LPA Receptors: Subtypes and Biological Actions

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Key Words

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Abstract

Lysophosphatidic acid (LPA) is a small, ubiquitous phospholipid that acts as
an extracellular signaling molecule by binding to and activating at least five
known G protein–coupled receptors (GPCRs): LPA_1–LPA_5. They are en-
coded by distinct genes named *LPAR1–LPAR5* in humans and *Lpar1–Lpar5*
in mice. The biological roles of LPA are diverse and include developmental,
physiological, and pathophysiological effects. This diversity is mediated by
broad and overlapping expression patterns and multiple downstream sig-
naling pathways activated by cognate LPA receptors. Studies using cloned
receptors and genetic knockout mice have been instrumental in uncovering
the significance of this signaling system, notably involving basic cellular pro-
cesses as well as multiple organ systems such as the nervous system. This has
further provided valuable proof-of-concept data to support LPA receptors
and LPA metabolic enzymes as targets for the treatment of medically im-
portant diseases that include neuropsychiatric disorders, neuropathic pain,
infertility, cardiovascular disease, inflammation, fibrosis, and cancer.

INTRODUCTION

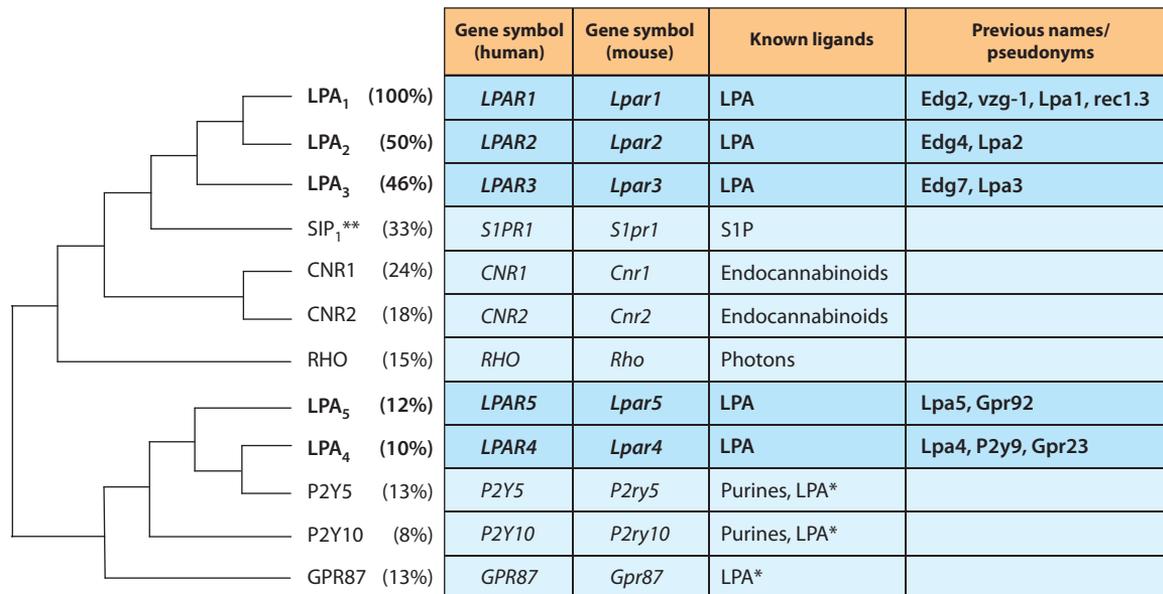Lysophosphatidic acid (LPA) is a small glycerophospholipid (molecular weight: 430–480 Da) that is present in all eukaryotic tissues at low concentrations, relative to major phospholipid species, and at higher concentrations (sub-micromolar range) in blood plasma. In 1996, the first high-affinity, cognate cell surface receptor for LPA was identified (LPA$_1$) (1). This quickly led to the identification of two additional, closely related receptors (LPA$_2$ and LPA$_3$) and the recent identification of two more, somewhat divergent, receptors (LPA$_4$ and LPA$_5$) (**Figure 1**). All five receptors are type I, rhodopsin-like G protein–coupled receptors (GPCRs) that differ in their tissue distribution (**Figure 2**) and downstream signaling pathways (**Figure 3**).

Because of this heterogeneity of receptor subtypes, expression patterns, and effector pathways, the effects of LPA are diverse and widespread, regulating many biological processes. A great deal of information regarding these biological roles was derived from genetic deletion studies. To date, knockout mice have been reported for four of the five known receptors (LPA$_{1-4}$), as well as the major LPA-generating enzyme, autotaxin (ATX) (2, 3). These mutant mice, in addition to emerging classes of chemical tools, have transitioned observations made through the use of in vitro studies into medically relevant contexts.

It is difficult to discuss LPA without some mention of the structurally similar lipid sphingosine 1-phosphate (S1P). S1P was also discovered to be an extracellular signaling lipid when its first cognate receptor (S1P$_1$) was deorphanized in 1998 (4). Although they represent distinct signaling systems, similarities between these two lipids extend to their tissue distribution and concentration, homology and effector pathways of their cognate receptors, and the broad range of their biological roles. However, because LPA and S1P signaling have become such a robust research area in recent

	Gene symbol (human)	Gene symbol (mouse)	Known ligands	Previous names/ pseudonyms
LPA$_1$ (100%)	*LPAR1*	*Lpar1*	LPA	Edg2, vzg-1, Lpa1, rec1.3
LPA$_2$ (50%)	*LPAR2*	*Lpar2*	LPA	Edg4, Lpa2
LPA$_3$ (46%)	*LPAR3*	*Lpar3*	LPA	Edg7, Lpa3
SIP$_1$** (33%)	*S1PR1*	*S1pr1*	S1P	
CNR1 (24%)	*CNR1*	*Cnr1*	Endocannabinoids	
CNR2 (18%)	*CNR2*	*Cnr2*	Endocannabinoids	
RHO (15%)	*RHO*	*Rho*	Photons	
LPA$_5$ (12%)	*LPAR5*	*Lpar5*	LPA	Lpa5, Gpr92
LPA$_4$ (10%)	*LPAR4*	*Lpar4*	LPA	Lpa4, P2y9, Gpr23
P2Y5 (13%)	*P2Y5*	*P2ry5*	Purines, LPA*	
P2Y10 (8%)	*P2Y10*	*P2ry10*	Purines, LPA*	
GPR87 (13%)	*GPR87*	*Gpr87*	LPA*	

Figure 1

Phylogenetic relationships among known and proposed human LPA receptors. Non-LPA GPCRs (rhodopsin, S1P$_1$, and cannabinoid receptors) are included for reference. Percent amino acid identity to LPA$_1$ is indicated in parentheses. *Low-affinity or unconfirmed ligand. **There are currently at least five receptor subtypes for S1P (S1P$_{1-5}$).
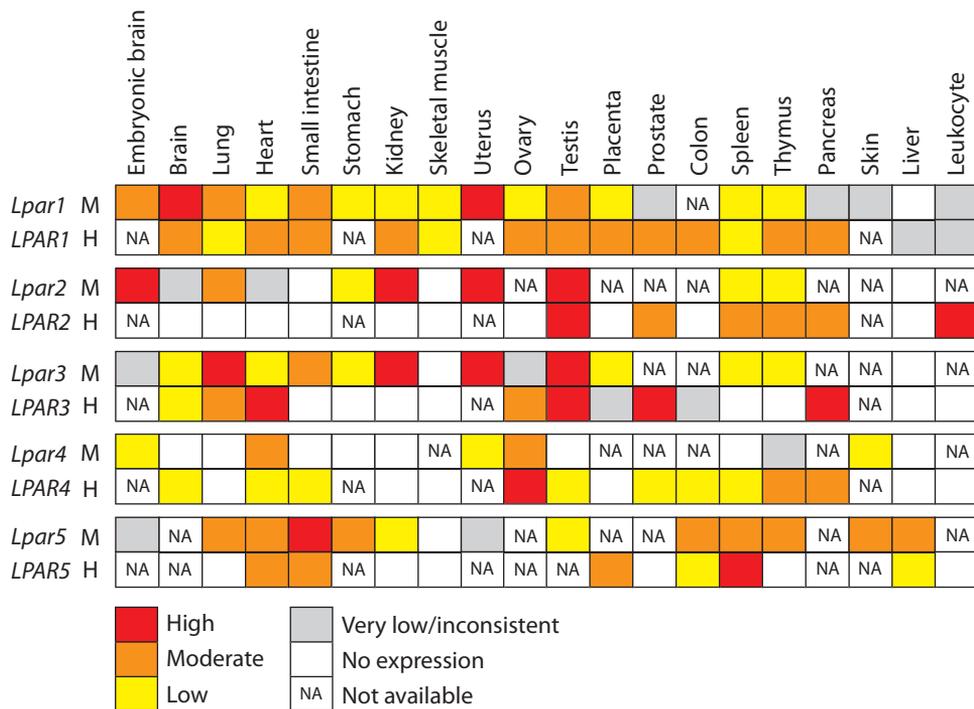
Figure 2

LPA receptor gene expression. Reported expression patterns of *Lpar1–5* in various tissues in mice (M) and humans (H) based on compiled data from multiple published works including Northern analyses, real-time PCR, and microarray data.

years, this review focuses specifically on biological roles of LPA. Comprehensive reviews of S1P signaling can be found elsewhere (5, 6).

