thematic review

Thematic Review Series: Lysophospholipids and their Receptors

LPA receptor signaling: pharmacology, physiology, and pathophysiology

Yun C. Yung,* Nicole C. Stoddard,*,† and Jerold Chun[1,]*

Department of Molecular and Cellular Neuroscience,* Dorris Neuroscience Center, The Scripps Research Institute, La Jolla, CA 92037; and Biomedical Sciences Graduate Program,† University of California, San Diego School of Medicine, La Jolla, CA 92037

Abstract Lysophosphatidic acid (LPA) is a small ubiquitous lipid found in vertebrate and nonvertebrate organisms that mediates diverse biological actions and demonstrates medicinal relevance. LPA's functional roles are driven by extracellular signaling through at least six 7-transmembrane G protein-coupled receptors. These receptors are named LPA_{1-6} and signal through numerous effector pathways activated by heterotrimeric G proteins, including $G_{i/o}$, $G_{12/13}$, G_q, and G_s. LPA receptor-mediated effects have been described in numerous cell types and model systems, both in vitro and in vivo, through gain- and loss-of-function studies. These studies have revealed physiological and pathophysiological influences on virtually every organ system and developmental stage of an organism. These include the nervous, cardiovascular, reproductive, and pulmonary systems. Disturbances in normal LPA signaling may contribute to a range of diseases, including neurodevelopmental and neuropsychiatric disorders, pain, cardiovascular disease, bone disorders, fibrosis, cancer, infertility, and obesity. These studies underscore the potential of LPA receptor subtypes and related signaling mechanisms to provide novel therapeutic targets.—Yung, Y. C., N. C. Stoddard, and J. Chun. **LPA receptor signaling: pharmacology, physiology, and pathophysiology. *J. Lipid Res.* 2014. 55: 1192–1214.**

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Lysophosphatidic acid (LPA) is a small glycerophospholipid (molecular mass: 430–480 Da) that acts as a potent extracellular signaling molecule through at least six cognate G protein-coupled receptors (GPCRs) in numerous developmental and adult processes involving virtually all vertebrate systems. All LPA molecules consist of a glycerol backbone connected to a phosphate head group and are commonly ester-linked to an acyl chain of varied length and saturation. These various chemical forms of LPA are derived from multiple sources, such as membrane lipids (1), and exist as bioactive ligands that signal through cognate receptors to produce a wide number of physiological responses (**Fig. 1**).

In the 1960s, studies on smooth muscle and blood pressure hinted at the bioactivity of LPA (2, 3). In later years, various LPA species were isolated and identified from soy beans (4). This raised intriguing questions regarding this lipid's mechanism of action, which was then thought to include membrane perturbation (5), calcium chelation (6), second messenger signaling (7), intracellular receptors (8), and cell-surface receptors (9). These contending theories were clarified upon the cloning and identification of the first lysophospholipid receptor, LPA_1. This GPCR was previously known as "ventricular zone (VZ) gene-1" because of its enriched expression in the embryonic neuroproliferative layer of the cerebral cortex (10, 11). The cloning and functional identification of LPA_1 led to the deorphanization of other putative receptor genes based upon sequence homology (12–14), particularly "endothelial differentiation gene" (EDG) members (15) that include LPA and sphingosine 1-phosphate (S1P) receptors. The significant homology between LPA_1

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Abbreviations: ATX, autotaxin; BrP-LPA, α-bromomethylene phosphonate; cPLA, cytosolic phospholipase A; CSF, cerebrospinal fluid; DC, dendritic cell; DGPP, diacylglycerol pyrophosphate; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; Enpp2, ectonucleotide pyrophosphatase/phosphodiesterase family member 2; FH, fetal hydrocephalus; GPCR, G protein-coupled receptor; IL, interleukin; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; LPP, lipid phosphate phosphatase; LPS, lysophosphatidylserine; $maLPA_1$, Málaga lysophosphatidic acid 1; NPC, neuroprogenitor cell; OL, oligodendrocyte; OMPT, 1-oleoyl-2-*O*-methyl-*rac*-glycerophospho-thionate; PA, phosphatidic acid; PI3K, phosphatidylinositol 3-kinase; PLA_1, phospholipase A1; PLA_2, phospholipase A2; PLC, phospholipase C; PSNL, partial sciatic nerve ligation; ROCK, Rho-associated kinase; SC, Schwann cell; SMC, smooth muscle cell; TGF, transforming growth factor; 7-TM, 7-transmembrane; VEGF, vascular endothelial growth factor; VZ, ventricular zone.

[1] To whom correspondence can be addressed.
e-mail: jchun@scripps.edu

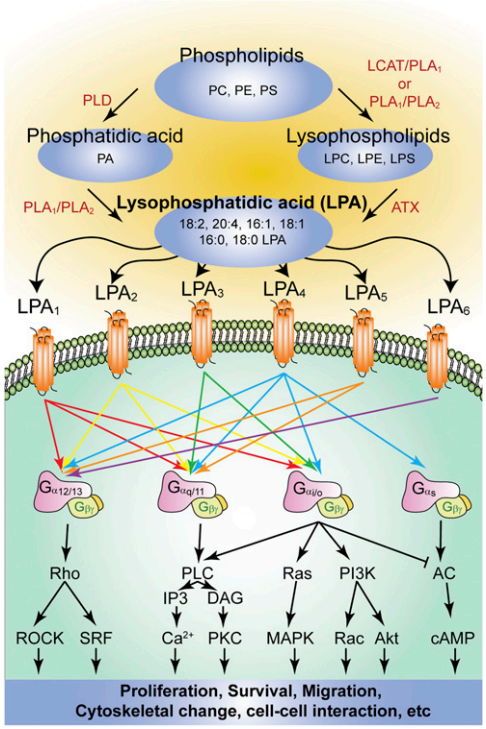

Fig. 1. Summary of the major routes of LPA synthesis and the activated signaling pathways via the six cognate LPA receptors. Enzymes are indicated in red. PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; PLD, phospholipase D.

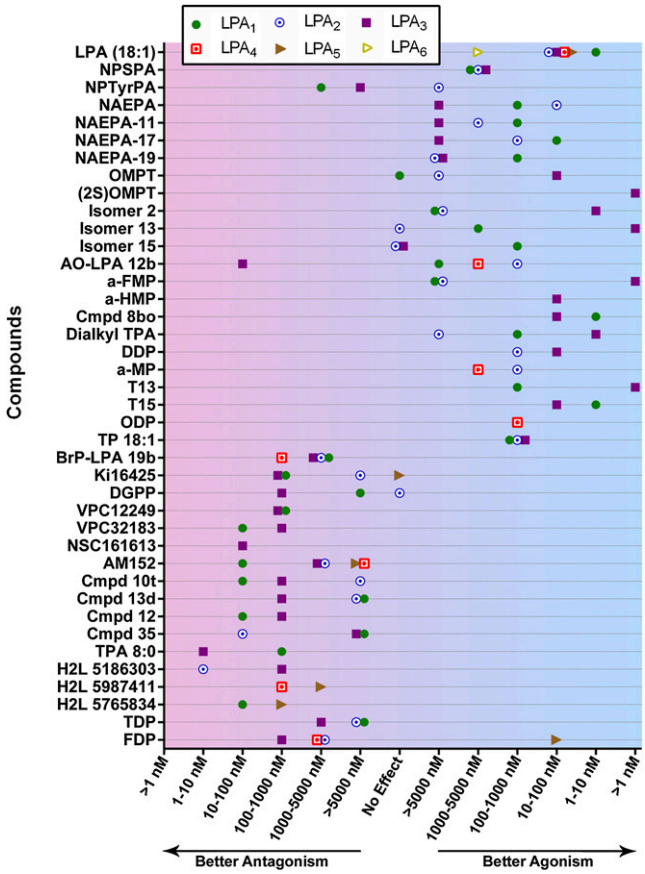

Fig. 2. Effects of LPA receptor agonists and antagonists. LPA receptor modulating compounds are classified according to their potency against each receptor, LPA_1–LPA_6. Ranges of compound EC_{50}, IC_{50}, or K_i values are given on the *x* axis, progressing from strong antagonism on the left to strong agonism on the right. A subset of these compounds is shown in more detail in Table 2. This graph was prepared using GraphPad Prism software. Cmpd, compound; NPSPA, *N*-palmitoyl serine phosphoric acid; NPTyrPA, *N*-palmitoyl tyrosine phosphoric acid; NAEPA, *N*-acyl ethanolamide phosphate; AO-LPA 12b, *sn*-2-aminooxy analog 12b; a-FMP, α-fluoromethylene phosphonate; a-HMP, α-hydroxymethylene phosphonate; TPA, thiophosphatidic acid; DDP, dodecyl phosphate; a-MP, α-methylene phosphonate; ODP, octadecenyl phosphate; TP 18:1, oleoyl-thiophosphate; BrP-LPA 19b, α-bromomethylene phosphonate analog 19b; TDP, tetradecyl phosphonate; FDP, farnesyl diphosphate.

and $S1P_1$ was underscored by early reports of EDG-1 as a LPA receptor (16). At the time of LPA_1 identification, the only functional homologous receptor was the cannabinoid receptor CB1 (encoded by *CNR1*) that interacts with the endogenous lipids anandamide and 2-arachidonoylglycerol (17, 18). Two other LPA receptors, LPA_2 and LPA_3, were subsequently discovered based on shared homology with LPA_1. In the past ten years, three additional LPA receptors have been discovered ($LPA_{4–6}$) (19–23) that are members of the P2Y purinergic family (Fig. 1). These receptors have significantly different encoding sequences than $LPA_{1–3}$, yet still bind and mediate LPA signaling effects. All six current LPA receptors are class A rhodopsin-like GPCRs with 7-transmembrane (7-TM) domains. Every receptor couples to at least one or more of the four heterotrimeric G_α proteins ($G_{12/13}$, $G_{q/11}$, $G_{i/o}$, and G_s) (Fig. 1), resulting in canonical downstream signaling that produces diverse physiological and pathophysiological effects. Other types of lysophospholipids, such as lysophosphatidylserine (LPS), lysophosphatidylinositol, and lysophosphatidylethanolamine (LPE), have some reported bioactivity and are being evaluated for the involvement of possible cognate receptors (24). An additional important aspect of LPA receptor biology is that various chemical forms of LPA may differentially activate LPA receptor subtypes (25). This finding has been supported by secondary readouts of receptor activity, because direct confirmation through classical receptor binding studies has been difficult.

