Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Pharmacology

Lysophosphatidic acid (LPA) and its receptors

Kyoko Noguchi, Deron Herr, Tetsuji Mutoh and Jerold Chun

Lysophosphatidic acid (LPA), a bioactive phospholipid, and its family of cognate G protein-coupled receptors have demonstrated roles in many biological functions in the nervous system. To date, five LPA receptors have been identified, and additional receptors may exist. Most of these receptors have been genetically deleted in mice toward identifying biological and medically relevant roles. In addition, small molecule agonists and antagonists have been reported. Here we review recent data on the nervous system functions of LPA signaling, and summarize data on reported agonists and antagonists of LPA receptors.

Address
The Department of Molecular Biology, Helen L. Dorris Institute for Neurological and Psychiatric Disorders, The Scripps Research Institute, La Jolla, CA 92037, United States

Corresponding author: Chun, Jerold (jchun@scripps.edu)

Current Opinion in Pharmacology 2009, **9**:15–23

This review comes from a themed issue on
Neurosciences
Edited by Daniele Piomelli

Available online 30th December 2008

1471-4892/$ – see front matter
Published by Elsevier Ltd.

DOI 10.1016/j.coph.2008.11.010

Introduction

Lysophosphatidic acid (LPA; 1- or 2-acyl-*sn*-glycerol-3-phosphate) is a bioactive phospholipid with diverse biological functions on many cell types. LPA is detected in serum, plasma, other biological fluids, and tissues including brain [1].

LPA is generated by the action of a number of different enzymes including phospholipase A_1 or A_2, monoacylglycerol kinase, glycerol-3-phosphate acyltransferase, and autotaxin (ATX), a lysophospholipase D (lysoPLD) [2•]. LPA is catabolized by a number of different pathways that include the actions of lipid phosphate phosphatases or LPA acyltransferase, thus terminating its signaling actions [2•].

LPA elicits its functions through receptors on plasma membranes. So far, there are five G protein-coupled receptors (GPCRs) identified as specific receptors for LPA that are referred to as LPA_1, LPA_2, LPA_3, LPA_4, and LPA_5 [3–8]. In addition, recent reports have suggested that three additional GPCRs, GPR87, P2Y5, and P2Y10, may be responsive to LPA [9•,10•,11•], although further study is required to validate these observations. Analyses of gene knockout mice for most of the five *bona fide* receptors have revealed physiological and pathological roles of LPA signaling including brain development [12–15], neuropathic pain [16], and female and male reproduction [17,18], to name a few (see below).

This review focuses on the functions of LPA signaling in the nervous system and briefly introduces LPA agonists/antagonists (Figure 2 and Table 2). Because of space limitations, additional characteristics of known LPA receptors are merely summarized in Table 1.

LPA signaling in the nervous system

Neural progenitor cells (NPCs)

The processes that mediate central nervous system (CNS) development include proliferation, differentiation, migration, and apoptosis. NPCs proliferate in the ventricular zone (VZ) to expand progenitor pools, and sequentially exit the cell cycle to differentiate into multiple cell types including neurons, astrocytes, and oligodendrocytes (Figure 1). During these processes, the cells change their morphology drastically and migrate out from the VZ toward their final destinations. The restricted expression of LPA_1 in the VZ of the developing cerebral cortex [3] and the presence of ATX in the embryonic brain [19•] suggested a role for LPA signaling in cortical development.

In vitro primary culture of mouse cortical NPCs and heterologous expression of LPA_1 in B103 rat neuroblastoma cells revealed the proliferative role of this receptor subtype [12,20]. However, a study using immortalized hippocampal progenitor cells, which express LPA_1 and LPA_4, suggests the effects of LPA signaling on neuronal differentiation. This may occur through LPA_4–G_s pathways: LPA stimulates cyclic AMP response element-binding protein (CREB) phosphorylation, which promotes neuronal differentiation [21]. In neurospheres consisting of NPCs, the effects of LPA signaling on both proliferation and differentiation have been reported; generation and growth via LPA_1 and/or LPA_3 [22], and neuronal differentiation via LPA_1 [23•]. Interestingly, these responses are inhibited by a pathological concentration (10 μM) of LPA [24]. *Ex vivo* culture of embryonic brain reveals that LPA promotes survival and differentiation of NPCs rather than proliferation through LPA_1 and/or LPA_2 [25]. Thus, the specific role of LPA signaling on proliferation or neuronal differentiation is highly complex and appears to depend on the stage of cortical

Table 1

Characteristics of LPA receptors.

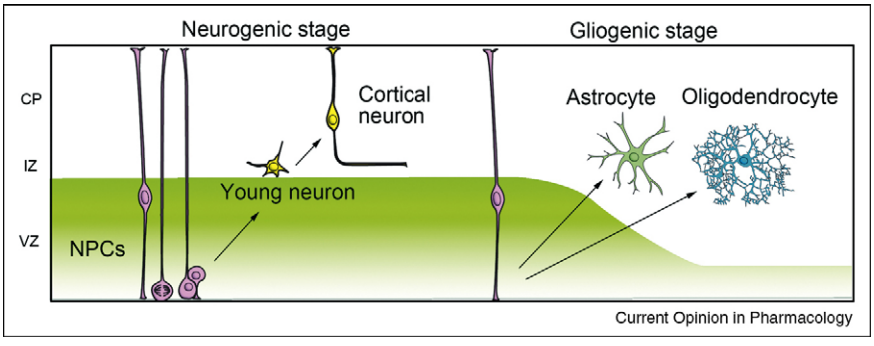
Receptor	Synonyms	Gene[a]/location	G-protein coupling	Cellular responses	Physiological/pathological functions
LPA_1	VZG-1 EDG2 Rec1.3 GPR26 GPCR26	*LPAR1*/chr9 (human) *Lpar1*/chr4 (mouse)	$G_{i/o}$, $G_{q/11}$, $G_{12/13}$	Proliferation [20] Survival [70] Stress fiber formation [20] Neurite retraction, cell rounding [3,20,26]	Brain development [14,15] Neuropathic pain [16] Pulmonary fibrosis [90] Renal fibrosis [91]
LPA_2	EDG4	*LPAR2*/chr19 (human) *Lpar2*/chr8 (mouse)	$G_{i/o}$, $G_{q/11}$, $G_{12/13}$	Cell rounding [26]	Vascular injury ($LPA_{1/2}$) [92]
LPA_3	EDG7	*LPAR3*/chr1 (human) *Lpar3*/chr3 (mouse)	$G_{i/o}$, $G_{q/11}$	Neurite elongation [26]	Embryo implantation and spacing [17] Spermatogenesis, male mating activity ($LPA_{1/2/3}$) [18]
LPA_4	GPR23 P2Y9 P2Y5-like	*LPAR4*/chrX (human) *Lpar4*/chrX (mouse)	$G_{i/o}$, $G_{q/11}$, $G_{12/13}$, G_s	Neurite retraction, cell rounding, cell aggregation [28,29]	N/D
LPA_5	GPR92 GPR93	*LPAR5*/chr12 (human) *Lpar5*/chr6 (mouse)	$G_{q/11}$, $G_{12/13}$	Stress fiber formation, neurite retraction, cell rounding [7]	N/D
GPR87[b]	GPR95	*GPR87*/chr3 (human) *Gpr87*/chr3 (mouse)	N/D	Ca^{2+} mobilization [9•]	N/D
P2Y5[b]		*P2YR5*/chr13 (human) *P2yr5*/chr14 (mouse)	N/D	CRE activation [10•]	Hair growth [10•,93]
P2Y10[b]		*P2YR10*/chrX (human) *P2yr10*/chrX (mouse)	N/D	Ca^{2+} mobilization [11•]	N/D