METABOLISM

The metabolism of LPA is complex and results in the production of numerous, chemically distinct species. In the context of LPA as a signaling molecule, the term *LPA* generally refers to 1-acyl-2-hydroxy-*sn*-glycero-3-phosphate, but other forms, such as 1-alkyl- or 2-acyl-LPA, exist (7, 8). The acyl chain length and degree of saturation vary considerably and depend on the precursor phospholipid. For example, 1-palmitoyl-phosphotidylcholine is metabolized to 1-palmitoyl-LPA (16:0-LPA). The most quantitatively abundant forms of LPA in human plasma are 16:0-, 18:2-, and 18:1-LPA (9). The last form is perhaps the most commonly used laboratory reagent for signaling studies.

LPA is produced from membrane phospholipids via two major pathways: (*a*) sequential activity of phospholipase D (PLD) and phospholipase A$_2$ (PLA$_2$) and (*b*) sequential activity of PLA$_2$ and lysophospholipase D (lysoPLD) (**Figure 4**). A previously known gene, *Enpp2*, encoded the ATX protein that was found to have lysoPLD activity (10, 11). Interestingly, ATX had previously been identified as a cancer-cell-motility-stimulating factor (12), which was originally attributed to its activity as a presumptive nucleotide phosphodiesterase (13). The promigratory effect on cancer cells now appears to be the result of autocrine signaling from the production of LPA (see below). The importance of ATX in LPA metabolism was not fully appreciated until phenotypes of the

lysoPLD: lysophospholipase D
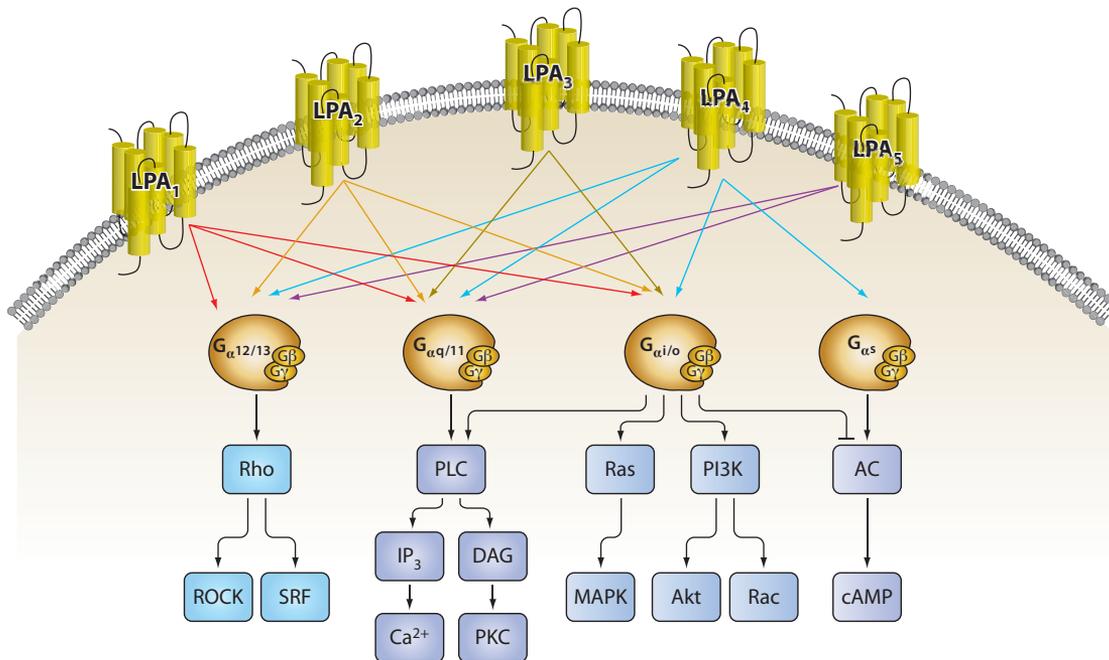
Figure 3

Signaling pathways activated by the five confirmed LPA receptors.

ATX knockout mouse were reported (14, 15). *Enpp2*$^{-/-}$ mice uniformly die at approximately embryonic day 9.5 with pronounced neural tube and vascular defects. Importantly, *Enpp2*$^{+/-}$ heterozygotes survive to adulthood but have plasma LPA levels that are half that of wild-type mice. This confirms that ATX activity is the major source of plasma LPA and that LPA signaling is essential for development. The source of tissue LPA that contributes to signaling pools likely involves not only ATX but other enzymes as well.

LPA RECEPTORS

Since the early twentieth century, lysophospholipids have been known to have biological activity, but these effects were long thought to be the result of nonspecific detergent-like disruptions of the plasma membrane. These studies, however, were performed at very high, nonphysiological concentrations. It is now known that the effects of LPA at physiological concentrations are mediated by five bona fide, high-affinity cognate receptors (LPA$_1$–LPA$_5$) and perhaps by additional recently proposed or as yet unidentified receptors (16–18).

LPA$_1$

LPA$_1$ is the first high-affinity receptor identified for LPA (1) (reviewed in 16, 17). The mammalian *LPAR1* gene (human chromosomal locus 9q31.3) encodes an approximately 41-kDa protein consisting of 364 amino acids with 7 putative transmembrane domains. In mice, the open reading frame is encoded on two of five exons with a conserved intron (shared with *Lpar2* and *Lpar3*)

LPAR: LPA receptor

Figure 4

LPA metabolism. The production of LPA from membrane phospholipids through two major metabolic pathways is shown. Other pathways exist for the production of LPA, as well as degradation (7, 203). *18:1-LPA is the most commonly used laboratory reagent for activation of LPA receptors. **16:0-LPA is reportedly the most abundant species in human plasma.

that interrupts transmembrane domain 6. One reported variant of *Lpar1* (mrec1.3), which may be produced by alternative exon usage or splicing, results in an 18-amino-acid deletion of the N terminus (19). The biological significance of this variant has not been established.

Wide expression of *Lpar1* is observed in adult mice, with clear presence in at least brain, uterus, testis, lung, small intestine, heart, stomach, kidney, spleen, thymus, placenta, and skeletal muscle (**Figure 2**) (20, 21). *LPAR1* is also widely expressed in humans (**Figure 2**) (22). Expression of *Lpar1* is more spatially restricted during embryonic development but is enriched in the brain (23). In particular, the developing nervous system is a major locus for *Lpar1* expression, where it is

spatially and temporally regulated (reviewed in 17, 20). During embryogenesis, central nervous system (CNS) expression is restricted to the neocortical neurogenic region called the ventricular zone (VZ) and superficially in a layer that includes the meninges (1). The VZ disappears at the end of cortical neurogenesis, just prior to birth, but *Lpar1* expression continues in the postnatal brain, where it is apparent in cells present within developing white matter tracts and coincides with myelination (24). In situ hybridization reveals *Lpar1* expression in oligodendrocytes and Schwann cells, the myelinating cells of the CNS and peripheral nervous system, respectively (24, 25).

CNS: central nervous system

VZ: ventricular zone of the embryonic cerebral cortex

LPA$_1$ couples with and activates three types of G proteins: G$_{\alpha i/o}$, G$_{\alpha q/11}$, and G$_{\alpha 12/13}$ (**Figure 3**) (26, 27). LPA$_1$ activation induces a range of cellular responses: cell proliferation and survival, cell migration, and cytoskeletal changes; altered cell-cell contact through serum-response element activation, Ca^{2+} mobilization, and adenylyl cyclase inhibition; and activation of mitogen-activated protein kinase, phospholipase C, Akt, and Rho pathways (**Figure 3**) (reviewed in 16, 17, 20).