LPA METABOLISM

There are two major synthetic pathways for LPA. In the first pathway, the precursor phospholipids (phosphatidylcholine, phosphatidylserine, or phosphatidylethanolamine) can be converted to their corresponding lysophospholipids such as lysophosphatidylcholine (LPC), LPS, or LPE. In platelets, this occurs via phosphatidylserine-specific phospholipase A1 ($PS\text{-}PLA_1$) or secretory phospholipase A2 ($sPLA_2$) activity. In plasma, LPC is produced by LCAT and PLA_1 activity. In either location, lysophospholipids can then be converted to LPA via autotaxin (ATX) activity (Fig. 1). In the second major pathway, phosphatidic acid (PA) is first produced from phospholipids through phospholipase D or from diacylglycerol through diacylglycerol

kinase. Then, PA is converted directly to LPA by the actions of either PLA_1 or PLA_2 (26) (Fig. 1).

Through a separate mechanism, LPA can be generated through the acylation of glycerol-3-phosphate by glycerophosphate acyltransferase and the phosphorylation of monoacylglycerol by monoacylglycerol kinase (27). Additional LPA-producing pathways also exist (26, 28). LPA generation from membrane phospholipids occurs in both intracellular and extracellular fashions (28). Intracellular LPA is an important intermediate for the de novo biosynthesis of complex glycerolipids, including mono-, di-, and triglycerides, as well as phospholipids (28). Extracellular LPA is thought to mediate bioactive effects through LPA receptors (29). Furthermore, a report supporting LPA as a functional ligand for the intracellular transcription factor PPARγ exists, although it remains to be examined (30).

LPA has been found in all eukaryotic tissues examined. The formation of an LPA species depends on its precursor phospholipid, which can vary by acyl chain length and degree of saturation. The term LPA most often refers to 18:1 oleoyl-LPA (1-acyl-2-hydroxy-*sn*-glycero-3-phosphate), as it is the most commonly used laboratory species. However, there is a growing range of recognized chemical forms of LPA in various biological systems (31, 32) that have been observed in concentrations spanning low nanomolar to micromolar levels. LPA concentrations in blood can range from 0.1 μM in plasma and up to 10 μM in serum, which is well over the apparent nanomolar K_d of LPA_{1-6} (23, 33–35). The 18:2, 20:4, 16:1, 16:0, and 18:1 LPA forms are particularly abundant in plasma (36–38). Aside from blood, LPA has been quantified in a variety of species, tissues, and fluids, including neural tissue, cerebrospinal fluid (CSF), seminal fluid, urine, saliva, and aqueous humor (7, 36, 39–45) (**Table 1**). Current methods to detect LPA include indirect enzymatic assays (34), TLC-GC, LC-MS, and LC-MS/MS (46–48). These techniques have a growing number of predictive, diagnostic, and therapeutic uses (29, 43, 49, 50).

LPA degradation is mediated by several classes of enzymes, including three types of lipid phosphate phosphatases (LPPs) (51), LPA acyltransferase, and various phospholipases (e.g., PLA_1 or PLA_2) (28, 52, 53). LPA may be converted back to PA by LPA acyltransferase, hydrolyzed by LPP (1–3), or converted by phospholipases into glycerol-3-phosphate (28, 54).

ATX

ATX is one of the best studied enzymes associated with LPA signaling. ATX was first identified and purified as "autocrine motility factor" from human melanoma cells and was perceived to be an ectonucleotide pyrophosphatase/phosphodiesterase family member 2 (*Enpp2*). Furthermore, because the addition of pertussis toxin reduced cellular motility, ATX's effects were thought to involve $G_{i/o}$-mediated signaling (55). Extracellular LPA was found to be produced in sub-millimolar concentrations by lysophospholipase D activity in plasma (39). The responsible enzyme was subsequently identified as ATX (56, 57). It is clear now that ATX-mediated autocrine signaling induces cell motility through LPA production and $G_{i/o}$-mediated LPA receptor signaling (29, 58, 59).

ATX has broad tissue expression, with comparatively high levels in blood, brain (especially the choroid plexus and embryonic floor plate), kidney, and lymphoid organs (60–62). Secretion of ATX leads to high expression and concentration in CSF and in the high endothelial venules

TABLE 1. Summary of LPA concentrations in various tissues and biological fluids

Tissues/Fluids	LPA	LPC	Method of Measurement	References
Physiological conditions				
Embryonic brain	0.32–0.35 pmol/mg[a]	Not available	LC-MS	(43)
Adult brain	3.7–35 pmol/mg[a]	Not available	GC-MS, LC-MS/MS	(32, 47, 339, 340)
Nerve (spinal cord)	0.79 pmol/mg[a]	Not available	B103 bioassay	(42)
Plasma	0.7 μM[b]/0.17–0.63 μM[a]	100-140 μM[b]/440 μM[a]	LC-MS, RH7777 bioassay	(38, 239, 299, 341)
Serum	4–15.5 μM[b]	234 μM[b]	TLC-GC, enzymatic assay, LC-MS/MS	(166, 342, 343)
CSF	0.025–0.2 pM[a]	Not detected[a]	RH7777 bioassay	(344)
Seminal fluid	Negligible	8–19 μM[b]	RH7777 bioassay, enzymatic cycling	(41)
Saliva	0.785 nM[b]	Not available	FAB-MS	(345)
Lacrimal gland fluid	1.3 μM[a]	Not available	MS	(45)
Aqueous humor	0.2 μM[b]	Not available	MS	(45)
Follicular fluid	25.3 μM[b]	157 μM[b]	TLC-GC	(166)
Ascites	0.62 μM[b]	Not available	RH7777 bioassay	(299)
Fertilized hen white	8.0-9.6 μM[a]	Not available	LC-MS	(179)
Pathophysiological conditions				
Nerve (injury)	74.8 pmol/mg[a]	Not available	B103 bioassay	(42)
Serum (systemic sclerosis)	5.5 μM[b]	130 μM[b]	LC-MS/MS	(239)
Serum (sepsis)	Not available	43.5 μM[b]	Enzymatic assay	(343)
Ascites (pancreatic cancer patients)	2.7 μM[a]	Not available	RH7777 bioassay	(299)
Plasma (chronic liver injury)	0.3-0.4 μM[a]	Not available	Enzymatic assay	(346)
Plasma (obesity)	Not available	83.5–84.4 μM[b]/420–460 μM[a]	LC-MS	(341)

Measurements were performed using a variety of techniques under numerous conditions, resulting in a range of values (associated errors were omitted for simplicity). References are indicated in parentheses. FAB-MS, fast atom bombardment MS.

[a]Values from nonhuman organisms.

[b]Values from humans.

of lymphoid organs (63–66). Genetic deletion of ATX in mice (*Enpp2*$^{-/-}$ mutants) has contributed significant understanding to this enzyme's physiological role. These mice die at embryonic day (E)9.5 with obvious vascular and neural tube defects (67, 68). In addition, they have a poorly formed yolk sac vascular network, as well as enlarged embryonic vessels, malformed allantois, reduced axial turning, kinked neural tube, and an asymmetric neural head fold (68, 69). *Enpp2*$^{+/-}$ heterozygotes appear normal, but have a 50% reduction in LPA plasma levels compared with wild-type mice. Thus, ATX activity is significantly responsible for the correct concentration of LPA in plasma, as well as for proper vascular and embryonic development.

ATX and LPA signaling are involved in the vasoregulation and vascular biology of multiple species (4, 70, 71). ATX expression can be induced by vascular endothelial growth factor (VEGF), and the resultant elevation of LPA induces both proliferation and migration of endothelial cells, as well as barrier formation in vitro (72–75). Such endothelial cell behaviors require a variety of additional activated-platelet mediators, such as growth factors and cytokines. LPA is also released from activated platelets (36), which can induce platelet activation through positive feedback (40, 76). In general, LPA production and signaling can induce mitogenic and migratory effects on numerous cell types that are involved in angiogenesis and tissue repair (73, 77–79). Despite these data, some controversy exists as to whether LPA and ATX are truly angiogenic, although both appear to help in vessel maintenance. Interestingly, increased LPA levels can rapidly and reversibly increase blood brain barrier permeability (80), suggesting a concentration-dependent mechanism. Finally, LPA can also regulate vascular tone, such as posthemorrhagic vasoconstriction in cerebral microvasculature (81) or vasodilation in the thoracic aorta (82). These opposing actions may be context dependent.

LPA RECEPTORS

The diverse and numerous physiological effects of LPA are mediated through six currently recognized LPA receptors, $LPA_{1–6}$: protein names LPA_1–LPA_6 and gene names *LPAR1–LPAR6* (human) and *Lpar1–Lpar6* (nonhuman) (11, 83). These 7-TM GPCRs couple to at least one or more of the four G_α proteins ($G_{12/13}$, $G_{q/11}$, $G_{i/o}$, and G_s) that initiate a variety of signaling cascades. The spatiotemporal distribution of LPA and LPA receptors, typically differential receptor subtypes in specific tissues, drives the abundance of the physiological and pathophysiological processes noted here.