CRE, cyclic AMP response element and N/D, not determined.
[a] Gene names are referred to Human Genome Nomenclature Committee (http://www.genenames.org/) and Mouse Genome Informatics (http://www.informatics.jax.org/).
[b] Preliminary identification as LPA receptors, requiring further confirmation.

development, surrounding conditions, and ligand concentration.

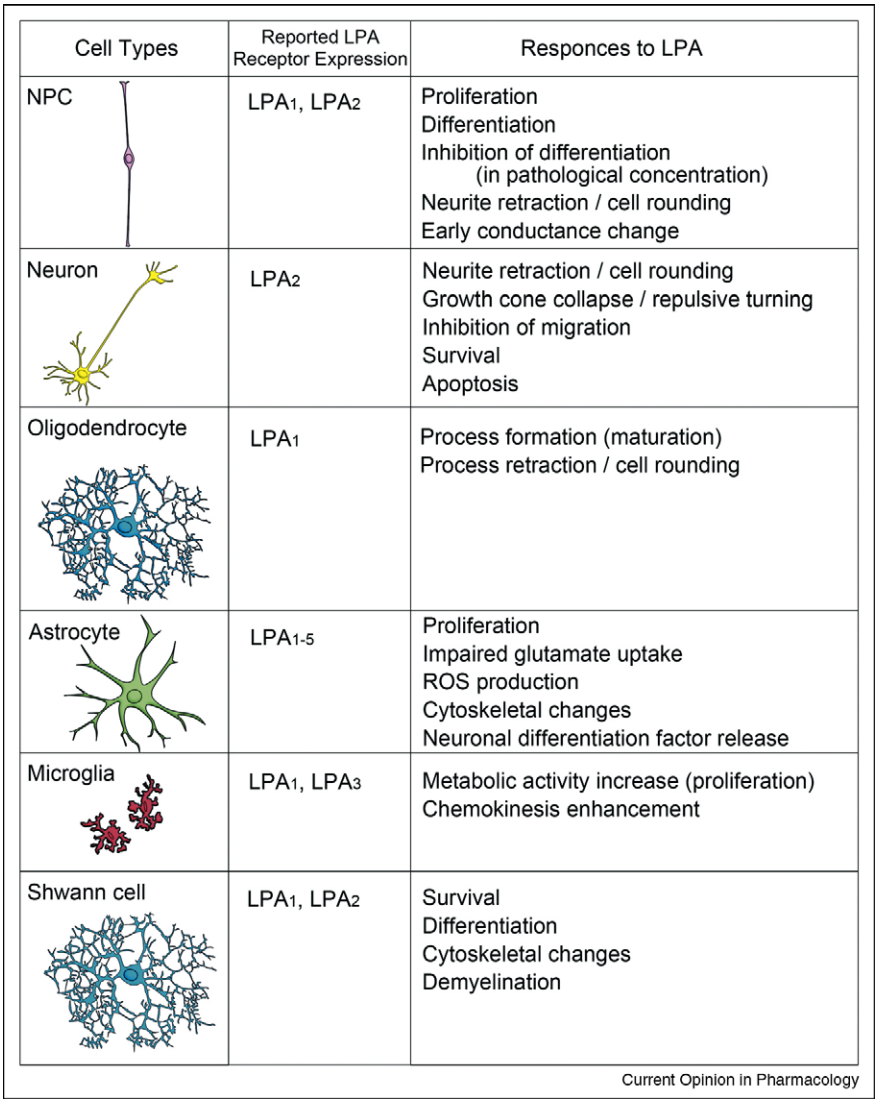
LPA signaling induces morphological changes of NPCs in cell lines, primary culture, and whole brain culture. Heterologous expression of $LPA_{1–5}$ in NPC cell lines such as TSM mouse immortalized NPCs and B103 cells revealed the ability of individual LPA receptors to mediate different morphological changes. Neurite retraction and cell rounding are induced by LPA in cells expressing LPA_1, LPA_2, LPA_4, or LPA_5 through Rho-mediated pathways [3,7,20,26–29]. Additionally, cell aggregation and cadherin-dependent cell adhesion are observed in LPA_4-expressing cells following LPA-treatment [28].

Figure 1



General scheme of neural cell production during CNS development. In the early stage of CNS development, NPCs proliferate in the VZ to expand progenitor pools. As development proceeds, NPCs sequentially differentiate into neurons, astrocytes, and oligodendrocytes. Microglia are derived from peripheral mesodermal tissue [89] and not shown here. CP, cortical plate; IZ, intermediate zone.

Figure 2



LPA receptor expression and responses to LPA in each neural cell type. Each neural cell type has a different LPA receptor expression pattern and exhibits distinct responses to LPA.

Interestingly, LPA_3 expression results in neurite elongation and inhibition of LPA-induced cell rounding in B103 cells and TR cells (a mouse NPC line) respectively [26]. In NPC cluster culture, LPA induces neurite retraction and cluster compaction which reflects both cell migration, and cell rounding within clusters, accompanied by nuclear movement toward the center of clusters [30], and the compaction by LPA is severely attenuated in LPA_1-null clusters [12]. Cortical explant studies show rounded morphologies of NPCs and accumulation of NPC nuclei at the VZ surface produced by LPA-treatment [30]. These *in vitro* observations resemble morphological changes and nuclear/cellular migration of NPCs in the VZ during cortical development (Figure 1). In addition, LPA stimulates conductance changes in early cortical NPCs preceding that of the neurotransmitters GABA and L-glutamate, and is considered as one of the earliest extracellular stimuli of ionic conductance changes for cortical NPCs [31].