The targeted disruption of *Lpar1* in mice revealed unanticipated in vivo functions of this receptor (28). *Lpar1$^{-/-}$* mice show 50% perinatal lethality in a mixed (C57Bl/6J x 129) genetic background and further decreased survival in pure (C57Bl/6J or Balb/cByJ) genetic backgrounds (J. Chun, unpublished observations). Survivors have a reduced body size, craniofacial dysmorphism with blunted snouts, and increased apoptosis in sciatic nerve Schwann cells (28, 29). Defective suckling, attributed to olfactory defects, likely accounts for perinatal lethality. Small fractions of *Lpar1$^{-/-}$* embryos have exencephaly (∼5%) or frontal cephalic hemorrhage (∼2.5%). Loss of LPA response in embryonic neuroblasts and fibroblasts demonstrates nonredundant functions and roles for *Lpar1* in vivo (28, 30). In addition, during colony expansion of the original line (28), an *Lpar1$^{-/-}$* substrain arose spontaneously, which was called the "Màlaga variant" and exhibits more severe developmental brain defects (31) (see below).

LPA$_2$

Lpar2 was identified from GenBank searches of orphan GPCR genes because of its ∼60% amino acid similarity to *Lpar1*. In humans, *LPAR2* (chromosomal locus 19p12) encodes a protein that has a predicted amino acid sequence of 348 residues, yielding a calculated molecular mass of ∼39 kDa (32).

The expression pattern of *Lpar2* is relatively restricted spatiotemporally compared to that of *Lpar1* (20, 22). In mouse, *Lpar2* is highly expressed in kidney, uterus, and testis and moderately expressed in lung; and lower levels of expression are found in stomach, spleen, thymus, brain, and heart (**Figure 2**) (20). *Lpar2* is also expressed in embryonic brain but decreases within a week after birth (20). In human tissues, high expression of *LPAR2* is detected in testis and leukocytes, with moderate expression found in prostate, spleen, thymus, and pancreas (**Figure 2**) (22). In cancer cells, aberrant expression of *LPAR2* has been reported in several cases, suggesting a tumor-promoting role for LPA$_2$ (see below).

LPA$_2$ couples to the G$_{\alpha i/o}$, G$_{\alpha 11/q}$, and G$_{\alpha 12/13}$ family of heterotrimeric G proteins (**Figure 3**). These G proteins convey signals through downstream molecules that include Ras, mitogen-activated protein kinase, phosphatidylinositol 3-kinase, Rac, phospholipase C, diacylglycerol, and Rho, which is similar to LPA$_1$ (**Figure 3**) (28). LPA$_2$ is a bona fide high affinity cognate LPA receptor (33). Activation of LPA$_2$ signaling is generally associated with such processes as cell survival (34, 35) and cell migration (36–38). As a consequence, LPA$_2$ signaling has emerged as a potential factor for cancer metastasis (see below) (39–41).

Interestingly, several reports have provided evidence for the interaction of LPA$_2$ signaling with other pathways. For example, LPA$_2$ promotes cell migration through interactions with focal adhesion molecule TRIP6 (42, 43), and several PDZ proteins and zinc finger proteins are

also reported to interact directly with the carboxyl-terminal tail of LPA$_2$ (44). In addition, LPA$_2$-mediated signaling can provide inhibitory effects on the epidermal growth factor–induced migration and invasion of pancreatic cancer cells through the G$_{\alpha 12/13}$/Rho pathway (45). These studies provide evidence that LPA$_2$ signaling has cross-regulation between classical G protein signaling cascades and other signaling pathways to regulate the efficiency and specificity of signal transduction.

Mouse knockout studies demonstrate that *Lpar2*$^{-/-}$ mutant animals are viable, grossly normal, and born at normal Mendelian ratios without sexual bias, but *Lpar1*$^{-/-}$/*Lpar2*$^{-/-}$ mutants have an exacerbation of the frontal hematomas present in the *Lpar1*$^{-/-}$ mutant (28, 30). In addition, primary fibroblasts and embryonic cortical cells from the double-null mutants show vastly reduced responses to exogenous LPA (30, 46).

LPA$_3$

Lpar3 was discovered as an orphan GPCR gene using degenerate PCR-based cloning and homology searches (47, 48). *LPAR3* (human chromosomal locus 1p22.3-p31.1) encodes a ~40-kDa GPCR that is ~50% identical to mouse LPA$_1$ and LPA$_2$ in amino acid sequence. Expression of *LPAR3* (**Figure 2**) has been observed in human heart, testis, prostate, pancreas, lung, ovary, and brain (47, 48) and is most abundant in mouse testis, kidney, lung, small intestine, heart, stomach, spleen, brain, and thymus (20). Interestingly, it has been shown that, in the murine uterus, *Lpar3* mRNA is exclusively expressed in the luminal endometrial epithelium at the window of implantation (49) and that its expression is regulated by progesterone and estrogen (50).

Like LPA$_1$ and LPA$_2$, LPA$_3$ can couple with G$_{\alpha i/o}$ and G$_{\alpha q}$ to mediate LPA-induced phospholipase C activation, Ca^{2+} mobilization, adenylyl cyclase inhibition and activation, and mitogen-activated protein kinase activation (**Figure 3**) (27). However, LPA$_3$ is unable to couple with G$_{\alpha 12/13}$ (**Figure 3**) and therefore does not mediate cell rounding in neuronal cells in which G$_{\alpha 12/13}$ and Rho are involved (27). Also, LPA$_3$ is not as responsive as LPA$_1$ and LPA$_2$ to LPA species with saturated acyl chains but has a relatively high affinity for 2-acyl-LPA containing unsaturated fatty acids (47, 51).

Lpar3$^{-/-}$ mice are viable and grossly normal, but female nulls show a striking phenotype in the reproductive system (49) (see below). However, despite the fact that LPA$_3$ is expressed in the frontal cortex, hippocampus, and amygdala (47, 48), no phenotypes related to LPA$_3$ loss in the nervous system have been reported to date.

LPA$_4$

LPA$_4$ was originally identified as a putative GPCR from an analysis of the expressed sequence tag database (52, 53) and was found to be a specific receptor for LPA through ligand screening (54). LPA$_4$ is structurally distinct from classical LPA and S1P receptors that share significant homology and is more closely related to P2Y purinergic receptors. It does not, however, respond to any nucleotides or nucleosides tested (52, 54). In humans, the *LPAR4* gene is located on chromosome X, region q13–q21.1, and contains an intronless open reading frame of 1113 base pairs encoding 370 amino acids with a calculated molecular mass of ~42 kDa (52, 53). LPA$_4$ has a specific binding affinity to 18:1-LPA with a K_d value of 44.8 nM but not to other lysophospholipids and related lipids such as S1P and SPC (54). LPA$_4$ prefers structural analogs of LPA with a rank order of 18:1- > 18:0- > 16:0- > 14:0- > 1-alkyl- > 1-alkenyl-LPA (54).

Among 16 human tissues examined with quantitative real-time PCR, *LPAR4* mRNA is ubiquitously expressed and specifically abundant in the ovary (**Figure 2**) (54). Among mouse tissues

examined with Northern blot and real-time PCR, *Lpar4* mRNA is expressed in heart, skin, thymus, ovary, developing brain, and embryonic fibroblasts (**Figure 2**) (3, 55). Whole mount in situ hybridization detected *Lpar4* mRNA in limb buds, somites, facial processes, and developing brain (23).

In LPA$_4$-overexpressing cells, LPA induces morphological changes such as cell rounding and stress fiber formation through the G$_{\alpha12/13}$ and Rho/Rho-kinase pathways (**Figure 3**) (55, 56), as observed in LPA$_1$-, LPA$_2$-, and LPA$_5$-expressing cells. Additionally, Rho-kinase-mediated cell aggregation and N-cadherin-dependent cell adhesion are observed in LPA$_4$-expressing cells (56). LPA induces intracellular cAMP accumulation through G$_{\alpha s}$, and Ca^{2+} mobilization through G$_{\alpha q/11}$ and G$_{\alpha i}$ (**Figure 3**) (55, 56). Notably, G$_{\alpha s}$-coupling is not reported for classical LPA receptors. Recently, LPA$_4$-deficient mice have been reported, although they display no apparent abnormalities (3). However, LPA$_4$ has a suppressive effect on cell motility in that (*a*) LPA$_4$ deficiency enhances migratory response to LPA in fibroblasts and (*b*) heterologous expression of LPA$_4$ suppresses LPA$_1$-dependent migration of B103 cells and LPA-induced migration and invasion of colon cancer cells (3).