LPA_1

LPA_1 was the first lysophospholipid receptor identified (10) and is the best studied of the six LPA receptors. The *LPAR1* gene (human chromosome locus 9q31.3) encodes a 41 kDa protein containing 364 amino acids with 7-TM domains. In mice, the *Lpar1* gene (mouse chromosome locus 4, 32.2 cM) encodes five exons with a conserved intron (shared among *Lpar1–3*) interrupting TM domain 6. There is a variant of *Lpar1* (mrec1.3) that results in an 18 amino acid deletion of the N terminus (84), but its biological significance is unknown. LPA_1 shares ~50–60% amino acid sequence identity with LPA_2 and LPA_3. While no complete crystal structures have been reported for any LPA receptors to date, crystallization of other GPCRs have facilitated constraint modeling for LPA_1, particularly in the second extracellular loop (85). Additionally, computer-modeled mutagenesis studies have identified three key residues in $LPA_{1–3}$ signaling. R3.28A and K7.36A are both important for the efficacy and potency of LPA, while Q3.29A decreases ligand interaction and activation (86), based primarily on secondary readouts. Future structural analyses of LPA_1 will help clarify key residues.

LPA_1 couples with three types of G_α proteins: $G_{i/o}$, $G_{q/11}$, and $G_{12/13}$ (Fig. 1), which initiate downstream signaling cascades though phospholipase C, MAPK, Akt, and Rho. LPA_1 activation alters a range of cellular responses, including cell proliferation and survival, cell-cell contact through serum-response element activation, cell migration and cytoskeletal changes, Ca^{2+} mobilization, and adenylyl cyclase inhibition (15, 77, 87).

There is wide distribution of *Lpar1/LPAR1* expression in both adult mice and humans, including in the brain, uterus, testis, lung, small intestine, heart, stomach, kidney, spleen, thymus, placenta, and skeletal muscle (13, 87, 88). *Lpar1* expression is more restricted during embryonic development, including portions of the brain, dorsal olfactory bulb, limb buds, craniofacial region, somites, and genital tubercle (89, 90). *Lpar1* expression is regulated both spatially and temporally. For example, in the developing nervous system (77, 87), *Lpar1* is found in several areas, including the germinal neuroepithelium or VZ, portions of the midbrain, and superficially in the marginal zone and meninges (10, 43, 89, 91). Though the VZ disappears at birth, *Lpar1* expression continues in the hindbrain and the white matter tracks during oligodendrocyte (OL) myelination of the postnatal brain (92). Visualization of LPA_1 expression (as well as other LPA receptors) has been hampered by lack of validated antibodies.

LPA signaling has numerous effects on key neurodevelopmental processes, including cerebral cortex formation and function (93–95), neural cell proliferation, survival, growth cone retraction, migration, and adhesion (90, 95–102). Interestingly, studies have also found evidence of concentration-dependent LPA-mediated necrosis as well as apoptosis, possibly through oxidative stress (103–105). In vitro experiments have demonstrated the effects of LPA_1-mediated stimulation that increase the proliferation and differentiation on primary neuroprogenitor cell (NPC) cultures, neuronal cell lines, and primary neurons (90, 106, 107). Additional LPA_1-mediated neural effects have also been observed in nonmammalian organisms, in which analogs of LPA_1 and LPA_2 could regulate cortical actin assembly in *Xenopus* embryos (108).

LPA can generate diverse cellular responses, and the interacting proteins that mediate downstream signaling

pathways are being uncovered. Toward elucidating these interactions, one study demonstrated that LPA_1 (but not other tested LPA receptors) is trafficked to early endosomes through a PDZ-mediated motif that facilitates its binding to GAIP interacting protein, C-terminus (GIPC), which attenuates LPA-mediated Akt signaling from adaptor protein containing PH domain (APPL) signaling endosomes (109). Other studies identified LPA as a critical regulator of the Hippo-Yes-associated protein (YAP) pathway, which controls LPA-induced gene expression, cell migration, and cell proliferation. This pathway was predominantly activated through G_{13} stimulation, presumably via the RhoA-Rho-associated protein kinase (ROCK) pathway, while G_s activity inhibited YAP function (110, 111). While the critical LPA receptors in this pathway are still being investigated, there is evidence for varying LPA_1, LPA_2, and LPA_3 involvement within different cell types.

Removal of *Lpar1* by constitutive deletion has provided insight into the in vivo functions of this receptor. *Lpar1*$^{-/-}$ mouse litters have 50% perinatal lethality related to impaired suckling behavior (90), which was attributed to defective olfaction. Surviving *Lpar1*$^{-/-}$ mice have a significantly reduced body size, craniofacial dysmorphism with blunted snouts, and increased apoptosis in sciatic nerve Schwann cells (SCs) (90). When the original *Lpar1*$^{-/-}$ line was expanded, a spontaneous variant arose that was named "Málaga LPA_1" ($maLPA_1$) (93). The $maLPA_1$ variant has negligible perinatal lethality, but displays more severe brain defects than the *Lpar1*$^{-/-}$ line. Neurodevelopment defects in $maLPA_1$ include reduced NPC proliferation, increased cerebral cortical apoptosis, decreased cortical size, and premature expression of neuronal markers (93). Defects in the proliferation, differentiation, and survival of new neurons were also impacted during adult hippocampal neurogenesis (112). Additionally, $maLPA_1$ mice showed several behavioral deficits, including inhibition of fear extinction (113) and aggravation of chronic stress-induced impairment to hippocampal neurogenesis (114). Recently, an *Lpar1*$^{-/-}$ rat hypomorph generated by N-ethyl-N-nitrosourea (ENU) mutation also showed some physical defects reminiscent of the mouse knockout (115). In addition to NPC and neurons, LPA_1 signaling is also prominently involved in glial biology, which includes macroglia such as astrocytes, OLs, and SCs, as well as microglia. Astrocytes are the most abundant type of glia and play a significant role in developmental, functional, and pathological processes (116). While basal in vivo astrocytes have undetectable levels of LPA_1 (91, 92, 117), cultured astrocytes express LPA_{1-5} (118) and are responsive to LPA. Such effects include calcium influx, phosphorylation of ERK, morphological changes, and stabilization of stress fibers (119–121). LPA_1 is also implicated in astrocyte proliferation and astrogliosis, although the relevant receptors have not been conclusively identified (122). Lipopolysaccharide or interleukin (IL)-1β-primed astrocyte migration appears to involve a $G_{i/o}$/phosphatidylinositol 3-kinase (PI3K)/Rac1 response to LPA, in contrast to their normal proliferative response via $G_{12/13}$ (123). However, some controversy regarding this proliferation pathway exists, possibly due to different culture systems (124). In addition, both LPA_1 and LPA_2 signaling can increase neuronal differentiation by LPA-primed astrocytes through unidentified astrocyte-derived soluble factors (125), possibly epidermal growth factor (EGF) (126) or nerve growth factor (127), hinting at a rich LPA-mediated biology between astrocytes and neurons.

Another glial cell type, the OL, also expresses LPA_1 (91, 92, 128). These cells produce myelin, ensheathing neurons in the CNS. Basally, *Lpar1* colocalizes with proteolipid protein and myelin basic protein (MBP), but not glial fibrillary acidic protein (91, 92). During development, *Lpar1* expression in OLs emerges just prior to maturation/myelination, suggesting an important role in controlling these processes, although no effect of LPA on OL survival, maturation, myelination, or cytoskeleton organization was reported in vitro (129). However, both the rat OL precursor cell line CG-4 and freshly isolated precursors respond via Rho-ROCK cell rounding upon LPA exposure, in contrast to differentiated OLs (130). Similarly, LPA increases the network area of dendritic processes and MBP expression in differentiating OLs (131). Therefore, LPA may regulate OL function in a maturation stage-specific manner. Additional studies will better define LPA signaling activity in this cell type.

SCs, which are counterparts to OLs in the peripheral nervous system, have also been implicated in LPA signaling. Two main types of SCs exist: myelinating SCs express *Lpar1* and possibly *Lpar2* (100, 132), while terminal SCs express both *Lpar1* and *Lpar3* (100, 132). SC survival is increased by LPA through LPA_1 and G_i/PI3K/Akt in vitro (133), which is supported in vivo by observations that *Lpar1*$^{-/-}$ mice have increased apoptosis of SCs in sciatic nerves (90). In addition to SC survival, LPA also induces morphological and cell adhesion changes. In vitro, LPA induces SC wreath formation and enhances focal adhesions, as well as promoting N-cadherin-dependent cell aggregation (100), responses that are dramatically reduced in *Lpar1*$^{-/-}$ SCs (100). LPA can also increase the expression of P0 protein in SCs through LPA_2 signaling, possibly contributing to SC differentiation (134). Recently, LPA_1 was shown to influence embryonic SC migration, adult myelination, and cell-to-axon segregation, processes that appear to be defective in *Lpar1*$^{-/-}$ mice (135).

LPA_2

LPA_2 was first identified through a gene sequence search for orphan GPCRs. It shows 55% amino acid similarity to LPA_1. *LPAR2* (human chromosome 19p12) encodes a 351 amino acid protein with a calculated molecular mass of 39.1 kDa (136), while mouse *Lpar2* (mouse chromosome 8, 33.91 cM) encodes for a 348 amino acid protein with a molecular mass of 38.9 kDa. Mutagenesis studies of LPA_2 have found two key residues that, when altered, can decrease LPA_2 activation (Q3.29E and R5.38A) (86). During development, expression of *Lpar2* is more diffuse than *Lpar1*, although it is clearly present in the embryonic

brain, limb buds, craniofacial regions, and Rathke's pouch (89, 137–139).

Compared with *Lpar1/LPAR1*, *Lpar2/LPAR2* expression is more restricted in adult mice and humans, with high *LPAR2* in leukocytes and the testis, and *Lpar2* in the kidney, uterus, and testis (13, 87). More moderate levels of *LPAR2* are found in the prostate, spleen, thymus, and pancreas, and lower levels of *Lpar2* expression are found in the lung, stomach, spleen, thymus, postnatal brain, and heart (140).