Neurons

Early studies showed that LPA signaling induces neurite retraction and growth cone collapse in neuronal cell lines such as N1E-115, NG108-15, and differentiated PC12 cells, and in primary cultured chick neurons [32–34]. In mouse young postmitotic neurons, LPA induces rapid neurite retraction and cell rounding [35]. As neurons mature, these responses decrease, and instead, Rho-independent growth cone collapse appears [27]. In contrast, Rho-mediated growth cone collapse and repulsive turning by

LPA have been reported in chick dorsal root ganglion (DRG) neurons and in *Xenopus* spinal neurons, respectively [36,37]. Another LPA-induced collapse mechanism is rapid protein degradation in the growth cone of *Xenopus* retinal neurons, which involves activation of proteasome, p38 MAPK, and caspase-3 [38,39]. In addition, inhibitory effects of LPA on the migration of young postmitotic neurons are observed in mouse cortical and whole brain explant cultures [35]. Because mouse cortical plate neurons and primary cultures of mouse young postmitotic neurons mainly express LPA_2 [35,40], and some of these responses are still observed in LPA_1-null neurons [35], these suggest that LPA_2 and/or other as-yet unidentified LPA receptors may function in the developing brain.

Both apoptotic and survival effects of LPA signaling on neuronal cells have been reported [41–45]. In LPA_1-null mice, cortical apoptosis is increased in both the embryonic and postnatal brain (see below) [14]. Opposing effects of LPA signaling may result from concentration differences as well as differential expression of varied LPA receptor subtypes.

Oligodendrocytes

Oligodendrocytes, the myelin-forming glial cells in the CNS, express LPA_1 in a pattern that correlates temporally and spatially with maturation and myelination [46,47]. *In vitro* studies show cellular responsiveness to LPA including Ca^{2+} mobilization, ERK1/2 phosphorylation, process retraction, and cell rounding, depending on the maturity of oligodendrocytes [48–50]. However, some discrepancies remain with respect to the observed signaling pathways that are activated during oligodendrocyte development. LPA stimulates process formation, and increases the number of differentiating, but not mature, oligodendrocytes [51•].

Astrocytes

Cultured astrocytes express all five LPA receptors [52•], while the basal *in vivo* expression levels of these receptors appear to be below standard detection limits for at least LPA_1 [46,47,53]. Further examination of other receptors under basal conditions and *in situ* are needed, as are expression levels under non-basal conditions.

LPA induces proliferative effects on cultured astrocytes including intracellular Ca^{2+} mobilization, production of reactive oxygen species (ROS), and DNA synthesis [54–57], although some studies show no proliferative effect [58–61]. LPA also induces inhibition of glutamate uptake in cultured astrocytes [54]. Notably, the proliferative effect is abolished, but glutamate uptake inhibition is still observed in LPA_1-null astrocytes [52•]. Further, LPA induces Rho-mediated cytoskeletal changes such as rapid reversal of stellate morphology that are induced by cyclic AMP elevation or serum removal [62,63]. LPA also induces the stabilization of stress fibers, and stimulates actomyosin contraction [64]. *In vivo* LPA injection into the adult mouse striatum induces astrogliosis that occurs following brain injury and stroke [57]. Several observations also support roles for LPA signaling in neurodegeneration. These include upregulation of ATX in reactive astrocytes adjacent to injury lesion sites [19•], and proliferation, ROS production, and impaired glutamate uptake documented *in vitro*. Taken together, LPA signaling may have roles in exacerbating brain injury.

Recently, indirect effects of LPA signaling on neuronal differentiation were reported [65•]. LPA-primed astrocytes enhanced neuronal differentiation. This effect was dependent on LPA_1 and/or LPA_2 expression on astrocytes, but not NPCs. Experiments using conditioned medium from LPA-primed astrocytes demonstrated that a soluble factor is released from astrocytes to mediate these effects, although the identities of putative factors remain undetermined.

Microglia

Microglia prepared from rat and mouse predominantly express LPA_1 and/or LPA_3 [66,67] and respond to LPA to produce intracellular Ca^{2+} mobilization, increased metabolic activity (proliferation), enhanced chemokinesis, membrane ruffling, and brain-derived neurotrophic factor expression [66,68,69]. However, LPA receptor expression profiles and cellular responses vary with microglial maturation as well as species sources (e.g. rat versus mouse), which require further study.

Schwann cells (SCs)

SCs express LPA_1 and LPA_2 [47,70,71]. In cultured neonatal SCs, LPA promotes LPA_1-dependent survival and morphological changes, and LPA_2-dependent differentiation. LPA rescues SCs from apoptosis [70,72], and LPA_1-null SCs display increased apoptosis [12]. LPA induces actin cytoskeleton-based morphological changes, focal adhesion assembly, and *N*-cadherin-mediated cell–cell contacts, and these responses are diminished in LPA_1-null SCs [71]. LPA increases myelin P_0 protein expression in SCs; a response that is decreased by siRNA against LPA_2 [72]. In adult SCs isolated from axotomized sciatic nerve, LPA_1 and LPA_2 expression are upregulated coincident with postaxotomy SC proliferation, suggesting that LPA signaling promotes SC mitogenesis in regenerating peripheral nerves [71,73]. Moreover, LPA induces demyelination of SCs in *ex vivo* culture of the dorsal root (DR) and in mice that have received an intrathecal LPA injection (see below) [16,74].

Knockout mice

LPA_1-null mice have approximately 50% neonatal lethality, and exhibit craniofacial dysmorphism (shorter snouts and more widely spread eyes) and reduced body mass in survivors [12]. These mice are also characterized by the defects in normal suckling behavior, presumably

because of a lack of olfactant detection and/or processing, which accounts for increased neonatal death and decreased postnatal growth. However, no obvious abnormalities in olfactory/vomeronasal epithelia, olfactory bulb, or cortex are observed, except for occasional, slightly smaller cortical width and reduced wall thickness of brains/olfactory bulbs. A small fraction of embryonic and neonatal LPA_1-null mice have frontal cranial hemorrhage. An LPA_1-null substrain that arose spontaneously during colony expansion of the original line [12], called Malaga LPA_1 variant, exhibits more severe phenotypes [14]. The mutant mice exhibit smaller brains with reduced VZ and smaller cortices. Moreover, they show defects in hippocampal neurogenesis, which is stimulated by environmental enrichment and voluntary physical activity [15]. Independently generated LPA_1-null mice display deficits in prepulse inhibition, widespread changes in neurotransmitter 5-HT levels and turnover, and a brain region-specific alteration in amino acid levels, which resemble defects found in psychiatric diseases [75].

LPA_2-null mice display no obvious phenotypic abnormalities [13]. LPA_1/LPA_2-double-null mice display no additional phenotypes to LPA_1-null mice, except for an increased incidence of perinatal frontal hematoma [13]. Further analyses are needed to determine more subtle phenotypic differences.

