrotic responses of multiple cell types, including fibroblasts, endothelial cells and epithelial cells7-9). We and others have recently demonstrated that LPA-LPA_1 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 LPA_1 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 acid2, 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 skin8, 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 A_1 or A_2, 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 phosphateses (LPPs), LPA acyltransferase (LPAAT) or lysophospholipases24-25). Of these, hydrolysis of LPA by LPPs appears to the major pathway responsible for LPA degradation *in vivo*26).

LPA receptors

The six definitively identified LPA receptors, $LPA_{1\text{-}6}$, are all type 1 rhodopsin-like GPCRs with seven-transmembrane alpha helices2-3, 5-6, 27). Of these receptors, $LPA_{1\text{-}3}$ belong to

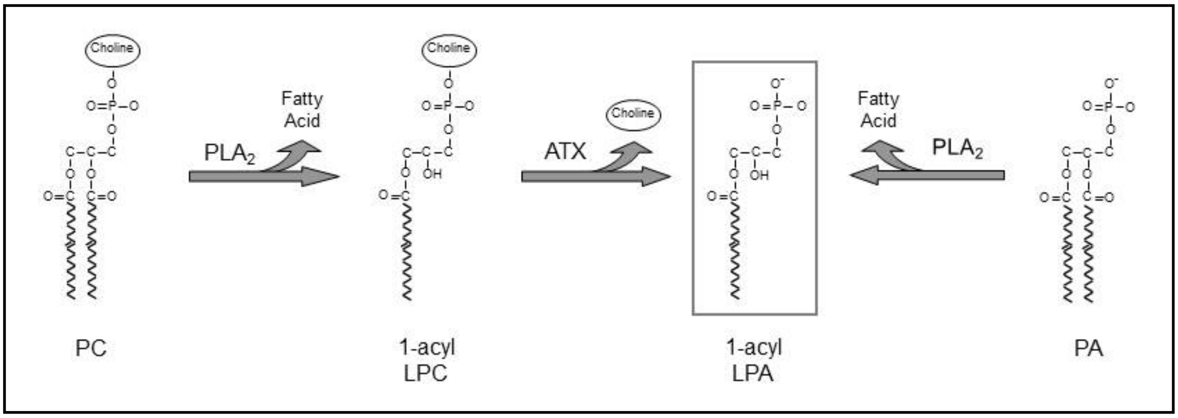

Fig.2 Major pathways of LPA synthesis

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 A$_2$ (PLA$_2$) 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, PLA$_2$ enzymes can produce LPA directly by hydrolysis of phosphatidic acid (PA). PLA$_1$ 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$_1$	$G\alpha_i$, $G\alpha_q$, $G\alpha_{12/13}$	Fibroblast migration, resistance to apoptosis and pro-fibrotic gene expression	8, 51-52, 81
		Epithelial cell apoptosis	9
		Vascular barrier disruption and vascular smooth muscle cell migration after injury	8, 82
		Inhibition of adipogenesis	83
		Brain and bone development	84-85
		Neuroprogenitor cell survival and differentiation	86
		Neuron survival, synaptic regulation and release of neurotransmitters	84, 87-88
		Neuropathic pain	89
		Cancer cell invasion and metastasis	90, 91
LPA$_2$	$G\alpha_i$, $G\alpha_q$, $G\alpha_{12/13}$	Activation of latent TGF-β	77-78
		Vascular smooth muscle cell migration after injury	82
		Inhibition of dendritic cell activation	92
		Neuroprogenitor cell survival and differentiation	86
		Colon carcinogenesis	93-94
		Ovarian and endometrial cancer cell proliferation, migration, and invasion	95-96
LPA$_3$	$G\alpha_i$, $G\alpha_q$	Timing and spacing of embryo implantation	97
		Spermatogenesis	98
		Chemotaxis of immature dendritic cells	99
		Neuropathic pain	100
P2Y family			
LPA$_4$	$G\alpha_s$, $G\alpha_i$, $G\alpha_q$, $G\alpha_{12/13}$	Blood and lymphatic vessel development	101
		Suppression of LPA$_1$-driven cell migration and invasion	102
LPA$_5$	$G\alpha_q$, $G\alpha_{12/13}$	Neuropathic pain	103
LPA$_6$	$G\alpha_s$, $G\alpha_i$, $G\alpha_{12/13}$	Vascular barrier disruption	79
		Hair growth	28, 104-105

the endothelial differentiation gene (EDG) family, and share substantial sequence homology. In contrast, LPA$_{4\text{-}6}$ all belong to the P2Y receptor family, whose ligands are typically nucleotides rather than lysophospholipids, and comprise a second subgroup of LPA receptors[28-29]. The LPA receptors consequently have evolved through at least two distinct lineages in the GPCR family.

LPA$_1$, 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 body[30]. LPA$_4$ and LPA$_5$ have also been found to be broadly expressed, whereas tissues with high expression of LPA$_2$, LPA$_3$ and LPA$_6$ appear to be more limited. LPA$_2$ is highly expressed in immune organs such as thymus and spleen[31], LPA$_3$ is highly expressed in reproductive organs such as testis and uterus[32], and LPA$_6$ is highly expressed in hair follicles, where it has been identified as an important mediator of hair growth[28].