LPA_2 couples to the $G_{i/o}$, $G_{q/11}$, and $G_{12/13}$ family of heterotrimeric G proteins, similar to LPA_1 (Fig. 1). These G proteins initiate downstream signaling pathways through molecules such as Ras, Rac, PI3K, MAPK, phospholipase C (PLC), diacylglyerol, and Rho (90). LPA_2 activation is associated with cell survival and cell migration. LPA_2-initiated migration appears to be promoted through interactions with the focal adhesion molecule TRIP6 (141, 142) and several PDZ-domain and zinc finger proteins, through interactions with the carboxy-terminal tail of LPA_2 (143). Notably, the PDZ-binding domain of LPA_2 regulates Na^+/H^+ exchanger regulatory factor 2 (NHERF2) behavior, activating PLC-β3 and AKT/ERK signaling while inhibiting cystic fibrosis transmembrane conductance regulator (CTFR). These pathways stimulate cell migration, enhance survival, and alter gene expression, accounting for many of the functions attributed to LPA_2. This intracellular coupling is a unique feature of LPA_2. Also, LPA_2 activation can inhibit EGF-induced migration and invasion of pancreatic cancer cells through the $G_{12/13}$/Rho pathway (144). These data lend support to the pattern of transactivation and cross-regulation between GPCRs and receptor tyrosine kinases in a variety of settings (145) and expand the signaling effects of LPA beyond single subtype receptor mechanisms.

Phenotypically, *Lpar2*$^{-/-}$ mice appear mostly normal, with expected Mendelian birth ratios and normal prenatal and postnatal viability (146). Like LPA_1, LPA_2 is involved in several aspects of nervous system function and development. Activation of LPA_2 increases P0 protein in cultured SCs, implicating this receptor in myelination. In fact, LPA_2 is upregulated, along with LPA_1, after neural injuries such as nerve transection and neuropathic pain (100, 147). The interaction of LPA_2 with plasticity-related gene-1 (PRG-1) signaling has also been reported to modulate excitatory transmission in the hippocampus (148).

Mice that are *Lpar1*$^{-/-}$/*Lpar2*$^{-/-}$ null have also been generated. Such mutants mostly phenocopy *Lpar1*$^{-/-}$ mice and have similar body size reduction, craniofacial dysmorphism with blunted snouts, and 50% perinatal lethality, but also exhibit an increased incidence of frontal hematomas. Studies in these mice have also shed light on LPA_1 and LPA_2 signaling redundancy in distinct neural and vascular phenotypes. *Lpar1*$^{-/-}$/*Lpar2*$^{-/-}$ cells display altered responsiveness to LPA in vitro, ranging from significant reduction to complete abrogation (95, 149). Exogenous LPA exposure in ex vivo cerebral cortical cultures decreased cell death, increased NPC cell cycle exit, and produced early terminal mitosis. This resulted in precocious neuronal production, cortical thickening, and folding which resembles gyri in humans (95). These effects were abolished in *Lpar1*$^{-/-}$/*Lpar2*$^{-/-}$ embryonic cerebral cortices.

Lpar1$^{-/-}$/*Lpar2*$^{-/-}$ mice have also been helpful in understanding the effects of LPA on the vascular system. Specifically, LPA_1 and LPA_2 were found to exhibit opposite effects on primary vascular smooth muscle cells and injury-induced neointimal hyperplasia (149). Vascular smooth muscle cell (SMC) migration was increased in *Lpar1*$^{-/-}$ mice but was partially attenuated in *Lpar1*$^{-/-}$/*Lpar2*$^{-/-}$ mice, demonstrating LPA_1 and LPA_2's opposition as negative and positive chemotactic mediators, respectively. Additionally, exogenous LPA exposure can increase vascular permeability, which was blocked using the dual $LPA_{1/3}$ receptor antagonist Ki16425 (150). Ki16425 also inhibited neointima formation and SMC recruitment to the injury site after wire-induced carotid injury (151). Neither LPA_1 nor LPA_2 was required for dedifferentiation of SMCs following vascular injury in vivo or LPA exposure ex vivo, nor were they required for LPA-induced blood pressure increases (149). These observations indicate the likely involvement of other LPA receptor subtypes in these processes.

A similar dynamic between LPA_1 and LPA_2 signaling also exists in immune system function. LPA receptors are found on virtually all immune cell types and organs, including lymphocytes (144), dendritic cells (DCs) (152, 153), thymus, and spleen (20, 77, 154). In T cells, LPA can stimulate or attenuate cellular activity, depending on the cell's activation state and receptor expression. In unstimulated T cells, LPA augments chemotaxis and blocks IL-2 production through LPA_2 (155, 156). In activated T cells, where LPA_2 is downregulated and LPA_1 is upregulated, the reverse is true; LPA inhibits chemotaxis, activates IL-2 and IL-13 production, and promotes cell proliferation (156, 157). In addition, LPA affects immature and mature DCs differently. $LPA_{1–3}$ are expressed in both immature and mature DCs, and LPA appears to affect immature DCs by enhancing maturation and cytokine production (152, 153). Furthermore, LPA_3-specific activation induces chemotaxis of immature, but not mature, DCs (158). DCs from *Lpar2*$^{-/-}$ mice are hyperactive compared with wild-type counterparts and less susceptible to inhibition by different LPA species, suggesting that LPA via LPA_2 may inhibit DC activation (159). Thus, LPA may differentially affect DC maturity and stage-specific functions through multiple LPA receptors.

LPA_3

Lpar3 was discovered and cloned in a similar fashion to *Lpar2*, using homology searches for orphan GPCRs and a degenerate PCR-based cloning method (14, 160). *LPAR3/Lpar3* (human chromosomal locus 1p22.3; mouse chromosome locus 3, 71.03 cM) encodes a 353 amino acid sequence GPCR with a molecular mass of ~40 kDa that, in humans, is ~54% identical to LPA_1 and ~49% identical to LPA_2 (14). Mutagenesis studies on LPA_3 have identified two specific residues involved in LPA_3 activation (W4.64A and R5.38N), as well as a residue that increased the EC_{50} of

LPA_3 by a factor of 10 (K7.35A) (86). During development, *Lpar3* expression is observed in the heart, mesonephros, and in three spots in the otic vesicle (89). In the adult, *LPAR3/Lpar3* expression is most prominent in the human heart, testis, prostate, and pancreas (14, 160), as well as mouse lung, kidney, uterus, and testis. *LPAR3/Lpar3* is less highly expressed in the human lung, ovary, and brain, as well as mouse small intestine, brain, heart, stomach, placenta, spleen, and thymus (87, 140). Expression differences of LPA_3 between human and mouse tissue warrant further study.

LPA_3 couples with $G_{\alpha i/o}$ and $G_{\alpha q/11}$ to mediate LPA-induced Ca^{2+} mobilization, adenylyl cyclase inhibition and activation, PLC activation, and MAPK activation (Fig. 1) (161). LPA_3 has been reported to prefer 2-acyl-LPA containing unsaturated fatty acids (14, 162). In addition, *Lpar3*$^{-/-}$ mice are viable and appear normal, with no reported neural deficits, even though LPA_3 is found in the frontal cortex, hippocampus, and amygdala (14, 160). However, female null mutants have a striking reproductive phenotype, with delayed embryo implantation, embryo crowding, and reduced litter size (163). In the uterus, *Lpar3* is solely found in the endometrial epithelium of the lumen during the transient window of embryo implantation (163, 164) and is regulated by progesterone and estrogen (165). LPA is found in follicular fluid from healthy women, which underscores the LPA-LPA_3 signaling axis in the uterus (166). During pregnancy, ATX concentration is upregulated in the serum and placenta of healthy women in the third trimester. Interestingly, patients with pregnancy-induced hypertension (preeclampsia) harbored decreased ATX levels in the third trimester compared with healthy women (56, 167, 168). LPA receptors are also expressed in the testis (19, 77, 88), suggesting a role for LPA signaling in male sperm behavior and fertility. These data support numerous LPA-mediated roles in reproduction.

In addition, LPA_3 appears to be involved in determining vertebrate left-right patterning during embryogenesis, a crucial process for proper organ formation and function. Downregulation of *Lpar3* or inhibition of LPA_3 signaling with Ki16425 disrupted asymmetric gene expression and organ asymmetry in zebrafish, a phenotype which was rescued by *Lpar3* overexpression (169). Downregulation of ATX by oligonucleotide knockdown or inhibition of ATX by HA130 similarly disrupted left-right patterning and developmental asymmetry.

LPA_4

LPA_4 was the first identified lysophospholipid receptor to show a dissimilar amino acid sequence from the other lysophospholipid receptors, LPA_{1-3}, sharing only ~20% amino acid identity with LPA_1 (140) and slightly greater homology to other LPA receptors (19). It was previously known as the orphan GPCR P2Y9, based on its similarity to P2Y purinergic receptors. However, it was reclassified as LPA_4 after demonstrating responsiveness to LPA, but not to any nucleotides or nucleosides during ligand screening using a calcium mobilization assay (11, 19). *LPAR4/Lpar4* (human chromosome Xq21.1, mouse chromosome X region D) encodes a 370 amino acid protein with predicted molecular mass of 41.9 kDa.

During development, *Lpar4* is found in the mouse embryonic brain, maxillary processes, branchial arches, limb buds, liver, and somites (89). In adults, *LPAR4* is prominently found in the human ovary, while less prominent *LPAR4* can be found in the thymus, pancreas, brain, heart, small intestine, testis, prostate, colon, and spleen. *Lpar4* is present in mouse heart, ovary, skin, thymus, and bone marrow (89, 140).

LPA_4 is a 7-TM GPCR that couples with G_α proteins, including $G_{12/13}$, $G_{q/11}$, $G_{i/o,}$ and G_s (170). This receptor induces neurite retraction and stress fiber formation through $G_{12/13}$ and subsequent Rho/ROCK pathway activation, as seen with activation of other LPA receptors (170, 171). In addition, LPA_4 facilitates both ROCK-dependent cell aggregation and N-cadherin-dependent cell adhesion, using a cell line that heterologously expresses this receptor (171). Moreover, LPA_4 induces intracellular cAMP accumulation through G_s activation; currently this is the only known LPA receptor with this activity (170). LPA_4 can also influence the differentiation of immortalized hippocampal progenitor cells (172). LPA-induced cell migration (e.g., via LPA_1) is inhibited by activation of LPA_4, and LPA_4-deficient cells have increased sensitivity to LPA exposure, with increased lamellipodia formation and transwell movement (173). This noteworthy ability of LPA_4 to negatively regulate cell motility opposes LPA's traditional status as a chemoattractant and indicates that differential effects may be achieved through combinatorial LPA receptor expression.