LPA_3-null females have a significantly reduced litter size that is due to delayed implantation, altered embryo spacing, and prolonged pregnancy [17], whereas LPA_1/LPA_2/LPA_3-triple-null male mice show a testosterone-independent reduction of mating activity and spermatogenesis [18]. No phenotypes related to LPA_3 loss in the nervous system have been reported to date.

ATX-null embryos die around E9.5–E10.5 with severe vascular defects in the yolk sac and embryo [76•,77•]. ATX-null embryos at E8.5–E9.5 show various defects including allantois malformation, growth retardation, neural tube malformation, incomplete turning, reduced number of somites, and asymmetric headfolds [76•,77•]. Allantois culture system shows that LPA and ATX are not angiogenic but stabilize preformed vessels by preventing endothelia disassembly [77•]. Since these phenotypes are much more severe than those observed in $LPA_{1–3}$ single-null or multiple-null mice, and stabilization of preformed vessels by LPA or ATX is not blocked by LPA_1/LPA_3-specific antagonist Ki16425 [77•], it is strongly suggested that other LPA receptors such as LPA_4 and LPA_5 or unidentified LPA receptors are involved in vascular stabilization. In contrast, ATX heterozygous mice appear healthy but show half-normal ATX activity and plasma LPA levels [76•,77•], indicating that ATX is the major LPA-producing enzyme *in vivo*.

LPA signaling in pain

Intraplantar injection of LPA into the mouse hind limb induces peripheral nociception, which is markedly reduced by PTX-pretreatment or substance P receptor antagonist-pretreatment, and partially blocked by LPA_1 antisense oligodeoxynucleotide administration [78,79]. Taken together with a finding that LPA_1 mRNA is detected in DRG [79], it appears that LPA induces peripheral nociception through LPA_1 and $G_{i/o}$ by releasing substance P from nociceptor endings.

Intrathecal injection of LPA into mice induces neuropathic pain and demyelination of the DR similar to those observed after nerve injury. Strikingly, however, LPA_1-null mice are refractory to nerve injury-induced neuropathic pain [16]. Further studies demonstrate that the conversion of LPC to LPA via the action of ATX may be an essential component of this process *in vivo* [80,81]. *Ex vivo* culture of the DR reveals a direct effect of LPA on demyelination in SCs that may underlie this process [74]. A recent study suggests that LPA_3 is potentially involved in mechanical, cold, and inflammatory pain, but not neuropathic pain [82].

LPA receptor agonists/antagonists

In recent years, several groups have reported the generation of agonist and antagonist compounds for LPA receptors that vary in specificities and apparent affinities (Table 2). Several have been reportedly used as study compounds in a number of *in vitro* applications. Notably, Ki16425 is commercially available and acts as

Table 2

Reported LPA receptor compounds.

Compound	Activity	Characteristics
Ki16425	LPA_1/LPA_3 antagonist	Isolated from a compound library, chemically dissimilar to LPA
VPC32183	LPA_1/LPA_3 antagonist	LPA analog
VPC12249	LPA_1/LPA_3 antagonist	LPA analog
Diacylglycerol pyrophosphate	LPA_1/LPA_3 antagonist	Naturally occurring lipid
OMPT	LPA_3 agonist	Thiophosphate derivative of LPA
T13	LPA_3 agonist	LPA analog with carbohydrate scaffold
Cyclic carba analogs	Compounds vary in specificity and efficacy	Analogs of a naturally occurring cyclic derivative of LPA
Phosphonate compounds	Compounds vary in specificity and efficacy	Metabolically stabilized LPA analogs

an LPA_1/LPA_3-specific antagonist [83]. It has been used in cell culture experiments to inhibit such LPA-mediated processes as Ca^{2+} mobilization, migration, and neurite retraction in a number of different cell types and tissue explants. This compound has recently been licensed by Debiopharm Group (Switzerland) under the name ''Debio 0719'' and is in preclinical development as an antitumor drug.

In addition, an extensive series of LPA analogs has produced a number of interesting study compounds. VPC12249 has been used *in vitro* and *in vivo* as a low affinity antagonist that is somewhat selective for LPA_1 and LPA_3 [84]. Modification of this lead compound has improved the specificity and affinity for $LPA_{1/3}$ and provides another useful, commercially available compound, VPC32183 [84]. A different approach provides a number of LPA analogs with carbohydrate scaffolds [85]. One interesting compound, T13, demonstrates LPA_3-specific *agonism* and has been used in explant cultures to confirm the involvement of this receptor in uterine contraction [86•]. Another LPA analog, 1-oleoyl-2-*O*-methyl-rac-glycerophosphothionate (OMPT), has also shown selective *agonism* for LPA_3. OMPT is notable in that it has been used *in vivo* to investigate the involvement of LPA_3 in renal ischemia–reperfusion injury [87]. Other compounds based on phosphonates or cyclic-phosphatidic acid have been reported [88].

The encouraging development of chemical tools for interrogating receptor-mediated LPA signaling will provide additional mechanistic approaches to understanding roles for LPA signaling in the nervous system. Caution must be used when interpreting data generated through the use of partially validated compounds, particularly for *in vivo* studies where pharmacokinetic and pharmacodynamic variables are often not known or ignored. These *in vivo* variables include compound half-life, receptor occupancy, brain penetration, and off-target activities, all of which should be considered.

Conclusions

LPA signaling is remarkably complex and heterogeneous and has been shown to influence all neural cell types. The developmental, physiological, and pathological significance of these responses *in vivo* is only beginning to be appreciated, due largely to the studies that have recently been performed on LPA receptor knockout mice. These studies have revealed that LPA influences such processes as the development of the CNS, the function of neurons and glia, and the onset of neuropathic pain. Continued study on existing and new LPA receptor-null mutants combined with appropriate pharmacological approaches will further elucidate mechanisms and therapeutic strategies that may lead to new medicines based on receptor-mediated LPA signaling.

Acknowledgements

We thank Danielle Letourneau for critical reading of the manuscript. This work was supported by the National Institute of Mental Health (grant no. MH051699 (JC)), the National Institute of Neurological Disorders and Stroke (grant no. NS048478 (JC)), and the National Institute of Child Health and Human Development (grant no. HD050685 (JC)).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest

1. Tokumura A: **Metabolic pathways and physiological and pathological significances of lysolipid phosphate mediators**. *J Cell Biochem* 2004, **92**:869-881.

2. • Pebay A, Bonder CS, Pitson SM: **Stem cell regulation by lysophospholipids**. *Prostaglandins Other Lipid Mediat* 2007, **84**:83-97.
This review provides LPA's effect on stem cells and progenitors in neural and other lineages.