The different LPA receptors couple to different extents with heterotrimeric G-proteins containing different Gα subunits, including Gα_i, Gα_s, Gα_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 organs[34]. LPA$_1$ and LPA$_2$ couple to Gα_i-containing G-proteins, through which these receptors suppress cAMP levels and activate Ras, Rac and ERK[27, 30, 35]. LPA$_1$ and LPA$_2$ also couple to G$\alpha_{12/13}$-containing G-proteins to induce actin cytoskeleton rearrangements through activation of the small GTPase RhoA[35]. Each of the EDG subfamily of LPA receptors, LPA$_1$, LPA$_2$ and LPA$_3$, couple to Gα_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 Gα_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-LPA$_1$ 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 LPA$_1$, leading to the recognition of LPA$_1$ 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 LPA$_1$-deficient mice are dramatically protected from fibrosis and mortality[8]. Administration of an LPA$_1$-specific antagonist also suppresses the development of pulmonary fibrosis induced by bleomycin[10]. 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 LPA$_1$ attenuates the extent of fibrosis produced[12-13]. Further, genetic deletion or pharmacological inhibition of LPA$_1$ 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 LPA$_1$ 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 neutrophils[37].

Molecules such as LPA and LPA$_1$ 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 fibrosis[38]. 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 organ[38]. Pathways such as LPA-LPA$_1$ 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 pathways[38].

LPA-LPA$_1$ 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 homeostasis[39]. Pathologic 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 LPA_1. $LPA-LPA_1$ 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 $LPA-LPA_1$ signaling in fibroblasts, epithelial cells and endothelial cells may contribute to the pathogenesis of fibrosis.

1)LPA-LPA_1 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 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 $LPA-LPA_1$ signaling is predominantly responsible for fibroblast recruitment to sites of lung injury in the bleomycin mouse model of lung fibrosis. Consistent with this hypothesis, LPA_1-deficient mice demonstrated diminished fibroblast accumulation in their lungs after bleomycin challenge8). We found analogous evidence that $LPA-LPA_1$ 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, LPA_1 was highly expressed by fibroblasts recovered from these samples, and inhibition of LPA_1 markedly reduced fibroblast responses to the chemotactic activity of those BAL samples8).

2)LPA-LPA_1 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 LPA_1-deficient, LPA_2-deficient, and LPA_1-LPA_2-doubly deficient mice have suggested that LPA-induced fibroblast proliferation *in vitro* can be mediated by either LPA_1 or $LPA_2$35), although LPA-induced fibroblast proliferation was recently demonstrated to be inhibited in a dose-dependent manner by an LPA_1-selective antagonist53).

We have recently demonstrated a specific requirement for LPA_1 for fibroblast proliferation *in vivo*, in the chlorhexidine gluconate mouse model of peritoneal dialysis-associated peritoneal fibrosis11). Genetic deletion or selective pharmacological antagonism of LPA_1 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, $LPA-LPA_1$ signaling is at the center of a pro-fibrotic collaboration between peritoneal mesothelial cells and fibroblasts, in which $LPA-LPA_1$ 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 consistent with accumulating evidence that paracrine interactions between multiple cell types are central to the development of pathological fibrosis[54]. 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 LPA_1. LPA activation of LPA_1 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) pathway[11]. 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 response[55]. 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 profibrotic 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 LPA_1 can completely suppress primary mouse lung fibroblast apoptosis induced by serum deprivation[9], suggesting that promotion of fibroblast resistance to apoptosis is another mechanism through which LPA-LPA_1 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 bronchial epithelia of patients with IPF[60-61], and alveolar and bronchial epithelial cell apoptosis is also prominent in the bleomycin model of pulmonary fibrosis[62]. Induction of pulmonary epithelial cell apoptosis in mice by anti-Fas antibody or transgenic overexpression of TGF-β results in the development of fibrosis[63-65], as does targeted injury of alveolar epithelial cells[66]. 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 produced[67], and inhibition of tubular apoptosis in rodent models attenuates fibrosis and/or progressive renal dysfunction[68-69]. Finally, targeted injury of renal epithelial cells has recently been demonstrated to induce renal fibrosis[70], as is the case with targeted injury of alveolar epithelial cells leading to pulmonary fibrosis.

We found evidence that LPA-LPA_1 signaling contributes to epithelial apoptosis during the development of pulmonary fibrosis in the bleomycin mouse model[9]. The number of apoptotic cells present in the alveolar and bronchial epithelia of LPA_1-deficient mice was significantly reduced compared with wild-type mice post-bleomycin challenge, suggesting that LPA-LPA_1 signaling promotes epithelial apoptosis after injury[9]. Consistent with these *in vivo* results, we found that LPA signaling through LPA_1 induced apoptosis in cultured bronchial and alveolar epithelial cells[9]. In these *in vitro* studies, LPA-LPA_1 signaling appeared to specifically mediate anoikis, the apoptosis of anchorage-dependent cells induced by their detachment[71].

LPA-LPA_1 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 others[72]. 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 apoptosis[59]. 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 LPA_1, may contribute both to the increased epithelial apoptosis and the fibroblast resistance 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 outcomes[73-74]. 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 repair[75]. 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 gaps[76]. 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 (AM095[14], 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 though 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 $\alpha v\beta 6$ integrin though signaling pathways shown to involve LPA2, Gαq, RhoA and Rho kinase in cultured human lung epithelial cells and renal proximal tubule cells[77-78]. Expression levels of both LPA2 and the $\alpha v\beta 6$ 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 model[77]. LPA2 and β6 integrin expression were similarly increased in a rat model of renal fibrosis induced by ischemic reperfusion injury[78]. In contrast, LPA2-deficient mice were not protected from bleomycin-induced dermal fibrosis in a mouse model of scleroderma[14], 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 fibrosis[51]. 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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