Adult *Lpar4*$^{-/-}$ mice appear grossly normal (173), yet exhibit increased trabecular bone volume, number, and thickness (174, 175). This is in contrast to *Lpar1*$^{-/-}$ mice, which display decreased bone mass (176). This suggests that LPA_4 negatively regulates osteogenesis and may counteract LPA_1-initiated osteogenesis. Consistent with these observations, knockdown of *LPAR4* in a human mesenchymal stem cell line resulted in the inhibition of its differentiation into osteoblasts (177). During embryo development, there is decreased prenatal survival for *Lpar4*$^{-/-}$ mutants. Observed phenotypes in these null mice include pericardial effusions, severe edema and hemorrhage, abnormally dilated blood and lymphatic vessels and lymph sacs, and impaired pericyte recruitment (178). This indicates important pleiotropic roles for LPA_4 in circulatory and lymphatic system development. Vasculogenesis in extraembryonic membranes (such as the chorioallantoic membrane) has also been recently linked to an ATX-mediated product ion of LPA. The responsible receptor may be LPA_4, although the concomitant presence of *Lpar1*, *Lpar2*, and *Lpar6* make this subtype identification unclear (179).

LPA_5

In 2006, LPA_5 was identified through unbiased screening approaches that led to the deorphanization of GPR92 (20, 21). *LPAR5* shares 35% homology with *LPAR4*, but only ~22% homology to *LPAR1–3* (21). *LPAR5/Lpar5* (human chromosome 12p13.31; mouse chromosome 6, 59.21 cM) encodes a 372 amino acid protein. *LPAR5* is highly expressed

in spleen, and to a lesser degree in heart, small intestine, placenta, colon, and liver. *Lpar5* in murine tissues is highly expressed in small intestine, and more moderately in lung, heart, stomach, colon, spleen, thymus, skin, liver, platelets, mast cells, gastrointestinal lymphocytes, and dorsal root ganglia (20, 21, 180, 181). Additionally, *Lpar5* was found in the early embryonic mouse forebrain, rostral midbrain, and hindbrain. This expression pattern becomes more ubiquitous from E9.5–E12.5, showing signals throughout the embryo, as well as diffuse patterns in the developing brain and choroid plexus that suggest a possible role for LPA_5 in brain development (89). Mutagenesis studies have found that several residues are likely involved in the binding of LPA to LPA_5, including one mutant that abolished receptor activation (R2.60N) and three separate mutants that greatly reduced receptor activation (H4.64E, R6.62A, and R7.32A) (182).

LPA_5 couples to $G_{12/13}$ and $G_{q/11}$ (21). LPA_5-expressing cell lines demonstrate LPA-induced neurite retraction, stress fiber formation, and receptor internalization in vitro through the $G_{12/13}$ pathway (21). LPA_5 can also activate G_q to increase intracellular calcium levels and induce cAMP accumulation (21). However, this cAMP accumulation is not changed by G_s minigene administration, suggesting the involvement of an alternative G protein (20, 21). In melanoma cells, LPA inhibits migration through LPA_5 and the cAMP-protein kinase A pathway, acting as a chemorepellent that is similar to its LPA_4-mediated effect. Moreover, LPA_5 demonstrated a 10-fold preference for alkyl, rather than acyl, 18:1 LPA (183). LPA_5 signaling may also affect the colon, where it may be involved in water absorption (184). In intestinal epithelial cells, LPA promoted Na^+-dependent water absorption through Na^+/H^+ exchanger 3 (NHE3) via an interaction between LPA_5 and Na^+/H^+ exchanger regulatory factor 2 (NHERF2), which then recruits NHE3 to the microvilli (184). In mast cells, LPA_5 is the main LPA receptor responsible for LPA-induced release of MIP-1β (also known as chemokine ligand 4 or CCL-4) (181). The diverse expression patterns of LPA_5 suggest that additional physiological effects will be uncovered in the future.

LPA_6

The most recent addition to the LPA receptor family is LPA_6. In 1993, receptor 6H1 was isolated from a chicken T cell library (185) and subsequently renamed to $p2y_5$ because of sequence homology with P2Y receptors (186). Genetic studies indicated roles for LPA_6 in hypotrichosis simplex, a complex of diseases involving familial hair loss (22). Most recently, studies using a chimeric G_{13} protein indicated that LPA induced multiple effects, including $p2y_5$-mediated cAMP accumulation, Rho-dependent changes in cell morphology, [^{3}H]LPA binding, and [^{35}S]guanosine 5′-3-*O*-(thio)triphosphate binding (23). The $p2y_5$ has now been reclassified as an LPA receptor and renamed LPA_6 (22, 83). 2-Acyl-LPA appears to have a higher activity to LPA_6 than 1-acyl-LPA. Interestingly, many of the performed assays require extraordinarily high concentrations of LPA (up to 10 μM) to show an effect, compared with the nanomolar concentrations needed for activating $LPA_{1–5}$. When LPA_6 was coexpressed with a promiscuous G_α protein, LPA_6 was activated by LPA and resulted in increased intracellular Ca^{2+}, reduced forskolin-stimulated $[cAMP]_I$, and ERK1/2 activation (187).

While several studies have now identified LPA_6 mutations in hypotrichosis patients (22, 188, 189), there have also been reports of lipase member H (LIPH) (also known as PA-$PLA_1\alpha$) mutations in hypotrichosis that are associated with both a decrease in LPA production as well as reduced or abrogated LPA_6 activation in cells expressing the receptor (190, 191). An additional study has demonstrated that LIPH regulates hair follicle development by modulating epidermal growth factor receptor (EGFR) signaling through a tumor necrosis factor α converting enzyme and the transforming growth factor (TGF)-α pathway (192). These findings suggest LPA_6, and possibly EGFR, as candidates for therapeutic intervention in forms of human hair loss.

LPA SIGNALING AGONISTS AND ANTAGONISTS

There is a rapidly growing number of reported LPA signaling agonists and antagonists, all with varying selectivity and potency (**Fig. 2**, **Table 2**). Most of these receptor modulators are directed at LPA receptors, particularly against $LPA_{1–3}$, although a few compounds have demonstrated some LPA_4 and LPA_5 activity with limited selectivity (182, 193, 194). Additionally, several compounds target enzymes that regulate the production of LPA, notably ATX and LPPs (195, 196). The vast majority of these studies have relied heavily upon in vitro assays for validation thus far, but a growing number of compounds have some demonstrated in vivo efficacy (Table 2). An LPA_1 antagonist named AM966 has shown efficacy in inhibiting lung fibrosis in a bleomycin injury model (197). The dual $LPA_{1/3}$ antagonist Ki16425 has shown preventative efficacy in a mouse model of hydrocephalus (43), as well as therapeutic reduction of bone metastases from breast cancer in a xenograft tumor model (198). In murine renal ischemia-reperfusion injury, opposing effects can be seen in which the LPA_3-selective agonist 1-oleoyl-2-*O*-methyl-*rac*-glycerophospho-thionate (OMPT) enhanced kidney damage, whereas the $LPA_{1/3}$ dual antagonist VPC12249 reduced the injury via LPA_3 inhibition (199). These compounds require further validation in vivo. LPA_1 antagonists are also being tested clinically for disease amelioration: SAR-100842 for systemic sclerosis and AM-152 for idiopathic pulmonary fibrosis (200). Exogenous LPA exposure can also increase blood brain barrier permeability, which may be relevant to diseases and drug delivery into the brain (80). In the next section, LPA-mediated pathophysiologies across organ systems will be discussed, with specific mention of LPA signaling modulators in therapeutic contexts (Table 2).

PATHOPHYSIOLOGY

Neurological disorders

Many neurodevelopmental disorders have unclear etiologies, yet are associated with prenatal and perinatal risk factors

TABLE 2. Summary of LPA receptor modulators, receptor subtype target and activity, and disease relevance