3. Hecht JH, Weiner JA, Post SR, Chun J: **Ventricular zone gene-1 (vzg-1) encodes a lysophosphatidic acid receptor expressed in neurogenic regions of the developing cerebral cortex**. *J Cell Biol* 1996, **135**:1071-1083.

4. An S, Bleu T, Hallmark OG, Goetzl EJ: **Characterization of a novel subtype of human G protein-coupled receptor for lysophosphatidic acid**. *J Biol Chem* 1998, **273**:7906-7910.

5. Bandoh K, Aoki J, Hosono H, Kobayashi S, Kobayashi T, Murakami-Murofushi K, Tsujimoto M, Arai H, Inoue K: **Molecular cloning and characterization of a novel human G-protein-coupled receptor, EDG7, for lysophosphatidic acid**. *J Biol Chem* 1999, **274**:27776-27785.

6. Noguchi K, Ishii S, Shimizu T: **Identification of p2y9/GPR23 as a novel G protein-coupled receptor for lysophosphatidic acid, structurally distant from the Edg family**. *J Biol Chem* 2003, **278**:25600-25606.

7. Lee CW, Rivera R, Gardell S, Dubin AE, Chun J: **GPR92 as a new G(12/13)- and G(q)-coupled lysophosphatidic acid receptor that increases cAMP, LPA5**. *J Biol Chem* 2006, **281**:23589-23597.

8. Kotarsky K, Boketoft A, Bristulf J, Nilsson NE, Norberg A, Hansson S, Owman C, Sillard R, Leeb-Lundberg LM, Olde B: **Lysophosphatidic acid binds to and activates GPR92, a G protein-coupled receptor highly expressed in gastrointestinal lymphocytes**. *J Pharmacol Exp Ther* 2006, **318**:619-628.

9. • Tabata K, Baba K, Shiraishi A, Ito M, Fujita N: **The orphan GPCR GPR87 was deorphanized and shown to be a lysophosphatidic acid receptor**. *Biochem Biophys Res Commun* 2007, **363**:861-866.
This study used receptor–$G_{16\alpha}$ fusion protein to detect responsiveness to LPA. Further study is required to validate this receptor.

10. • Pasternack SM, von Kugelgen I, Aboud KA, Lee YA, Ruschendorf F, Voss K, Hillmer AM, Molderings GJ, Franz T, Ramirez A *et al.*: **G protein-coupled receptor P2Y5 and its ligand LPA are involved in maintenance of human hair growth**. *Nat Genet* 2008, **40**:329-334.
A GPCR linked to hair growth showing some LPA responsivity. Approximately 10–100-fold higher concentrations of LPA are needed to activate P2Y5 compared to LPA_{1-5} activation. Further study is required to validate this receptor.

11. • Murakami M, Shiraishi A, Tabata K, Fujita N: **Identification of the orphan GPCR, P2Y(10) receptor as the sphingosine-1-phosphate and lysophosphatidic acid receptor**. *Biochem Biophys Res Commun* 2008, **371**:707-712.
This study used receptor–$G_{16\alpha}$ fusion protein to detect responsiveness to LPA. Further study is required to validate this receptor.

12. Contos JJ, Fukushima N, Weiner JA, Kaushal D, Chun J: **Requirement for the lpA1 lysophosphatidic acid receptor gene in normal suckling behaviour**. *Proc Natl Acad Sci U S A* 2000, **97**:13384-13389.

13. Contos JJ, Ishii I, Fukushima N, Kingsbury MA, Ye X, Kawamura S, Brown JH, Chun J: **Characterization of lpa(2) (Edg4) and lpa(1)/lpa(2) (Edg2/Edg4) lysophosphatidic acid receptor knockout mice: signaling deficits without obvious phenotypic abnormality attributable to lpa(2)**. *Mol Cell Biol* 2002, **22**:6921-6929.

14. Estivill-Torrus G, Llebrez-Zayas P, Matas-Rico E, Santin L, Pedraza C, De Diego I, Del Arco I, Fernandez-Llebrez P, Chun J, De Fonseca FR: **Absence of LPA1 signaling results in defective cortical development**. *Cereb Cortex* 2008, **18**:938-950.

15. Matas-Rico E, Garcia-Diaz B, Llebrez-Zayas P, Lopez-Barroso D, Santin L, Pedraza C, Smith-Fernandez A, Fernandez-Llebrez P, Tellez T, Redondo M *et al.*: **Deletion of lysophosphatidic acid receptor LPA(1) reduces neurogenesis in the mouse dentate gyrus**. *Mol Cell Neurosci* 2008, **39**:342-355.

16. Inoue M, Rashid MH, Fujita R, Contos JJ, Chun J, Ueda H: **Initiation of neuropathic pain requires lysophosphatidic acid receptor signaling**. *Nat Med* 2004, **10**:712-718.

17. Ye X, Hama K, Contos JJ, Anliker B, Inoue A, Skinner MK, Suzuki H, Amano T, Kennedy G, Arai H *et al.*: **LPA3-mediated lysophosphatidic acid signalling in embryo implantation and spacing**. *Nature* 2005, **435**:104-108.

18. Ye X, Skinner MK, Kennedy G, Chun J: **Age-dependent loss of sperm production in mice via impaired lysophosphatidic acid signaling**. *Biol Reprod* 2008, **79**:328-336.

19. • Savaskan NE, Rocha L, Kotter MR, Baer A, Lubec G, van Meeteren LA, Kishi Y, Aoki J, Moolenaar WH, Nitsch R *et al.*: **Autotaxin (NPP-2) in the brain: cell type-specific expression and regulation during development and after neurotrauma**. *Cell Mol Life Sci* 2007, **64**:230-243.
Using a combination of *in situ* hybridization, quantitative RT-PCR, immunocytochemistry, and Western blot techniques, this paper systematically shows the expression of ATX mRNA and transcripts in the brain during development and following neurotrauma.

20. Fukushima N, Kimura Y, Chun J: **A single receptor encoded by vzg-1/lpA1/edg-2 couples to G proteins and mediates multiple cellular responses to lysophosphatidic acid**. *Proc Natl Acad Sci U S A* 1998, **95**:6151-6156.

21. Jin Rhee H, Nam JS, Sun Y, Kim MJ, Choi HK, Han DH, Kim NH, Huh SO: **Lysophosphatidic acid stimulates cAMP accumulation and cAMP response element-binding protein phosphorylation in immortalized hippocampal progenitor cells**. *Neuroreport* 2006, **17**:523-526.