LPA$_5$

Recently, an orphan GPCR (GPR92) was identified as an LPA receptor and was renamed LPA$_5$ to reflect this identity (57, 58). Human *LPAR5* is located on chromosome 12p13.31 and encodes a ~41 kDa protein consisting of 372 amino acids. Like other LPA receptors (LPA$_{1-4}$), LPA$_5$ also belongs to the rhodopsin-GPCR family and, although structurally different from LPA$_{1-3}$, it shares 35% homology with LPA$_4$ (58). *Lpar5* is broadly expressed in murine tissues such as embryonic brain, small intestine, skin, spleen, stomach, thymus, lung, heart, liver, and embryonic stem cells (**Figure 2**) (57, 58).

LPA induces neurite retraction and stress fiber formation in LPA$_5$-expressing cells by coupling to G$_{\alpha12/13}$ and increases intracellular calcium levels by activation of G$_{\alpha q}$ (**Figure 3**) (58). Furthermore, LPA increases cAMP levels and inositol phosphate production in LPA$_5$-expressing cells (**Figure 3**) (57, 58). Recently, two other lipid-derived molecules (farnesyl pyrophosphate and *N*-arachidonylglycin) were characterized as LPA$_5$ ligands (59). In this study, farnesyl-pyrophosphate activated G$_{\alpha q/11}$- and G$_{\alpha s}$-mediated signaling, whereas *N*-arachidonylglycin was able to activate only G$_{\alpha q/11}$-mediated signaling. It has been suggested that those ligands interact differently with the ligand-binding pocket of LPA$_5$ (59). However, subsequent studies confirm that LPA$_5$ is a bona fide LPA receptor that can also be activated by farnesyl pyrophosphate at much higher concentrations relative to 18:1-LPA, leaving open the question of the biological relevance of these alternative ligands (60, 61).

Other Proposed Receptors

Recently, three more orphan GPCRs have been published as new, putative LPA receptors: GPR87, P2Y5, and P2Y10 (62–64). Each of these orphan GPCRs belongs to the purinergic receptor P2Y family and is more closely related to LPA$_4$ and LPA$_5$ than to LPA$_{1-3}$. Of these, P2Y5 is likely to join the LPA receptor family as LPA$_6$, based on recent published and unpublished data. P2Y5 was identified as a critical mediator for human hair growth and is a causal gene of a rare familial form of human hair loss (63, 63a), and recent studies of this putative LPA$_6$ support activation of this receptor by uncharacteristically high concentrations of LPA [EC$_{50}$ in the low micromolar range for some assays (65)]. This suggests an identity of P2Y5 as a relatively low-affinity LPA receptor,

distinct from LPA_{1-5} (65), perhaps requiring a distinct ligand or other explanations. GPR87 and P2Y10 were reported to increase intracellular Ca^{2+} mobilization using a promiscuous $G_{\alpha16}$ fusion system (62, 64). $P2Y10$-$G_{\alpha16}$ also can induce Ca^{2+} transients by S1P as well as LPA (EC_{50} = 53 and 130 nM, respectively) (62). More detailed investigations are required to confirm these three candidates as bona fide LPA receptors. Non-GPCR LPA receptors have been reported, but their validity remains to be established (66).

BIOLOGICAL FUNCTIONS OF LPA

The first known in vivo biological function attributed to LPA was the regulation of blood pressure (67, 68). Whereas this was thought to be due to its role as a metabolic intermediate, most biological functions of LPA have since been discovered to be mediated by specific interaction with its five cognate receptors (LPA_{1-5}) (17, 69). Many gain- and loss-of-function studies have evaluated a variety of biological, LPA receptor-mediated functions, including mitogenic effects, cell differentiation, cell survival, cytoskeletal reorganization, process retraction, and cell migration (2, 17, 69). These LPA-mediated processes involve nervous system function, vascular development, immune system function, cancer, reproduction, fibrosis, and obesity (**Tables 1** and **2**). This section provides a snapshot of the expanding range of LPA functions.

Nervous System

The nervous system is one of the major loci for LPA receptor expression (**Figure 2**), and LPA exists in the brain at relatively high concentrations (8). The restricted expression of LPA_1 within the proliferative cortical VZ of the embryonic brain (see above) (1, 26), unlike that of other important growth factor receptors, indicated a significant role for LPA signaling in the development of VZ cells. Subsequent gain- and loss-of-function studies have characterized LPA receptor expression and functions in this system: (*a*) LPA receptors are expressed in most cell types of the nervous system, including neural progenitors, primary neurons, astrocytes, microglia, oligodendrocytes, and Schwann cells (reviewed in 70). (*b*) LPA signaling influences several developmental processes within the nervous system, including cortical development and function (31, 71), growth and folding of the cerebral cortex (46), growth cone and process retraction (72–74), survival (46), migration (75), adhesion (29), and proliferation (28, 46). (*c*) LPA signaling may be involved in neurological disorders such as schizophrenia and neuropathic pain (28, 71, 76–78). These observations underscore the importance of LPA signaling in normal development as well as pathological settings in the nervous system.

LPA signaling has significant influences on neuroprogenitor cells (NPCs) that abundantly express *Lpar1*, *Lpar2*, and *Lpar4* (J. Chun, unpublished observations). Heterologous expression studies in neural precursor cell lines have revealed specific effects of LPA receptors on cellular morphology (reviewed in 17, 70). In addition, LPA signaling controls proliferation and differentiation of primary NPCs (26, 28) and neurosphere cultures (79) via LPA_1 and differentiation of immortalized hippocampal progenitor cells via LPA_4 (80). LPA signaling also has significant effects on the morphology of NPCs, such as the induction of neurite retraction and compaction in the VZ (28, 73). Additionally, LPA was identified as the earliest known stimulus for ionic conductance changes in cortical NPCs, implicating LPA as a novel, physiological component in CNS development (81). The effects of LPA signaling on cortical neurogenesis have been addressed using an organotypic, whole-cortex, ex vivo culture system (46). Exogenous LPA exposure increases terminal mitosis of NPCs, resulting in cortical thickening and folding that resembles gyri. These effects are absent

Table 1 Physiological roles for LPA signaling

	Phenotype	Established roles for LPA signaling
Nervous system	Growth/development	Proliferation and differentiation of neural progenitor cells (NPCs) Neurogenesis Ionic conductance changes Neuronal survival LPA production by neurons Astrocyte proliferation
	Morphology	Morphological changes in NPCs, neurons, and astrocytes Cortical actin assembly in *Xenopus* neurons Synapse formation
	Cellular interaction	Neuronal differentiation by astrocyte-derived soluble factors
	Myelination	Differentiation of oligodendrocytes Morphological changes in Schwann cells Proliferation and survival of Schwann cells Upregulation of myelin P0 protein
Vascular system	Vasculogenesis Angiogenesis	Frontal cephalic hemorrhages in $Lpar1^{-/-}$ and $Lpar1^{-/-}/Lpar2^{-/-}$ Severe vascular defects in ATX null Vasculature maintenance
	Vasoregulation	Hypertension or hypotension by LPA Endothelial cell death Loss of vascular integrity Increase in hydraulic permeability
Immune system	T cell functions	Chemotaxis Cytokine production Apoptosis Trafficking (regulation by ATX)
	Dendritic cell functions	Maturation Chemotaxis of immature dendritic cells
Reproductive system	Embryo implantation	Timing and spacing of implantation Regulation of prostaglandin pathways
	Spermatogenesis	Survival factor for germ cell Sperm motility
	Others	Possible role in male sexual function, ovarian functions, fertilization, decidualization, pregnancy maintenance, and parturition

in embryonic cerebral cortices from $Lpar1^{-/-}/Lpar2^{-/-}$ mice exposed to LPA, demonstrating the LPA$_{1/2}$ dependency of the process. Surprisingly, LPA exposure does not increase proliferation in this system, but instead results in a decrease in cell death and an early cell cycle exit (increased terminal mitosis).