Compound	Target	Characteristics	Physiology or Disease Relevance	References
LPA (18:1)	$LPA_{1–5}$ and weak LPA_6 agonist	Lysophospholipid present in blood and tissues	Appropriate levels of signaling are essential for development, neurogenesis, cell migration, cell survival, vasculogenesis, and reproduction, among other processes	(25, 140, 319)
N-palmitoyl serine phosphoric acid	Weak $LPA_{1–3}$ agonist	Lipid analog	Agonizes intracellular Ca^{2+} mobilization in mammalian cells (antagonizes in *Xenopus*)	(320–322)
N-acyl ethanolamide phosphate	$LPA_{1/2}$ and weak LPA_3 agonist	Lipid analog	Agonizes platelet aggregation	(25, 323)
Oleoyl-thiophosphate	$LPA_{1–3}$ agonist	Thiophosphate lipid analog	Elevates intracellular Ca^{2+} mobilization	(322, 324)
Oleoyl-*sn*-glycero-3-phosphate	$LPA_{1/2}$ agonist	LPA analog	Increases uterine smooth muscle contraction tension, amplitude, and frequency	(325)
Dialkyl thiophosphatidic acid 8:0	$LPA_{1/3}$ and weak LPA_2 agonist	Thiophosphate lipid analog	Elevates intracellular Ca^{2+} mobilization	(322)
T13	LPA_1 and weak LPA_3 agonist	Thiophosphate lipid analog	Elevates intracellular Ca^{2+} mobilization	(322, 326)
T15	$LPA_{1/3}$ agonist	Thiophosphate lipid analog	Activates cell migration	(322, 326)
Dodecyl phosphate	$LPA_{2/3}$ agonist	Lipid analog	Elevates intracellular Ca^{2+} mobilization	(322, 327)
α-Methylene phosphonate	LPA_2 and weak LPA_4 agonist	Lipid analog	Elevates intracellular Ca^{2+} mobilization	(193, 322)
OMPT	LPA_3 and weak LPA_2 agonist	Lipid analog, S-enantiomer is more potent and LPA_3-selective	Enhances kidney damage after renal ischemia-reperfusion injury, increases uterine smooth muscle contraction tension and amplitude but decreases frequency	(25, 199, 325)
Alkyl OMPT	$LPA_{1/3/6}$ agonist	Lipid analog	Induces cancer cell migration and fibroblast proliferation, activates Ca^{2+} mobilization	(322, 328)
α-Fluoromethylene phosphonate	LPA_3 and weak $LPA_{1/2}$ agonist	Lipid analog	Activates LPARs in TGF-α shedding assay	(329)
α-Hydroxymethylene phosphonate	LPA_3 agonist	Lipid analog	Activates LPA_3 in TGF-α shedding assay	(329)
Octadecenyl phosphate	LPA_4 agonist	Lipid analog	Induces platelet shape change	(182, 322)
N-palmitoyl tyrosine phosphoric acid	Weak $LPA_{1/3}$ antagonist, weak $LPA_{2/6}$ agonist	Lipid analog	Agonizes intracellular Ca^{2+} mobilization in mammalian cells (antagonizes in *Xenopus*)	(320–322)
sn-2-Aminooxy analog 12b	LPA_2 and weak $LPA_{1/4}$ agonist, LPA_3 antagonist	Aminooxy lipid analog	Enhances intestinal endothelial cell migration, activates Rho/Rac1 signaling, potential use in repair of gastrointestinal epithelium	(194)
Farnesyl diphosphate	LPA_5 agonist, LPA_3 and weak $LPA_{2/4}$ antagonist	Lipid analog	Farnesyl phosphates selectively induce and inhibit Ca^{2+} mobilization	(182, 322)
α-bromomethylene phosphonate (BrP-LPA)	Antagonizes of ATX and all LPA receptors	Lipid analog, diastereomer	Attenuates arthritis, reduces breast cancer migration and invasion, causes tumor regression, radiosensitizes tumor vasculature	(195, 196, 330)
HLZ-56	Antagonizes all LPA receptors	Lipid analog	Prevents SMAD2/TGF-β activation in kidney fibrosis	(193, 253)
Tetradecyl-phosphonate	Weak $LPA_{1–3}$ antagonist	Lipid analog	Inhibits intracellular Ca^{2+} mobilization	(322, 324)
Ki16425	$LPA_{1/3}$ and weak LPA_2 antagonist	Small molecule, oral activity, high selectivity, developed by Kirin	Inhibits cell migration, attenuates autoimmune arthritis, inhibits cancer metastasis, inhibits progesterone and PGE_2 secretion from bovine reproductive tract	(244, 262, 331–333)
Ki16198	LPA_1 and weak $LPA_{2/3}$ antagonist	Orally active, methyl ester of Ki16425	Attenuates pancreatic cancer invasion and migration	(316)
Debio 0719	$LPA_{1/3}$ antagonist	R-stereoisomer of Ki16425, higher potency	Inhibits dissemination of breast cancer cells, stops LPA_1-stimulated Ca^{2+} flux	(317, 334)
VPC12249	$LPA_{1/3}$ antagonist	Lipid analog of NAEPA	Reduces lung fibrosis from irradiation therapy, reduces kidney ischemia-reperfusion injury	(25, 199, 252)
VPC32183	$LPA_{1/3}$ antagonist	Lipid analog of NAEPA	Intravaginal injection abrogates LPA-induced PGE_2 production	(322)
Thiophosphatidic acid 8:0	$LPA_{1/3}$ antagonist	Lipid analog	May agonize LPA_5-mediated platelet shape change	(182, 324)
Compound 12	$LPA_{1/3}$ antagonist	Small molecule	Inhibits intracellular Ca^{2+} mobilization	(322, 335)
H2L-5186303	$LPA_{2/3}$ antagonist	Small molecule	Inhibits intracellular Ca^{2+} mobilization	(322, 335)
H2L-5765834	$LPA_{1/5}$ antagonist	Small molecule	Inhibits LPA-induced platelet shape change and platelet activation	(182, 322)
H2L-5987411	LPA_4 and weak LPA_5 antagonist	Small molecule	Inhibits LPA-induced platelet shape change and platelet activation	(182, 322)
AM095	LPA_1 antagonist	Small molecule, developed by Amira	Attenuates bleomycin-induced dermal/pulmonary/kidney fibrosis and reduces histamine release in mice, inhibits chemotaxis of human melanoma cells and LPA_1-overexpressing CHO cells	(254, 336)
AM966	LPA_1 antagonist	Small molecule, developed by Amira	Inhibits chemotaxis of fibroblasts, attenuates bleomycin-induced pulmonary fibrosis in mice	(197)

TABLE 2. Continued.

Compound	Target	Characteristics	Physiology or Disease Relevance	References
AM152	LPA_1 and weak LPA_{2-5} antagonist	Small molecule, developed by Amira	Passed phase I clinical trials for idiopathic pulmonary fibrosis (Bristol Myers Squibb)	(200)
Compound 35	LPA_2 and weak $LPA_{1/3}$ antagonist	Small molecule	Inhibits colon cancer cell growth and Erk activation	(25, 318)
diacylglycerol pyrophosphate (DGPP) 8:0	LPA_3 and weak LPA_1 antagonist	Lipid analog	Does not affect progesterone or PGE_2 production by endometrial cells.	(263, 322, 338)
NSC161613	LPA_3 antagonist	Small molecule	Inhibits intracellular Ca^{2+} mobilization	(322, 335)
SAR-100842	LPA_1 antagonist	Small molecule, developed by Sanofi	Passed phase I clinical trials for systemic sclerosis (Sanofi)	(200)

Activity, compound characteristics, and effects in various disease models are emphasized. LPAR antagonists are listed first, followed by compounds with both agonist and antagonist activity, and antagonists listed last. If information in a disease context was not available, effects on cellular physiology were included instead. "Weak" effects are classified as having EC_{50}, IC_{50}, or K_i values greater than 1,000 nM. Note that not all compounds were tested against all LPA receptors (see Fig. 2 for known interactions). References are indicated in parentheses. NAEPA, *N*-acyl ethanolamide phosphate.

such as hemorrhage, hypoxia, infection, and immune activation. These include CNS malformations such as heterotopias, layer malformations, and hydrocephalus, as well as neurological disorders such as cerebral palsy, schizophrenia, and autism (201–203). LPA signaling can be significantly altered during all of these insults, and could induce or contribute to developmental disturbances.

Recently, a prominent effect of LPA signaling on the developing brain was shown in relation to posthemorrhagic fetal hydrocephalus (FH) (43). FH is a neurodevelopmental disorder characterized by the excessive accumulation of CSF, macrocephaly, enlarged ventricles, and neurological dysfunction. A main risk factor for FH is bleeding within the germinal matrix of the cerebral cortex. Prenatal injections of LPA directly into fetal brains induced most of the symptoms of FH in an LPA_1-dependent manner. In a mouse model of intracranial hemorrhage (with lower levels of LPA), blood components induced FH with 25–50% penetrance, while *Lpar1*$^{-/-}$/*Lpar2*$^{-/-}$ mice were protected from developing FH (43). Additionally, the effects of hypoxia involve LPA_1 potentiation via the receptor kinase GRK2, linking LPA receptor signaling to another common FH risk factor (204). Postnatal brain exposure to blood appears to induce ventriculomegaly without hydrocephalus, possibly due to spatiotemporal LPA receptor and ligand distribution (205, 206).

Neuropsychiatric disorders are also thought to have a neurodevelopmental origin. Many share the same risk factors cited above, based on studies linking hypoxia, prenatal hemorrhage, and immune activation to diseases such as schizophrenia and autism (201, 208, 209). LPA, particularly through LPA_1, is involved in both immune system function and hypoxia. Indeed, the removal of LPA_1 signaling during development significantly alters the neuropsychiatric profile of mice. *Lpar1*$^{-/-}$ mice exhibit deficits in prepulse inhibition of the startle reflex, altered levels of serotonin, abnormalities in glutamatergic synapses (94, 210, 211), and a reduction in entorhinal cortex γ oscillations and parvalbumin-positive neurons (212). Furthermore, maLPA$_1^{-/-}$ mice display defects in olfaction, pain sensing, exploration, anxiety, and memory retention in addition to cortical developmental defects. These syndromic dysfunctions are reminiscent of the pathological and behavioral symptoms exhibited by schizophrenic patients and animal models (93, 94, 213, 214). Expression of the LPA-synthesizing enzyme cytosolic (c)PLA_2 is increased in schizophrenic patients, while cPLA_2 inhibition in control groups reduces deficits in prepulse inhibition (215). These observations suggest that altered LPA_1 signaling may be relevant to schizophrenia and related psychiatric symptoms. *Lpar1*$^{-/-}$ and maLPA$_1^{-/-}$ mice also display craniofacial dysmorphism and defects in adult hippocampal neurogenesis, traits that are associated with autism (112). These data strongly implicate LPA and LPA_1 receptor signaling in neurodevelopmental and neuropsychiatric disorders.

LPA and LPA_1 signaling are also involved in nerve injury responses. Neuropathic pain, with symptomatic allodynia and hyperalgesia, is often associated with peripheral neuropathy and SC demyelination, commonly caused by trauma or inflammation of the nervous system. Intrathecal injections of LPA over-activate LPA_1 and elicit both allodynia and hyperalgesia in wild-type mice, which were prevented in *Lpar1*$^{-/-}$ mice (147). LPA_1 activation also induces a nociceptive response that appears to mediate the release of substance P, a neuropeptide implicated in inflammation and pain (216). Furthermore, partial sciatic nerve ligation (PSNL) nociception was completely blocked in *Lpar1*$^{-/-}$ mice. Allodynia and demyelination were also reduced using Rho pathway inhibitors, implicating LPA_1-mediated Rho activation in these neuropathic pain-associated pathologies (147). Finally, PSNL-induced neuropathic pain was inhibited through a distinct pathway involving LPA_5 and cAMP in the spinal cord dorsal horn neurons despite continued upregulation of several pain-related markers (217).