22. Svetlov SI, Ignatova TN, Wang KK, Hayes RL, English D, Kukekov VG: **Lysophosphatidic acid induces clonal generation of mouse neurospheres via proliferation of Sca-1- and AC133-positive neural progenitors**. *Stem Cells Dev* 2004, **13**:685-693.

23. • Fukushima N, Shano S, Moriyama R, Chun J: **Lysophosphatidic acid stimulates neuronal differentiation of cortical neuroblasts through the LPA1-G(i/o) pathway**. *Neurochem Int* 2007, **50**:302-307.
This paper revealed signaling pathways of LPA-induced neurogenesis using genetic and pharmacological approaches.

24. Dottori M, Leung J, Turnley AM, Pebay A: **Lysophosphatidic acid inhibits neuronal differentiation of neural stem/progenitor cells derived from human embryonic stem cells**. *Stem Cells* 2008, **26**:1146-1154.

25. Kingsbury MA, Rehen SK, Contos JJ, Higgins CM, Chun J: **Non-proliferative effects of lysophosphatidic acid enhance cortical growth and folding**. *Nat Neurosci* 2003, **6**:1292-1299.

26. Ishii I, Contos JJ, Fukushima N, Chun J: **Functional comparisons of the lysophosphatidic acid receptors, LP(A1)/VZG-1/EDG-2, LP(A2)/EDG-4, and LP(A3)/EDG-7 in neuronal cell lines using a retrovirus expression system**. *Mol Pharmacol* 2000, **58**:895-902.

27. Fukushima N, Ishii I, Habara Y, Allen CB, Chun J: **Dual regulation of actin rearrangement through lysophosphatidic acid receptor in neuroblast cell lines: actin depolymerization by Ca(2+)-alpha-actinin and polymerization by rho**. *Mol Biol Cell* 2002, **13**:2692-2705.

28. Yanagida K, Ishii S, Hamano F, Noguchi K, Shimizu T: **LPA4/p2y9/GPR23 mediates rho-dependent morphological changes in a rat neuronal cell line**. *J Biol Chem* 2007, **282**:5814-5824.

29. Lee CW, Rivera R, Dubin AE, Chun J: **LPA(4)/GPR23 is a lysophosphatidic acid (LPA) receptor utilizing G(s)–G(q)/G(i)-mediated calcium signaling and G(12/13)-mediated Rho activation**. *J Biol Chem* 2007, **282**:4310-4317.

30. Fukushima N, Weiner JA, Chun J: **Lysophosphatidic acid (LPA) is a novel extracellular regulator of cortical neuroblast morphology**. *Dev Biol* 2000, **228**:6-18.

31. Dubin AE, Bahnson T, Weiner JA, Fukushima N, Chun J: **Lysophosphatidic acid stimulates neurotransmitter-like conductance changes that precede GABA and L-glutamate in early, presumptive cortical neuroblasts**. *J Neurosci* 1999, **19**:1371-1381.

32. Jalink K, Eichholtz T, Postma FR, van Corven EJ, Moolenaar WH: **Lysophosphatidic acid induces neuronal shape changes via a novel, receptor-mediated signaling pathway: similarity to thrombin action**. *Cell Growth Differ* 1993, **4**:247-255.

33. Tigyi G, Fischer DJ, Sebok A, Yang C, Dyer DL, Miledi R: **Lysophosphatidic acid-induced neurite retraction in PC12 cells: control by phosphoinositide-Ca^{2+} signaling and Rho**. *J Neurochem* 1996, **66**:537-548.

34. Saito S: **Effects of lysophosphatidic acid on primary cultured chick neurons**. *Neurosci Lett* 1997, **229**:73-76.

35. Fukushima N, Weiner JA, Kaushal D, Contos JJ, Rehen SK, Kingsbury MA, Kim KY, Chun J: **Lysophosphatidic acid influences the morphology and motility of young, postmitotic cortical neurons**. *Mol Cell Neurosci* 2002, **20**:271-282.

36. Arimura N, Inagaki N, Chihara K, Menager C, Nakamura N, Amano M, Iwamatsu A, Goshima Y, Kaibuchi K: **Phosphorylation of collapsin response mediator protein-2 by Rho-kinase. Evidence for two separate signaling pathways for growth cone collapse**. *J Biol Chem* 2000, **275**:23973-23980.

37. Yuan XB, Jin M, Xu X, Song YQ, Wu CP, Poo MM, Duan S: **Signalling and crosstalk of Rho GTPases in mediating axon guidance**. *Nat Cell Biol* 2003, **5**:38-45.

38. Campbell DS, Holt CE: **Chemotropic responses of retinal growth cones mediated by rapid local protein synthesis and degradation**. *Neuron* 2001, **32**:1013-1026.

39. Campbell DS, Holt CE: **Apoptotic pathway and MAPKs differentially regulate chemotropic responses of retinal growth cones**. *Neuron* 2003, **37**:939-952.

40. McGiffert C, Contos JJ, Friedman B, Chun J: **Embryonic brain expression analysis of lysophospholipid receptor genes suggests roles for s1p(1) in neurogenesis and s1p(1–3) in angiogenesis**. *FEBS Lett* 2002, **531**:103-108.

41. Holtsberg FW, Steiner MR, Keller JN, Mark RJ, Mattson MP, Steiner SM: **Lysophosphatidic acid induces necrosis and apoptosis in hippocampal neurons**. *J Neurochem* 1998, **70**:66-76.

42. Holtsberg FW, Steiner MR, Bruce-Keller AJ, Keller JN, Mattson MP, Moyers JC, Steiner SM: **Lysophosphatidic acid and apoptosis of nerve growth factor-differentiated PC12 cells**. *J Neurosci Res* 1998, **53**:685-696.

43. Zheng ZQ, Fang XJ, Qiao JT: **Dual action of lysophosphatidic acid in cultured cortical neurons: survival and apoptogenic**. *Sheng Li Xue Bao* 2004, **56**:163-171.

44. Zheng ZQ, Fang XJ, Zhang Y, Qiao JT: **Neuroprotective effect of lysophosphatidic acid on AbetaP31–35-induced apoptosis in cultured cortical neurons**. *Sheng Li Xue Bao* 2005, **57**:289-294.

45. Fujiwara Y, Sebok A, Meakin S, Kobayashi T, Murakami-Murofushi K, Tigyi G: **Cyclic phosphatidic acid elicits neurotrophin-like actions in embryonic hippocampal neurons**. *J Neurochem* 2003, **87**:1272-1283.

46. Weiner JA, Hecht JH, Chun J: **Lysophosphatidic acid receptor gene vzg-1/lpA1/edg-2 is expressed by mature oligodendrocytes during myelination in the postnatal murine brain**. *J Comp Neurol* 1998, **398**:587-598.