These studies provide evidence for a significant role of LPA signaling in controlling the organization of the developing cortex. Unexpectedly, however, genetic deletion of *Lpar1* and/or *Lpar2* was reportedly associated with only minor defects in brain development (28, 30). More recently, the characterization of a spontaneously arising $Lpar1^{-/-}$ variant revealed new in vivo roles of LPA$_1$. The Málaga variant demonstrated that LPA$_1$ deficiency resulted in defects in cortical development, including reduced proliferative populations and increased cortical apoptosis (31), with similar effects on hippocampal neurogenesis (82). Studies of nonmammalian models demonstrate the conservation of LPA signaling in the CNS. In *Xenopus*, for example, LPA$_1$ and LPA$_2$

Table 2   Pathophysiological roles for LPA signaling

Pathological conditions	Established roles for LPA signaling		
Neuro-inflammation	Astrogliosis by LPA injection LPA$_3$ upregulation in activated microglia		
Nerve injury	LPA$_1$ and LPA$_2$ upregulation after nerve transection Neuropathic pain by LPA injection Substance P release by LPA Resistance to partial sciatic nerve ligation–induced neuropathic pain in $Lpar1^{-/-}$ or ATX null		
Schizophrenia	Cranial dysmorphism in $Lpar1^{-/-}$ Defect in the prepulse inhibition in $Lpar1^{-/-}$ Alteration of 5-HT system in $Lpar1^{-/-}$ Reduction of Risperidone efficacy		
Atherosclerosis	LPA accumulation in atherosclerotic plaques Platelet activation De-differentiation of vascular smooth muscle cells (VSMCs) by LPA Defect in migration of SMCs from $Lpar1^{-/-}/Lpar2^{-/-}$ Reduction in neointimal lesions of carotid artery ligation in $Lpar1^{-/-}/Lpar2^{-/-}$		
Wound healing	Secretion of LPA from activated platelets Mitogenic/migratory effect on endothelial cells, SMCs, and fibroblasts Closure of wounded endothelial monolayers Promotion of repair processes in wounds		
Cancer	Ovarian	LPA as ovarian cancer activating factor Potent protumorigenic effect (by LPA$_2$; partially by LPA$_1$ or LPA$_3$) LPA$_2$ upregulation in some cancers Involvement in hypoxia-stimulated tumorigenic processes	
	Gastrointestinal	Protumorigenic effect (by LPA$_1$ and LPA$_2$) LPA$_2$-mediated tumor formation Regulation of known signaling molecules	
	Lung	Promotion of cancer aggressiveness	
	ATX as a motility stimulating factor for cancer cells Stimulation of angiogenesis during tumor formation Possible involvement in breast cancer, prostate cancer, and glioma		
Airway disease	Increased LPA levels in asthma Possible role for LPA signaling as an anti-inflammatory factor		
Fibrosis	Pulmonary fibrosis (PF)	Increased LPA level in PF Reduced mortality in $Lpar1^{-/-}$	
	Tubulo-interstitial fibrosis (TIF)	Reduced TIF by genetic and pharmacological inhibition of LPA$_1$ activity Enhanced LPA secretion and LPA$_1$ up-regulation in TIF	
	Liver fibrosis	Enhanced LPA level and ATX activity in patients or animal models LPA-induced proliferation of stellate cells and hepatocytes	
Obesity	ATX upregulation during adipocyte differentiation ATX upregulation in obese-diabetic mice or in glucose-intolerant obese women Anti-adipogenesis LPA or ATX secretion by adipocytes Stimulation of motility and proliferation in preadipocytes Higher adiposity in $Lpar1^{-/-}$ compared to wild type Regulation of blood glucose metabolism		

homologs were reported to regulate normal cortical actin assembly (83). Taken together, growing evidence has demonstrated multiple functions for LPA signaling in the brain during development, but more precise mechanisms need to be elucidated. Furthermore, the more recently identified LPA receptors (LPA$_4$ and LPA$_5$) are also expressed in the embryonic brain, and their roles remain to be determined, particularly in relation to other LPA receptors.

A number of in vitro studies have investigated the effects of LPA stimulation in a variety of neuronal cell lines and primary neuron preparations. In embryonic murine cortical neurons, LPA signaling inhibits migration by inducing neurite retraction and growth cone collapse (75). Additional studies have found similar morphological changes in neurons and neuronal cell lines (74, 75, 84, 85). Because LPA-mediated morphological changes are present even in neurons derived from *Lpar1*$^{-/-}$ animals (75), it is likely that these effects are mediated by other LPA receptors. In addition to regulating morphology, LPA signaling has been reported to influence survival (86, 87), synapse formation (88), and synaptic transmission (88a) of postmitotic neurons, indicating the possible role of LPA signaling in learning and memory.

Astrocytes are the most abundant glial cell type and play an important role in many neurodevelopmental and neurodegenerative processes. Astrocytes express all LPA receptors (89) and display a broad spectrum of LPA-induced responses in culture (90–92). Notably, a study using LPA$_1$-null astrocytes clearly identified the involvement of this receptor in LPA-mediated astrocyte proliferation (89). Some controversy, however, surrounds the proliferative role of LPA in astrocytes, which likely reflects differences in culture conditions (reviewed in 70). LPA signaling also regulates morphological changes of astrocytes via the Rho-cAMP pathway and stabilization of stress fibers (93, 94). Such responses may be relevant to neurodegeneration where astrogliosis occurs. Indeed, in vivo LPA injection into the striatum resulted in astrogliosis (92), although the receptors that mediate this response have not been identified. Recently, a new role for LPA signaling in astrocytes has been revealed in the context of neuronal differentiation (95). Astrocytes primed by LPA increase neuronal differentiation, likely through as yet unidentified soluble factors, and this activity is dependent on activation of LPA$_1$ and LPA$_2$ in astrocytes.

Microglia are CNS resident macrophages that have a variety of functions in the inflammation-challenged nervous system. They express LPA$_1$ and LPA$_3$ (96, 97), but the role of LPA signaling is only partially characterized in this system. Several cellular functions of LPA signaling in microglia have been observed, including proliferation, cell membrane hyperpolarization, enhanced chemokinesis, membrane ruffling, and growth factor upregulation (96, 98–100). It is notable that LPA$_3$ is upregulated in lipopolysaccharide-stimulated microglia (97), suggesting a role for LPA signaling in activated microglia during neuroinflammation. It is likely that other important functions, especially those that are pathologically relevant, remain to be identified in future studies.

Oligodendrocytes, the myelin-forming glial cells in the CNS, express LPA$_1$ and LPA$_3$ during differentiation (24, 101, 102). A significant role for LPA signaling in myelination was suggested by the *Lpar1* gene expression pattern that spatially and temporally correlated with oligodendrocyte maturation and myelination (24, 101, 103). This stimulated a number of in vitro studies that have revealed oligodendrocyte responses to LPA that are dependent on the maturity of oligodendrocytes (reviewed in 70). These studies, however, do not adequately characterize the functional roles for LPA signaling in oligodendrocytes because no significant role for LPA signaling in myelination has been discovered through either in vitro or in vivo studies (28, 104). Recently, however, an in vitro study reported that LPA has a positive effect on process formation and myelin basic protein production in oligodendrocytes (105). Moreover, some evidence suggests the biological significance of the related signaling lipid S1P in oligodendrocyte function. This appears to signal via cognate receptor S1P$_5$, although no specific myelination defects were detected in the knockout

mouse (106). Based on the overlapping expression of LPA_1 and $S1P_5$ and common downstream effector pathways, there is likely to be functional redundancy between these signaling pathways in oligodendrocytes.

Schwann cells (SCs) are the myelinating cells of the peripheral nervous system. SCs express LPA_1 and LPA_2 (25, 29, 101), and activation of these receptors is known to affect processes associated with myelination. LPA was first identified as a survival factor, because LPA prevents cell death of cultured neonatal rat SCs through $G_{\alpha i}$-mediated activation of a downstream antiapoptotic effector cascade (25, 107). LPA-mediated SC survival was confirmed in vivo, as mice deficient for LPA_1 revealed increased apoptosis of SCs in the sciatic nerves (28). In addition to SC survival, LPA also induced dynamic regulation of the actin cytoskeleton and cellular adhesion properties in primary rat SCs (29), which suggests a critical role for LPA signaling in SC motility and myelination. LPA_2 signaling also appears to be involved in SC function, because its activation results in the upregulation of myelin P0 protein in cultured SCs (107). In addition to the role for myelination during developmental stages, evidence indicates a role for LPA signaling in remyelination after injuries such as neuropathic pain (76) (see below) and nerve transection where LPA_1 and LPA_2 are upregulated (29, 108) despite very low levels under basal conditions (24).