In earlier ex vivo studies, LPA induced demyelination in isolated dorsal root fiber and decreased myelin basic protein expression (218). ATX has also been shown to induce neuropathic pain through the conversion of LPC to LPA (219). This is supported by the fact that *Enpp2*$^{+/-}$ mice, which have a 50% decrease in LPA plasma concentration, also have a 50% recovery from PSNL-induced neuropathic pain (220). Interestingly, intrathecal LPC-mediated pain involved the feed forward production of LPA through ATX and LPA_3 (221). Cyclic PA has been reported to attenuate PSNL-induced allodynia and hyperalgesia (222). LPA-mediated nociception may be dependent on specific LPA forms, as pain responses were strongly elicited by 18:1 LPA but

not by 16:0 LPA or 18:0 LPA (223). Interestingly, intraperitoneal administration of Ki16425 ($LPA_{1/3}$ antagonist) within a short window straddling the induction of pain appears to completely block LPA-induced nociception (223). These proof-of-concept studies indicate that LPA and LPA_1 signaling can serve as important therapeutic targets for myelinating diseases, including neuropathic pain.

Atherosclerosis and cardiovascular disease

As LPA receptors are integral to vascular integrity and the immune response, it comes as no surprise that dysregulated LPA signaling may be implicated in atherosclerosis. In particular, LPA is involved in inflammatory cytokine release, monocyte attraction and adhesion, abnormal endothelial cell behavior, endothelial permeability, and LDL uptake for plaque formation (224–228). These factors can lead to the excessive macrophage invasion seen in atherosclerosis. Additionally, LPA accumulation has been observed within the thrombogenic core of atherosclerotic plaques (76, 229), potentially implicating the presence of LPA in disease progression.

LPA signaling may also be involved in cardiovascular disease and myocardial infarction, as excessive platelet activation is associated with cardiovascular disease (230). Activated platelets release LPA which can initiate a positive feedback loop where LPA induces platelet activation and aggregation (36, 40, 76). During myocardial infarction, cardiac myocytes can sustain major damage due to ischemia and hypoxia. LPA signaling has also been implicated in both of these conditions. For example, elevated LPA levels have been detected in ischemia and have been shown to increase cardiomyocyte and mesenchymal stem cell survival (231–234). During injury recovery, LPA stimulates the immune cell reaction, endothelial cell migration, cell survival, and proliferation processes involved in repair and angiogenesis (73, 77, 140). While prolonged LPA expression may exacerbate ischemia, the involvement of LPA in injury response may be important during myocardial infarction recovery. In addition to the potential cardioprotective effects of LPA, LPA signaling has been shown to be neuroprotective during ischemic injury. Treatment of a rat model of retinal ischemia/reperfusion injury with an LPA analog protected neural cells from apoptosis and improved recovery outcomes (235). However, these data are inconclusive, as LPA has also been shown to induce cell death in cerebral vascular cells, umbilical endothelial cells, brain explants, and retinas (236). This apoptotic response was reduced with an LPA_1 antagonist

Inflammation and autoimmunity

LPA is a potent mediator of the immune response and can contribute to improper immune activation, upregulating the production of inflammatory cytokines such as IL-2 and IL-6 (140, 237). In addition, LPA_1 and LPA_2 signaling can activate microglial cells in the brain, triggering immune invasion. Importantly, LPA has been linked to several inflammatory and autoimmune disorders, including systemic sclerosis, asthma, and arthritis.

Abnormally high levels of LPA have been identified in fibroblasts from systemic sclerosis patients. These primary cells are hypersensitive to Cl^--current activation during LPA exposure (238, 239). The bronchoalveolar fluids of allergen-provoked asthmatic patients showed concomitant increases in ATX levels and LPA concentration with increased 22:5 and 22:6 polyunsaturated fatty acids (240). In a mouse model of allergic asthma, the blockade of ATX activity and LPA_2 knockdown attenuated the Th2 cytokines and allergic lung inflammation (240).

LPA is also involved in several aspects and forms of arthritis. Rheumatoid arthritis patients display increased ATX concentrations in synovial fluid, and elevated cytokine production was found in patient fibroblast-like synoviocytes treated with LPA (241). Recent studies have also demonstrated that LPA/LPA_1 contributes to the development of rheumatoid arthritis via cellular infiltration, Th17 differentiation, and osteoclastogenesis (242), underlining LPA's effects on inflammation and immune regulation. Consistent with LPA receptor activation in this context, a functional single-nucleotide polymorphism discovered in the promoter region of LPA_1 increased susceptibility to knee osteoarthritis, possibly through LPA_1 upregulation (243). These results support the proposal that ATX and LPA are involved in facilitating immune system functions via modulation of lymphocyte trafficking and sensitization of affected cells during autoimmunity.

Understanding these pathways could lead to the use of LPA signaling modulators in the treatment of human autoimmune disorders. Use of Ki16425 or α-bromomethylene phosphonate (BrP-LPA) (a pan-LPA antagonist) attenuated arthritis in a mouse model of inflammatory joint disease (244). Specifically, treatment with Ki16425 reduced synovial inflammation, cell infiltration, and bone destruction, while decreasing the presence of inflammatory mediators in the joint tissue (242). These studies suggest that LPA receptor inhibition may be a future treatment option for arthritic patients.

Fibrosis

LPA signaling has been linked to injury response and fibrosis, which can involve the formation of excess fibrous connective tissues in a wide range of organ systems, resulting in complications such as pulmonary, renal, and tubulointerstitial fibrosis. Increased LPA has been found in bronchoalveolar fluid in pulmonary fibrosis after bleomycin-induced lung injury, which was associated with increased vascular leakage, fibroblast recruitment, and mortality. These pathologies were significantly reduced in *Lpar1*$^{-/-}$ mice, linking LPA_1 signaling to this disorder (245). Renal fibrosis is also linked to LPA_1 signaling, albeit through a slightly different mechanism that also involves LPA_3 (246). In particular, LPA_1 activation in mesothelial cells can lead to stimulated migration, cell proliferation, and upregulated expression of a profibrotic factor called connective tissue growth factor in epithelial cells and fibroblasts (247). The subsequent cell growth can result in the pathogenic fibroblast proliferation seen in fibrosis. *Lpar2* may also be involved in pulmonary fibrosis, as knockout mice demonstrated protection against bleomycin-induced lung injury, fibrosis, and death (248). In addition, LPA and ATX levels

are increased following hepatitis C-induced liver fibrosis, presumably through induction of stellate cell and hepatocyte proliferation (35, 249), which are the main contributors to extracellular matrix accumulation in the liver (250).

Furthermore, LPA_2 signaling can activate $\alpha_V\beta_6$ integrin, causing TGF-β1 activation in epithelial cells and stimulating growth (200). Both LPA_2 and $\alpha_V\beta_6$ integrin have been shown to be upregulated in animal models and patient samples of lung fibrosis. Not only does LPA mediate the progression of fibrosis via cell growth, but LPA_1 has also been implicated in the initiation of disease through excessive fibroblast recruitment and persistent maintenance of leaky vasculature (245). While fibroblast presence and vascular permeability are important factors in the early stages of injury repair, high fibroblast levels and prolonged vascular leakage have both been implicated in disease.

Inhibition of LPA signaling has been demonstrated to attenuate many of the negative responses seen in fibrosis. For example, administration of Ki16425 in an animal model of lung fibrosis inhibited fibroblast chemotaxis (200). Usage of LPA_1/LPA_3 dual antagonist VPC12249 reduced the incidence of lung fibrosis from radiation therapy, counteracting the increased LPA_1/LPA_3 and connective tissue growth factor (CTGF) expression seen in these mice (252). Administration of this drug pre- and postirradiation resulted in a dose-dependent response including prolonged survival, inhibited fibroblast growth, reduced collagen deposits, and recovered lung structure. Another study utilized ischemia-reperfusion injury to the kidney as a model of fibrosis (253). This study implicated LPA_2-stimulated Smad2 phosphorylation and TGF-β transactivation in proximal tubule cells as mediators of kidney fibrosis. In the presence of the pan-LPA receptor antagonist HLZ-56, but not the LPA_1/LPA_3-specific antagonist Ki16425, Smad2 activation was attenuated. Reduced Smad2 prevented the activation of pro-fibrotic factors TGF-β, CTGF, and PDGF-β. Another model simulated dermal fibrosis in the mouse by measuring changes in collagen content and dermal thickness (254). This study showed that the fibrosis was prevented in *Lpar1*$^{-/-}$ mice and its severity reduced by administration of the LPA_1 antagonist AM095. In addition, myofibroblast differentiation into smooth muscle was diminished in *Lpar1*$^{-/-}$ mice and nuclear Smad2 reduced in null and drug-treated mice. The disease course was unaffected in *Lpar2*$^{-/-}$ mice. These data show that LPA_1 or LPA_2 inhibition may be therapeutically beneficial in patients with varying types of fibrosis. In particular, phase I clinical trials are already being carried out with LPA_1 antagonists; Sanofi is testing SAR-100842 for systemic sclerosis and Bristol-Myers Squibb is assessing AM152 for idiopathic pulmonary fibrosis (200).