47. Allard J, Barron S, Diaz J, Lubetzki C, Zalc B, Schwartz JC, Sokoloff P: **A rat G protein-coupled receptor selectively expressed in myelin-forming cells**. *Eur J Neurosci* 1998, **10**:1045-1053.

48. Moller T, Musante DB, Ransom BR: **Lysophosphatidic acid-induced calcium signals in cultured rat oligodendrocytes**. *Neuroreport* 1999, **10**:2929-2932.

49. Stankoff B, Barron S, Allard J, Barbin G, Noel F, Aigrot MS, Premont J, Sokoloff P, Zalc B, Lubetzki C: **Oligodendroglial expression of Edg-2 receptor: developmental analysis and pharmacological responses to lysophosphatidic acid**. *Mol Cell Neurosci* 2002, **20**:415-428.

50. Dawson J, Hotchin N, Lax S, Rumsby M: **Lysophosphatidic acid induces process retraction in CG-4 line oligodendrocytes and oligodendrocyte precursor cells but not in differentiated oligodendrocytes**. *J Neurochem* 2003, **87**:947-957.

51. • Nogaroli L, Yuelling LM, Dennis J, Gorse K, Payne SG, Fuss B: **Lysophosphatidic acid can support the formation of membranous structures and an increase in MBP mRNA levels in differentiating oligodendrocytes**. *Neurochem Res* 2009, **34**:182-193.

LPA's effects on oligodendrocytes were observed only when ATX expression was downregulated. The authors showed that endogenous ATX activities (lysoPLD activity and simulation of process formation) in oligodendrocytes masked exogenous LPA effects. This may help to explain inconsistencies of earlier studies regarding LPA effects on oligodendrocytes (see the main text).

52. • Shano S, Moriyama R, Chun J, Fukushima N: **Lysophosphatidic acid stimulates astrocyte proliferation through LPA1**. *Neurochem Int* 2008, **52**:216-220.

Dual LPA signaling pathways in astrocytes are demonstrated: LPA_1-mediated proliferation and non-LPA_1-mediated inhibition of glutamate uptake.

53. Cervera P, Tirard M, Barron S, Allard J, Trottier S, Lacombe J, Daumas-Duport C, Sokoloff P: **Immunohistological localization of the myelinating cell-specific receptor LP(A1)**. *Glia* 2002, **38**:126-136.

54. Keller JN, Steiner MR, Holtsberg FW, Mattson MP, Steiner SM: **Lysophosphatidic acid-induced proliferation-related signals in astrocytes**. *J Neurochem* 1997, **69**:1073-1084.

55. Ramakers GJ, Moolenaar WH: **Regulation of astrocyte morphology by RhoA and lysophosphatidic acid**. *Exp Cell Res* 1998, **245**:252-262.

56. Tabuchi S, Kume K, Aihara M, Shimizu T: **Expression of lysophosphatidic acid receptor in rat astrocytes: mitogenic effect and expression of neurotrophic genes**. *Neurochem Res* 2000, **25**:573-582.

57. Sorensen SD, Nicole O, Peavy RD, Montoya LM, Lee CJ, Murphy TJ, Traynelis SF, Hepler JR: **Common signaling pathways link activation of murine PAR-1, LPA, and S1P receptors to proliferation of astrocytes**. *Mol Pharmacol* 2003, **64**:1199-1209.

58. Tigyi G, Dyer DL, Miledi R: **Lysophosphatidic acid possesses dual action in cell proliferation**. *Proc Natl Acad Sci U S A* 1994, **91**:1908-1912.

59. Pebay A, Torrens Y, Toutant M, Cordier J, Glowinski J, Tence M: **Pleiotropic effects of lysophosphatidic acid on striatal astrocytes**. *Glia* 1999, **28**:25-33.

60. Fuentes E, Nadal A, McNaughton PA: **Lysophospholipids trigger calcium signals but not DNA synthesis in cortical astrocytes**. *Glia* 1999, **28**:272-276.

61. Furukawa A, Kita K, Toyomoto M, Fujii S, Inoue S, Hayashi K, Ikeda K: **Production of nerve growth factor enhanced in cultured mouse astrocytes by glycerophospholipids, sphingolipids, and their related compounds**. *Mol Cell Biochem* 2007, **305**:27-34.

62. Manning TJ Jr, Sontheimer H: **Bovine serum albumin and lysophosphatidic acid stimulate calcium mobilization and reversal of cAMP-induced stellation in rat spinal cord astrocytes**. *Glia* 1997, **20**:163-172.

63. Suidan HS, Nobes CD, Hall A, Monard D: **Astrocyte spreading in response to thrombin and lysophosphatidic acid is dependent on the Rho GTPase**. *Glia* 1997, **21**:244-252.

64. Manning TJ Jr, Rosenfeld SS, Sontheimer H: **Lysophosphatidic acid stimulates actomyosin contraction in astrocytes**. *J Neurosci Res* 1998, **53**:343-352.

65. • de Sampaio ESTC, Choi JW, Gardell SE, Herr DR, Rehen SK, Gomes FC, Chun J: **Lysophosphatidic acid receptor-dependent secondary effects via astrocytes promote neuronal differentiation**. *J Biol Chem* 2008, **283**:7470-7479.

This paper shows LPA's secondary effect on differentiation of NPCs via astrocytes by using both coculture systems and conditioned media from LPA-primed astrocytes. The factor mediating this effect is not determined.

66. Moller T, Contos JJ, Musante DB, Chun J, Ransom BR: **Expression and function of lysophosphatidic acid receptors in cultured rodent microglial cells**. *J Biol Chem* 2001, **276**:25946-25952.

67. Tham CS, Lin FF, Rao TS, Yu N, Webb M: **Microglial activation state and lysophospholipid acid receptor expression**. *Int J Dev Neurosci* 2003, **21**:431-443.

68. Schilling T, Stock C, Schwab A, Eder C: **Functional importance of Ca^{2+}-activated K^+ channels for lysophosphatidic acid-induced microglial migration**. *Eur J Neurosci* 2004, **19**:1469-1474.

69. Fujita R, Ma Y, Ueda H: **Lysophosphatidic acid-induced membrane ruffling and BDNF gene expression are mediated by ATP release in primary microglia**. *J Neurochem* 2008, **107**:152-160.

70. Weiner JA, Chun J: **Schwann cell survival mediated by the signaling phospholipid lysophosphatidic acid**. *Proc Natl Acad Sci U S A* 1999, **96**:5233-5238.

71. Weiner JA, Fukushima N, Contos JJ, Scherer SS, Chun J: **Regulation of Schwann cell morphology and adhesion by receptor-mediated lysophosphatidic acid signaling**. *J Neurosci* 2001, **21**:7069-7078.