An intriguing link may exist between LPA signaling and neurological diseases such as schizophrenia and autism, on the basis of phenotypic and molecular similarities. Craniofacial dysmorphism (28, 71, 109), defects in prepulse inhibition (71, 109a), and widespread brain alterations in serotonin (5-HT) neurotransmitter levels (71, 109b) are present in both *Lpar1*$^{-/-}$ mice and patients suffering from schizophrenia. LPA can interfere with glial cell signaling and morphology induced by the atypical antipsychotic agent Risperidone (110), used in the treatment of both schizophrenia and autism. Interestingly, some epidemiological studies link environmental perturbations such as prenatal fetal or maternal bleeding, among other factors, to autism (111) and schizophrenia (112). In this regard, it is notable that LPA is a major component of blood serum, with reported concentrations ranging from 1–20 μM (113, 113a), raising the possibility that brain exposure to LPA could occur through hemorrhage. Embryonic brain exposure to 1 μM LPA in an ex vivo murine model demonstrated altered gyrification-like changes in the cerebral cortex (46), consistent with observations in autism (114) and schizophrenia (115).

Because LPA and its metabolic precursors are present in blood (reviewed in 7), conditions where the blood-brain barrier is compromised and/or LPA production is altered may generate abnormal LPA signaling and lead to neurological pathologies. Indeed, a pathologically high concentration of LPA (10 μM) inhibits neurogenesis in neurosphere culture (116), which may be relevant to neurotraumatic injury. Taken together, a growing body of evidence points to novel roles for LPA signaling in multiple disease processes in the CNS, but further mechanistic studies are needed to elucidate these links more precisely.

Another pioneering study in this field revealed a critical association between LPA signaling and diseases of the peripheral nervous system, such as neuropathic pain. It was shown that LPA is able to initiate neuropathic pain, which occurs through the activation of LPA_1 (76) and subsequent release of the pronociceptive factor substance P (78, 117, 118). Furthermore, *Lpar1*$^{-/-}$ mice are resistant to neuropathic pain induced by partial sciatic nerve ligation (76). The importance of LPA signaling in this process is further supported by the findings that (*a*) ATX induces neuropathic pain through the conversion of LPC to LPA (77) and (*b*) heterozygous ATX knockout mice (ATX$^{+/-}$) show a 50% decrease in ATX activity and a 50% recovery from the neuropathic pain induced by partial sciatic nerve ligation (119). This novel, critical role for LPA signaling may be important for the development of drug compounds because there currently are no approved therapeutics that are highly and specifically effective in preventing or treating neuropathic pain.

Vascular System

The development of the vascular system involves the proliferation, migration, adhesion, differentiation, and assembly of vascular endothelial cells and vascular smooth muscle cells (VSMCs). Recently, evidence has emerged that identifies LPA as a mediator in angiogenesis and vascular maturation. An initial characterization of knockout mice revealed the presence of frontal cephalic hemorrhages in $Lpar1^{-/-}$ mice, with an increased frequency of occurrence in $Lpar1^{-/-}/Lpar2^{-/-}$ mice (28, 30). Another link between LPA signaling and vascular development was established from the phenotype of ATX-null mice: These mice are embryonically lethal, dying at embryonic day 9.5, with severe vascular defects in both the yolk sac and embryo (14). LPA was also found to prevent disassembly of blood vessels in cultured allantois explants, supporting a role for LPA signaling in the maintenance of existing vasculature (15). Further studies are required to characterize fully the mechanisms that mediate the effects of LPA on formation and maintenance of blood vessels.

LPA has been shown to induce a variety of responses in endothelial cells, including cell death, proliferation, migration, and vasoconstriction. In porcine cerebral microvascular and human umbilical vein endothelial cells, LPA was found to induce oncotic cell death via protein nitrosylation. This endothelial cytotoxicity was reproduced in brain explants and retinas in vivo that exhibit diminished vasculature. This was reported to be LPA_1 mediated, based on the preventive effect of a reported, very low-affinity, putative antagonist, THG1603 (120). LPA also induced an increase in hydraulic permeability in rat mesenteric venules in vivo, which is indicative of endothelial dysfunction (121). On the other hand, LPA has been shown to induce the proliferation (122) and migration (123) of endothelial cells. Notably, the latter has been linked to wound healing (see below). Similarly, LPA stimulated endothelial cell invasion in a Matrigel migration assay. This was due to an induction of matrix metalloproteinase-2, a proteolytic enzyme involved in endothelial cell migration and matrix remodeling during angiogenesis (124).

Furthermore, vasoregulatory actions of LPA in hypertension and hypotension (68, 125) have demonstrated the involvement of LPA signaling in the cardiovascular system. LPA was implicated in the pathology of posthemorrhagic vasoconstriction, because the injection of blood was found to induce the release of LPA to a concentration of 1–10 μM, and topical application of LPA was capable of inducing vasoconstriction in the cerebral circulation of piglets (125). In addition, emerging evidence has established a role of LPA signaling in pathological cardiovascular responses. LPA has been implicated in the development of atherosclerosis during early (barrier dysfunction and monocyte adhesion of the endothelium) and later phases (platelet activation and thrombosis) (126). LPA was found to accumulate in the thrombogenic lipid-rich core of atherosclerotic plaques (127, 128). This in turn activates platelets, resulting in various platelet responses such as platelet shape change and Ca^{2+} mobilization (126). Moreover, pharmacological studies identified LPA_1 and LPA_3 as primary mediators of LPA-induced platelet activation (128). However, the effect of LPA on platelets may be species-specific, because LPA was found to inhibit platelet activation in mice (129).

LPA also acts as a phenotypic modulator on VSMCs in the development of atherosclerotic lesions and in response to vascular injury by inducing the dedifferentiation of VSMCs (130). Also, LPA induces the proliferation and migration of VSMCs (131). Specifically, LPA_1 and LPA_2 were found to exhibit opposing effects on primary VSMCs derived from knockout mice (38). The migration of SMCs was increased in $Lpar1^{-/-}$ mice but attenuated in $Lpar1^{-/-}/Lpar2^{-/-}$ mice, thus identifying LPA_1 and LPA_2 as negative and positive chemotactic mediators, respectively. In a similar manner, neointimal lesions after carotid artery ligation injury were reduced in size in double-null mice, whereas lesions in $Lpar1^{-/-}$ mice were larger. However, in contrast to these in vitro findings, neither LPA_1 nor LPA_2 was required for dedifferentiation of SMCs following vascular injury in vivo or LPA exposure in vitro. These results may indicate that additional LPA receptor subtypes are required for this process.

Numerous bioactive mediators, including growth factors and cytokines, are released by activated platelets following tissue trauma. These factors initiate tissue repair processes in concert with functional changes such as proliferation, migration, and cell-matrix adhesion in endothelial cells, SMCs, and fibroblasts. LPA has recently been investigated as a mediator of these processes because it is released from activated platelets (9) and induces mitogenic and migration effects in those surrounding cell types (17, 69, 123, 132). Indeed, several lines of evidence suggest that LPA mediates wound healing: (*a*) LPA induced the closure of wounded endothelial monolayers in vitro (123), and (*b*) in vivo LPA application promoted repair processes in cutaneous wounds (133, 134) and in intestinal wounds (135). Moreover, migration of fibroblasts into the fibrin wound matrix is an essential step in the wound-healing process in injured tissues, and LPA_1 signaling regulates migration of mouse embryonic fibroblasts (136, 137). Despite abundant evidence implicating LPA signaling in the wound repair process, the specific LPA receptors that mediate these processes remain unidentified.

Immune System

Whereas studies of the roles of LPA signaling in the immune system have been overshadowed by the roles of S1P (138), LPA signaling may also act as an important regulatory factor in this system, specifically in the context of airway diseases and inflammatory response. LPA is present in human bronchoalveolar lavage fluid and increased in such inflammatory conditions as asthma and pulmonary fibrosis (137, 139). The precise mechanism and cell types that mediate LPA responses in these diseases remain to be determined, but reports have indicated that LPA signaling may have anti-inflammatory roles through modulating cytokines, lipid mediators, and transcription factors in epithelial cells (reviewed in 140).