Bone development and disease

LPA signaling has also been implicated in aspects of bone development and pathology (255). The two major cell classes in bone are osteoblasts and osteoclasts, which build and remove bone, respectively. LPA can induce differentiation of human mesenchymal stem cells into osteoblasts through LPA_1 and LPA_4 (177), although these receptors appear to mediate opposing actions. *Lpar4*$^{-/-}$ mice have increased trabecular bone volume, number, and thickness (177). An interplay between osteoblasts and osteoclasts has also been hypothesized (256), based on observations that osteoblasts can produce LPA, while exposure to LPA causes osteoclast lamellipodia retraction, disrupted peripheral actin belts, increased survival, and resorptive activity (257). This process was driven mainly by LPA_1 $G_{i/o}$ coupling. However, $G_{12/13}$ coupling with an as yet unidentified LPA receptor (LPA_2, LPA_4, LPA_5, or LPA_6) may also underlie osteoclast function (257).

Reproductive system and infertility

LPA_3 signaling has an established role in regulating aspects of male and female reproduction and its dysregulation is implicated in mammalian infertility and reproductive problems (258). In fact, *Lpar3*$^{-/-}$ null mice have delayed embryo implantation, embryo crowding, and reduced litter size. These defects were traced to maternal influences, as wild-type embryos transferred into *Lpar3*$^{-/-}$ dams failed to implant normally (163). Mice lacking cyclooxygenase-2, an enzyme that produces prostaglandins downstream of LPA_3, also have similar defective phenotypes. Mechanistically, exogenous prostaglandin administration to *Lpar3*$^{-/-}$ dams rescues delayed implantation and reduced litter size, demonstrating that LPA_3-mediated signaling is upstream of prostaglandin synthesis (163). However, this treatment failed to rescue embryo crowding, indicating that LPA_3 signaling mediates aspects of implantation in both prostaglandin-dependent and -independent fashions (259). The mechanism underlying spacing defects in *Lpar3*$^{-/-}$ mice remains to be fully understood, but may involve cytosolic phospholipase A2α (cPLA$_{2\alpha}$) or Wnt/β-catenin signaling, as cPLA$_{2\alpha}$ removal or Wnt/β-catenin signaling inhibition result in similar embryo crowding phenotypes (260, 261). Injection of Ki16425 into bovine blood decreased progesterone and PGE_2 secretion, suggesting yet another role for LPA signaling in the reproductive system and pregnancy (262). This change in progesterone and PGE_2 secretion is LPA_1-specific, because use of an LPA_3-selective inhibitor, diacylglycerol pyrophosphate (DGPP), did not alter production (263).

In addition to being integral to female reproduction, LPA_3 appears to play an important role in male fertility (88). One study demonstrated that LPP-1 overexpression resulted in impaired spermatogenesis (264), suggesting that the presence of LPA may be important in sperm development. There is also evidence for LPA involvement in sperm motility (265), although triple genetic deletion of LPA_{1-3} showed no detectable deficits in sperm motility. However, deletion of LPA_{1-3} did result in decreased germ cell survival and increased prevalence of azoospermia in aging mice (264). In addition to the above reproductive phenotypes, additional studies implicate LPA signaling in male sexual function, ovarian function, fertilization, decidualization, pregnancy maintenance, and parturition (88). This indicates that LPA_{1-3} signaling is important in both male and female reproduction.

Obesity

Obesity is quickly becoming one of the greatest problems in the developed world. Not only is obesity the most common childhood disorder, but it raises the risk of other potentially fatal comorbidities (266). The long-term effects of being overweight correlate with premature death, cardiovascular disease, metabolic morbidities, and asthma, among other problems (267). Many factors modulate the propensity to accumulate fat cells, including an increased ratio of adipocyte precursor cells to differentiated adipocytes (268). In this vein, LPA signaling may play a role in fat storage, as LPA influences adipocyte precursor differentiation. Additionally, ATX is secreted during adipocyte differentiation and LPA is produced by mature adipocytes (269–271). When obesity and type II diabetes are genetically induced in *db/db* mice, LPA production increases (241). Moreover, LPA and ATX production have been linked to preadipocyte proliferation (270, 272), a process which may be LPA_1 dependent (195). LPA_1-mediated activation of the mitogenic Erk1/2 pathway (273) and the differentiation-inhibiting PPARγ2 receptor (274) has been implicated in this response. These data are supported by the fact that *Lpar1*$^{-/-}$ mice have higher adiposity compared with wild-type littermates, despite lowered body weight (149, 275).

In addition to affecting adipocyte proliferation, LPA_1 signaling may be more directly involved in mediating glucose and insulin in diabetic patients. LPA has been shown to lower glucose levels in normal and type I diabetic mice, though LPA production was unaltered (276). Furthermore, administration of LPA to obese prediabetic glucose-intolerant mice inhibited insulin secretion and lowered glucose tolerance (277, 278). This effect was prevented by the antagonist Ki16425. These studies also showed that circulating LPA levels were elevated in the high-fat diet mice compared with normal diet controls and that long-term administration of Ki16425 improved insulin tolerance, glycogen storage, and glucose use in these mice, possibly by increasing the population of pancreatic islets. Therefore, ATX, LPA production, and LPA_1 signaling have been implicated in the propagation of adipose tissue and the instigation of abnormal glucose and insulin levels in obese patients and mice. These data suggest that reducing LPA levels or inhibiting LPA_1 signaling in obese or diabetic patients may be a possible treatment option for these disorders.

Cancer

LPA and ATX signaling are implicated in the cancer field as important factors in the migration, invasion, metastasis, proliferation, survival, and angiogenesis processes of tumorigenic cells (140, 279–281). Increased LPA levels have been measured in ovarian cancer patients and several cell lines (282–286). In particular, LPA_2 overexpression has been observed in several cancers in vivo and in vitro (287, 288). LPA_2 signaling has been associated with invasion and metastasis of ovarian, endometrial, mesothelioma, and colon cancer cells (289, 290), likely through the activation and induction of VEGF, EGFR, metalloproteinases, urokinase-type plasminogen activator, cyclooxygenase-2, or Akt/Erk1/2 (289, 291–294). LPA_3 may play a complementary role, initiating invasion and metastasis of the same cancer cell types (295–297).

LPA_1 is also upregulated in many cancer cell lines and primary tumors and may play an important role in regulating cancer malignancy. Studies showed that induction of LPA_1 expression induced metastasis in breast cancer cells (296, 298) and initiated motility in human pancreatic cancer cells (299). Additionally, genetic knockdown or LPA_1 inhibition reduced cytokine production, tumor proliferation, and bone lesions or metastases with breast and ovarian cancer cells (198). *LPAR1* mutations were also found in an osteosarcoma cell line (300) and in lung and liver tumors in rats (301). Moreover, LPA_1-initiated colony scattering (a prerequisite for metastasis) occurred in some, but not all, gastrointestinal epithelial cancer lines (302), suggesting that this phenomenon may require cross-talk with other signaling molecules. It was even reported that LPA_2 inhibited pancreatic cancer cell migration while LPA_1 induced migration in response to LPA (144). LPA receptor signaling promotes invasion and metastasis of several cancer types, but the role of each receptor may be different in each case. These pro- and anti-tumorigenic effects of LPA_{1-3} may reflect the differential expression of various growth factors and receptors.

Finally, ATX itself has been implicated in stimulating cancer cell motility (58), and may promote bone metastasis (303). Additionally, ATX was shown to be overexpressed in several primary tumor types (175, 304–307). ATX expression may also confer resistance to cancer treatments such as Taxol (308). Overexpression of LPA_{1-4} and ATX has been reported to enhance tumor aggression for numerous cancer types, whereas knockdown studies mitigate tumorigenic behaviors (309, 310). These responses may be mediated, at least in part, by G_α-induced RhoA and Rac signaling leading to cytoskeletal remodeling and migration (311). In addition, LPA receptor signaling stimulates cell proliferation through Ras signaling and suppresses apoptosis through PI3K and Akt activation (279).

LPA is also a known vasculature-altering factor, participating in the formation and stabilization of new blood vessels (70). These properties may cause LPA signaling to assist invasion and metastasis more indirectly by stimulating the rapidly growing vasculature of the cancer microenvironment to form leaky blood vessels, feeding the cancer cells and allowing easier extravasation of malignant cells. To this end, LPA has been reported to stimulate VEGF production, a prominent angiogenic factor and target for cancer therapy research (312–314). In addition to enhancing blood supply to tumors, VEGF has been shown to increase cancer cell migration, proliferation, invasion, and survival. In a study involving epithelial ovarian cancer, LPA-induced VEGF expression was discovered to be mediated by NF-κB through G_i signaling (315).

Several LPA receptor antagonists have been utilized in the study of cancer development. Notably, these drugs seem to attenuate metastatic and migratory behaviors in cancer cells. In one study, the pan-LPA antagonist BrP-LPA was synthesized and applied to MDA-MB-231 breast cancer cells in

vitro and in a mouse xenograft model (195). The treated cancer cells demonstrated reduced migration, inhibition of cancer cell invasion, tumor regression, and decreased blood vessel density surrounding the tumor. In addition, use of LPA_1/LPA_3-specific inhibitors reduced pancreatic and breast cancer invasion and metastasis, but not tumor size (316, 317), while administration of the LPA_2-selective antagonist Compound 35 to HCT-116 colorectal cancer cells inhibited mitogenic Erk phosphorylation and reduced cell proliferation (318). Finally, BrP-LPA sensitized the radiation-resistant vascular endothelial cells surrounding mouse gliomas to radiation therapy (196). This evidence points to active LPA signaling as an important factor in the cancer field and a possible target for cancer therapies.

CONCLUSION

The past 20 years have seen the cloning and identification of a growing family of LPA receptors and signaling pathways, coupled with a rapidly burgeoning field aimed at understanding the physiological and pathophysiological relevance of these lipids. It is now an exception, rather than the rule, to find an organ system that is not impacted by LPA and LPA signaling. Moreover, there is ever-growing understanding and appreciation that numerous human disease mechanisms are implicitly or explicitly linked to altered LPA signaling. Most exciting is the development of novel pharmacological modulators that serve as both research tools and potential medicinal therapies aimed at reducing human suffering. The prospects are bright for expanding insights and contributions in LPA biology.

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