72. Li Y, Gonzalez MI, Meinkoth JL, Field J, Kazanietz MG, Tennekoon GI: **Lysophosphatidic acid promotes survival and differentiation of rat Schwann cells**. *J Biol Chem* 2003, **278**:9585-9591.

73. Frohnert PW, Stonecypher MS, Carroll SL: **Lysophosphatidic acid promotes the proliferation of adult Schwann cells isolated from axotomized sciatic nerve**. *J Neuropathol Exp Neurol* 2003, **62**:520-529.

74. Fujita R, Kiguchi N, Ueda H: **LPA-mediated demyelination in ex vivo culture of dorsal root**. *Neurochem Int* 2007, **50**:351-355.

75. Harrison SM, Reavill C, Brown G, Brown JT, Cluderay JE, Crook B, Davies CH, Dawson LA, Grau E, Heidbreder C *et al.*: **LPA1 receptor-deficient mice have phenotypic changes observed in psychiatric disease**. *Mol Cell Neurosci* 2003, **24**:1170-1179.

76. • van Meeteren LA, Ruurs P, Stortelers C, Bouwman P, van Rooijen MA, Pradere JP, Pettit TR, Wakelam MJ, Saulnier-Blache JS, Mummery CL *et al.*: **Autotaxin, a secreted lysophospholipase D, is essential for blood vessel formation during development**. *Mol Cell Biol* 2006, **26**:5015-5022.

Genetic deletion of ATX, a major enzyme for LPA production, resulted in more severe phenotypes than those reported earlier for LPA_{1-3} single/multiple-null mice.

77. • Tanaka M, Okudaira S, Kishi Y, Ohkawa R, Iseki S, Ota M, Noji S, Yatomi Y, Aoki J, Arai H: **Autotaxin stabilizes blood vessels and is required for embryonic vasculature by producing lysophosphatidic acid**. *J Biol Chem* 2006, **281**:25822-25830.

An independently derived and analyzed line of ATX-null mice showing a consistent phenotype compared to other ATX-KO.

78. Renback K, Inoue M, Ueda H: **Lysophosphatidic acid-induced, pertussis toxin-sensitive nociception through a substance P release from peripheral nerve endings in mice**. *Neurosci Lett* 1999, **270**:59-61.

79. Renback K, Inoue M, Yoshida A, Nyberg F, Ueda H: **Vzg-1/lysophosphatidic acid-receptor involved in peripheral pain transmission**. *Brain Res Mol Brain Res* 2000, **75**:350-354.

80. Inoue M, Xie W, Matsushita Y, Chun J, Aoki J, Ueda H: **Lysophosphatidylcholine induces neuropathic pain through an action of autotaxin to generate lysophosphatidic acid**. *Neuroscience* 2008, **152**:296-298.

81. Inoue M, Ma L, Aoki J, Chun J, Ueda H: **Autotaxin, a synthetic enzyme of lysophosphatidic acid (LPA), mediates the induction of nerve-injured neuropathic pain**. *Mol Pain* 2008, **4**:6.

82. Abrahamsen B, Zhao J, Asante CO, Cendan CM, Marsh S, Martinez-Barbera JP, Nassar MA, Dickenson AH, Wood JN: **The cell and molecular basis of mechanical, cold, and inflammatory pain**. *Science* 2008, **321**:702-705.

83. Ohta H, Sato K, Murata N, Damirin A, Malchinkhuu E, Kon J, Kimura T, Tobo M, Yamazaki Y, Watanabe T *et al.*: **Ki16425, a subtype-selective antagonist for EDG-family lysophosphatidic acid receptors**. *Mol Pharmacol* 2003, **64**:994-1005.

84. Heasley BH, Jarosz R, Lynch KR, Macdonald TL: **Initial structure–activity relationships of lysophosphatidic acid receptor antagonists: discovery of a high-affinity LPA1/LPA3 receptor antagonist**. *Bioorg Med Chem Lett* 2004, **14**:2735-2740.

85. Tamaruya Y, Suzuki M, Kamura G, Kanai M, Hama K, Shimizu K, Aoki J, Arai H, Shibasaki M: **Identifying specific conformations by using a carbohydrate scaffold: discovery of subtype-selective LPA-receptor agonists and an antagonist**. *Angew Chem Int Ed Engl* 2004, **43**:2834-2837.

86. • Hama K, Aoki J, Inoue A, Endo T, Amano T, Motoki R, Kanai M, Ye X, Chun J, Matsuki N *et al.*: **Embryo spacing and implantation timing are differentially regulated by LPA3-mediated lysophosphatidic acid signaling in mice**. *Biol Reprod* 2007, **77**:954-959.

In a study of the roles of LPA on embryo implantation, the authors describe the first functional use of a novel LPA_3-specific agonist.

87. Okusa MD, Ye H, Huang L, Sigismund L, Macdonald T, Lynch KR: **Selective blockade of lysophosphatidic acid LPA3 receptors reduces murine renal ischemia–reperfusion injury**. *Am J Physiol Renal Physiol* 2003, **285**:F565-574.

88. Prestwich GD, Gajewiak J, Zhang H, Xu X, Yang G, Serban M: **Phosphatase-resistant analogues of lysophosphatidic acid: agonists promote healing, antagonists and autotaxin inhibitors treat cancer**. *Biochim Biophys Acta* 2008, **1781**:588-594.

89. Chan WY, Kohsaka S, Rezaie P: **The origin and cell lineage of microglia: new concepts**. *Brain Res Rev* 2007, **53**:344-354.

90. Tager AM, LaCamera P, Shea BS, Campanella GS, Selman M, Zhao Z, Polosukhin V, Wain J, Karimi-Shah BA, Kim ND *et al.*: **The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak**. *Nat Med* 2008, **14**:45-54.

91. Pradere JP, Klein J, Gres S, Guigne C, Neau E, Valet P, Calise D, Chun J, Bascands JL, Saulnier-Blache JS *et al.*: **LPA1 receptor activation promotes renal interstitial fibrosis**. *J Am Soc Nephrol* 2007, **18**:3110-3118.

92. Panchatcharam M, Miriyala S, Yang F, Rojas M, End C, Vallant C, Dong A, Lynch K, Chun J, Morris AJ *et al.*: **Lysophosphatidic acid receptors 1 and 2 play roles in regulation of vascular injury responses but not blood pressure**. *Circ Res* 2008, **103**:662-670.

93. Shimomura Y, Wajid M, Ishii Y, Shapiro L, Petukhova L, Gordon D, Christiano AM: **Disruption of P2RY5, an orphan G protein-coupled receptor, underlies autosomal recessive woolly hair**. *Nat Genet* 2008, **40**:335-339.