LPA receptors are expressed in immune cells, including lymphocytes (34, 37, 141, 142) and dendritic cells (DCs) (143, 144), and in lymphoid organs such as the spleen and thymus (17, 57, 59). LPA has been shown to regulate immunological responses by modulating the activities of T cells or DCs. In T cells, LPA can stimulate or attenuate cellular activity depending on cell activation-state and predominantly expressed LPA receptors. LPA enhances chemotaxis and inhibits interleukin-2 (IL-2) production in unstimulated T cells that predominantly express LPA_2 (36, 37, 141). In activated T cells where LPA_2 is downregulated while LPA_1 is upregulated, LPA inhibits chemotaxis, activates IL-2 production and cell proliferation through LPA_1 (37), and upregulates IL-13 (142). Furthermore, LPA promotes cell survival in T cells in a process that seems to require both receptor subtypes: LPA_1 and LPA_2 (34). LPA has also been shown to affect functions of antigen-presenting DCs. Whereas LPA_{1-3} are expressed in both immature and mature DCs, LPA enhanced maturation and cytokine production in immature DCs but had no detectable effect on the activity of mature DCs (143, 144). Furthermore, LPA_3 activation induced chemotaxis of immature, but not mature, DCs (145). Thus, the effect of LPA on DCs appears to be stage-specific, although the nature of this regulation remains uncharacterized.

Recently, a study identified ATX as a modulator of lymphocyte trafficking (146). Additional studies using single or multiple LPA receptor-null mice will be useful for better understanding the unique roles for LPA signaling in the immune system.

Reproductive System

Recently, a number of studies have provided mounting evidence for the involvement of LPA signaling in such reproductive processes as spermatogenesis, male sexual function, ovarian function, fertilization, embryo spacing, implantation, decidualization, pregnancy maintenance, parturition,

and related diseases (reviewed in 21). The presence of LPA in reproductive tissues provided an early indication that LPA mediates critical functions in these systems. For example, LPA is present in the follicular fluid of healthy individuals (147), and ATX activity is enhanced in serum of normal pregnant women at the third trimester of pregnancy, which is further increased in patients at risk for preterm delivery (11, 148).

Expression of LPA receptors in the testis (**Figure 2**) (17, 21, 54) suggested a role for LPA signaling in male reproduction. Overexpression of lipid phosphate phosphatase-1, an LPA-degrading enzyme, resulted in impaired spermatogenesis (149), indicating the importance of lipid phosphates in this process, which could include LPA. Indeed, triple genetic deletion of LPA_{1-3} resulted in pronounced defects in germ cell survival and azoospermia (150). In addition, although there is evidence of LPA functioning in sperm motility (151), no defects were observed, despite loss of LPA_{1-3} (150). This suggests the involvement of other receptor subtypes such as LPA_4, LPA_5, or as yet unidentified receptors.

To date, the most significant role of LPA signaling in reproductive function involves that of LPA_3-mediated embryo implantation into the uterine wall. LPA_3-deficient female mice showed delayed implantation, embryo crowding, and reduced litter size (49). This phenotype is intrinsic to the maternal tissues, because the transfer of wild-type embryos into $Lpar3^{-/-}$ dams failed to correct the implantation defects. Interestingly, these phenotypes are similar to those reported in mice lacking cyclooxygenase-2 (152), an enzyme that produces prostaglandins. LPA_3-mediated signaling appears to be upstream of prostaglandin synthesis in this system because the delayed implantation phenotypes of $Lpar3^{-/-}$ mice can be rescued by exogenous administration of prostaglandins (49). This treatment, however, was unable to rescue the embryo-crowding phenotype, indicating that separable LPA_3-mediated processes occur during implantation (49, 153). The mechanisms underlying LPA_3-mediated spacing remain to be elucidated but may involve cytosolic phospholipase $A_{2\alpha}$ ($cPLA_{2\alpha}$) or Wnt/β-catenin signaling because mice lacking $cPLA2\alpha$ (154) or inhibition of Wnt/β-catenin signaling (155) show similar embryo-crowding phenotypes as that observed in $Lpar3^{-/-}$ mice.

Cancer

Although the clinical relevance of LPA to cancer is still under investigation, a number of in vitro and in vivo studies suggest that LPA signaling has a protumorigenic role in the progression of cancer. The first suggestion of this involvement was reported in 1964 when LPA's metabolic precursor LPC (lysolecithin) was discovered to be significantly increased in the serum of an ovarian cancer patient (156). A later clue was the identification of ATX as a motility-stimulating factor for cancer cells (12). Interestingly, at the time of its initial identification, the enzymatic function of ATX was unknown. The role of LPA in this process was not discovered until 2002, when ATX was found to have lysoPLD activity (10, 11).

LPA was specifically implicated in promoting cancer aggressiveness with the observation that it enhances the invasiveness of lung cancer cells in vitro (157). Since then a particular emphasis has been placed on the relevance of LPA signaling in ovarian and other gynecological cancers. In 1995, LPA was shown to enhance the proliferation of ovarian cancer cells (OCCs) (158) and was identified as the ovarian cancer activating factor in malignant ascites (159). Although early reports suggested that LPA concentration is elevated in the plasma and ascites of ovarian cancer patients (160), this relationship remains unclear (160a). LPA was shown to have potent protumorigenic effects on OCCs including cell survival, proliferation, increased migration and tissue invasion, activation of vascular endothelial growth factor, metalloproteinase, and urokinase-type plasminogen activator, and protection from cisplatin toxicity (161–166). These effects are mediated primarily

by the activation of LPA_2, which is known to promote proliferation, migration, and invasion of gynecological cancer cells in vitro and in vivo (40, 167). LPA_2 is upregulated in OCCs (168) and can be activated by low nanomolar concentrations of LPA, well below the basal serum concentration. Therefore, the tumor-promoting effects of LPA appear to be regulated at the level of receptor expression rather than ligand concentration.

In addition to the involvement of LPA_2, there is evidence for contributions of LPA_1 and LPA_3 to the tumorigenic activity of LPA. For example, genetic and pharmacological inhibition of LPA_1 has been shown to reduce the proliferation and metastasis of OCCs and breast cancer cells in vitro and in vivo (169), and LPA_3, in addition to LPA_2, was associated with increased OCC aggressiveness in vivo (40). In addition to the proliferative effector pathways depicted in **Figure 3** (mitogen-activated protein kinase and Akt), the carcinogenic effects of LPA have been associated with activation of cyclooxygenase-2 (170) and p120-catenin (171). Furthermore, LPA signaling appears to mediate the tumorigenic processes that are stimulated by hypoxia (172).

A significant body of work has also implicated LPA in the progression of gastrointestinal cancers. As in ovarian cancer, LPA stimulates proliferation, migration, and invasion primarily through the activation of LPA_1 and LPA_2 (39, 173, 174). Genetic deletion of LPA_2 results in the attenuation of tumor formation in vivo (175). LPA signaling in gastrointestinal cancer cells is associated with activation of Her2, EGFR, beta-catenin, and sphingosine kinase, in addition to other known gene products and signals (176–178). Other malignancies with known or suspected involvement of LPA signaling include breast cancer, lung cancer, prostate cancer, mesothelioma, and glioma (179–183). Whereas blood serum contains a large signaling pool of LPA, pathological substrate concentrations likely include autocrine and paracrine sources (183, 184).

LPA is also likely to contribute to the development of cancer through its positive effect on angiogenesis because neovascularization is essential for the development of solid tumors. In addition to the known involvement of LPA in blood vessel formation during development (see above), a number of studies implicate LPA signaling in pathological angiogenesis during tumor formation. For example, it has been demonstrated in a number of cancer cell types that LPA stimulation causes the production and secretion of vascular endothelial growth factor (165). This may act either synergistically or downstream of hypoxia to activate HIF1α (185), but a recent report suggests that there are also HIF1α-independent pathways that promote angiogenesis (186). In addition, FTY720, which has been shown to reduce tumor angiogenesis in an orthotopic tumor model (187), may act in part by reducing LPA concentration through the inhibition of ATX (188).

Fibrosis

Fibrosis, the formation of excess fibrous connective tissues, is associated with a number of pathological conditions. Recently, a new aspect of LPA_1 signaling has been uncovered in pulmonary (137) and tubulointerstitial fibrosis (TIF) (189), suggesting LPA_1 signaling as a new therapeutic target in this disease. LPA levels were remarkably increased in bronchoalveolar lavage fluid after bleomycin-induced lung injury and resulted in pulmonary fibrosis, vascular leakage, and mortality. These pathologies were markedly reduced in $Lpar1^{-/-}$ mice (137). Likewise, in a unilateral ureteral obstruction model for TIF, the resulting kidney fibrosis was accompanied by an increase in LPA accumulation and LPA_1 expression (189). Fibrosis was markedly reduced in $Lpar1^{-/-}$ mice or following treatment with Ki16425, an LPA_1/LPA_3 antagonist (189). As a possible mechanism, LPA was reported to induce upregulation of connective tissue growth factor (190), a process that has been regarded to link directly to fibroproliferative disorders. LPA signaling may also play a role in liver fibrosis via as yet unidentified receptor signaling. Plasma levels of LPA and ATX are increased in rodent models (191), as well as in human patients (192) with hepatitis C–induced liver

fibrosis. Furthermore, LPA induced proliferation of stellate cells and hepatocytes, which are the main contributors to extracellular matrix accumulation in liver (193).

Obesity

Excessive adipose tissue accumulation is a key factor leading to type II diabetes. The ratio of adipocyte precursor cells to differentiated adipocytes is tightly controlled in individuals of normal weight, and the proliferation and differentiation of preadipocytes are modulated by numerous factors. In this regard, several lines of evidence suggest a relationship between LPA signaling and obesity, including roles for LPA metabolism and LPA signaling.

The first indications that LPA is involved in adipogenesis were based on the observations that (*a*) LPA is released by adipocytes, but not by preadipocytes, in vivo and in vitro, and (*b*) LPA stimulates motility and proliferation of preadipocytes through LPA$_1$ (194, 195). The release of LPA has since been linked to the secretion of ATX as an ectoenzyme during adipocyte differentiation, and this has been shown to result directly in the proliferation of preadipocytes (196). This process is also associated with obese adipocytes from genetic obese-diabetic *db/db* mice (type II diabetes) (196) and in adipose tissue from glucose-intolerant obese human subjects (197). However, LPA$_1$ signaling appears to be antiadipogenic because stimulation of LPA$_1$ signaling inhibits the differentiation of preadipocytes (198). This inhibitory effect is the result of the downregulation of PPARγ2 (198). Furthermore, despite a lower body weight, *Lpar1*$^{-/-}$ mice had a higher adiposity

Table 3   LPA agonists and antagonists and their effective concentrations[a,b]

	Compound	LPA$_1$	LPA$_2$	LPA$_3$	LPA$_4$	LPA$_5$
Agonist	LPA (18:1)	++++	+++	+++	+++	+++
	NAEPA, NAEPA-derivatives					
	NAEPA	++	+++	+/−	NA	NA
	NAEPA-11	++	+	+/−	NA	NA
	NAEPA-17	+++	++	+/−	NA	NA
	NAEPA-19	++	+/−	+/−	NA	NA
	OMPTs					
	Racemic OMPT	−	+/−	+++	NA	NA
	(2S)-OMPT	NA	NA	+++++	NA	NA
	Carbohydrate scaffolds					
	Isomer 2	+/−	+/−	++++	NA	NA
	Isomer 13	+	−	+++++	NA	NA
	Isomer 15	++	−	−		
	sn-2-aminooxy analog, 12b	+/−	++	+++ (Antagonist)	+	NA
Antagonist	DGPP 8:0	+/−	−	++	NA	NA
	NAEPA-derivatives					
	VPC12249	++	NA	++	NA	NA
	Compound 10t	+++	+/−	++	NA	NA
	Compound 13d	+/−	+/−	++	NA	NA
	Ki16425	++	+/−	++	NA	−
	Compound 35	+/−	+++	+/−	NA	NA
	α-bromomethylene phosphonate analog, 19b	+	+	+	++	NA
	NSC161613	NA	NA	+++	NA	NA

[a]Compounds reported by multiple independent laboratories.
[b]EC$_{50}$, IC$_{50}$ and/or Ki values are represented by +++++, < 1 nM; ++++, 1∼10 nM; +++, 10∼100 nM; ++, 100∼1000 nM; +, 1000∼5000 nM; +/−, >5000 nM; −, no activity; NA, not applicable.

than wild-type littermates, and their adipose tissue contained more preadipocytes that could be differentiated in culture, consistent with an antiadipogenic role for LPA_1 (198).

Another recent report indicates that LPA signaling, possibly through LPA_1, regulates blood glucose levels by enhancing glucose uptake by adipocytes (199). An LPA-induced glucose-lowering effect was observed in normal mice as well as streptozotocin-induced type I diabetic mice, but in the diabetic mouse, LPA production was not altered (199), unlike the type II diabetic mouse (196). Overall, these observations indicate that LPA signaling and ATX activity function in adipose tissue development and glucose uptake, thus presenting potential drug targets for such pathologies as obesity and diabetes.

LPA RECEPTOR AGONISTS AND ANTAGONISTS

Several reported LPA receptor agonists and antagonists vary in selectivity and potency (**Table 3**). Whereas most compounds are directed against LPA_{1-3}, a few recent studies have focused on LPA_4, although the resulting compounds have limited selectivity (200, 201).

The vast majority of these studies relied heavily on in vitro assays for validation, but a few compounds reportedly have proven efficacious in vivo. For example, in vivo administration of an LPA_3-selective agonist, OMPT, enhanced murine renal ischemia-reperfusion injury, whereas the $LPA_{1/3}$ dual antagonist VPC12249 reduced the injury by LPA_3 inhibition (202). In addition, administration of $LPA_{1/3}$-selective antagonist Ki16425 reduced the metastatic potential of breast cancer in a xenograft tumor model (169). All compounds require further validation within specific assays, especially if they involve delivery in vivo, where pharmacodynamic and pharmacokinetic issues are critical.

SUMMARY POINTS

1. To date, five bona fide LPA receptors, named LPA_{1-5}, have been identified (**Figure 1**). These receptors have apparent K_d or EC_{50}s that range from single- to double-digit nanomolar concentrations. They have broad and overlapping gene expression patterns (**Figure 2**). Additional LPA receptors, particularly $P2Y5/LPA_6$, have been proposed and await validation.

2. LPA receptors interact with multiple G proteins that can activate a diverse range of downstream signaling pathways, adding to the heterogeneity of cellular responses to LPA (**Figure 3**).

3. Gain- and/or loss-of-function studies on the roles of LPA signaling have produced an expanding range of biological functions. These functions include developmental and pathological processes of the nervous, vascular, immune, and reproductive systems and diseases such as cancer, fibrosis, and obesity (**Tables 1** and **2**).

4. Studies using mice deficient for a single LPA receptor subtype (LPA_1, LPA_2, LPA_3, or LPA_4) as well as multiple subtypes have been developed and used to clarify the specific functions of each receptor, and multiple receptor-null mice have revealed additional phenotypes in some systems.

5. In addition to the use of genetically null mice, LPA receptor subtype–selective agonists and antagonists are being developed toward producing useful biological tools for understanding functional roles for each receptor.

6. The rich biological and pathophysiological roles for receptor-mediated LPA signaling raise the possibility of pharmaceutical targeting of related pathways toward the generation of new medicines.

FUTURE ISSUES

1. In view of the complex expression patterns of LPA receptors and LPA metabolizing enzymes, many more physiological and pathophysiological functions of LPA signaling remain to be uncovered and characterized.

2. The relationship between signaling and structural pools of LPA, including the possible existence of local gradients, remains to be explored.

3. Considering the structural similarities among lysophospholipid species and their receptors, it is likely that interactions exist between distinct lysophospholipid pathways. Further study is required to characterize this relationship.

4. It would be of further interest to identify interactions between receptor-mediated LPA signaling and other receptor-mediated pathways that include other GPCRs, receptor tyrosine kinases, and nuclear receptors.

5. Further characterization of the enzymes involved in LPA metabolism is needed. Similarly, the biological roles for numerous LPA isoforms and their relationship to identified receptor subtypes remain to be determined.

6. Understanding the biochemistry of receptor-mediated LPA signaling at the level of single cells remains to be determined.

7. Additional LPA receptors have recently been proposed. Future and ongoing studies to validate proposed receptors and identify new candidates may add new members to the five proven LPA receptors.

8. Human validation of proposed disease modification through receptor-mediated LPA signaling is required. This will necessitate the generation of safe, pharmacokinetically and pharmacodynamically useful compounds.

DISCLOSURE STATEMENT

Jerold Chun is a SAB Member for Amira Pharmaceuticals.

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Errata

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