thematic review

Thematic Review Series: Lysophospholipids and their Receptors

Novel lysophosphoplipid receptors: their structure and function

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Abstract **It is now accepted that lysophospholipids (LysoGPs) have a wide variety of functions as lipid mediators that are exerted through G protein-coupled receptors (GPCRs) specific to each lysophospholipid. While the roles of some LysoGPs, such as lysophosphatidic acid and sphingosine 1-phosphate, have been thoroughly examined, little is known about the roles of several other LysoGPs, such as lysophosphatidylserine (LysoPS), lysophosphatidylthreonine, lysophosphatidylethanolamine, lysophosphatidylinositol (LPI), and lysophosphatidylglycerol. Recently, a GPCR was found for LPI (GPR55) and three GPCRs (GPR34/LPS$_1$, P2Y10/LPS$_2$, and GPR174/LPS$_3$) were found for LysoPS. In this review, we focus on these newly identified GPCRs and summarize the actions of LysoPS and LPI as lipid mediators.**—Makide, K., A. Uwamizu, Y. Shinjo, J. Ishiguro, M. Okutani, A. Inoue, and J. Aoki. **Novel lysophosphoplipid receptors: their structure and function. *J. Lipid Res.* 2014.** 55: **1986–1995.**

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Lysophospholipids (LysoGPs) (1-acyl-2-LPL or 2-acyl-1-LPL) are deacylated forms of phospholipids with a single fatty acid chain and are produced by either phospholipase A (PLA)$_1$ or PLA$_2$ (1, 2). Various LysoGPs have been detected in biological samples such as plasma, including lysophosphatidylcholine (LPC), lysophosphatidic acid (LPA), lysophosphatidylethanolamine (LPE), lysophosphatidylserine (LysoPS), lysophosphatidylinositol (LPI), lysophosphatidylglycerol (LPG), sphingosine-1-phosphate (S1P), and sphingosylphosphorylcholine (SPC) (**Fig. 1**). These LysoGPs serve as precursors of diacyl phospholipids and at least some of them are also lipid mediators. LPA and S1P (Fig. 1) are lysophospholipid mediators with plasma concentrations of 10–30 nM and several hundred nanomoles, respectively (3, 4). Both LPA and S1P have critical roles in multiple cellular events through G protein-coupled receptors (GPCRs). Six GPCRs have been identified for LPA (LPA$_{1-6}$) and five GPCRs have been identified for S1P (S1P$_{1-5}$) (5), and nomenclature of these LysoGPs receptors has recently been proposed by Kihara et al. (6). These receptors are grouped into two classes, the Edg and P2Y families, respectively. LPA$_{1-3}$ and all five of the S1P receptors, S1P$_{1-5}$, are members of the Edg family, while LPA$_{4-6}$ are members of the P2Y family. In addition, LPA is an endogenous ligand for PPARγ (7), and was shown to activate transient receptor potential cation channel subfamily V member 1 (TRPV1) channels leading to an influx of Ca^{2+} ions through TRPV1 (8). Studies on gene-targeted mice and human genetic diseases have clearly shown that each receptor has specific roles in both physiological and pathological conditions. For example, LPA has a pivotal role in neurogenesis (9) and has also been implicated in the development of lung fibrosis (10) via LPA$_1$. LPA exhibits unique roles in implantation of fertilized eggs via LPA$_3$ (11) and hair follicle formation via LPA$_6$ (12). LPA is produced by at least two pathways where multiple phospholipase activities are involved (3). Lysophospholipase D/autotaxin/NPP2 produces LPA from LysoGPs such as LPC, while phosphatidic acid (PA)-selective PLA$_1\alpha$ (PA-PLA$_1\alpha$) and PA-PLA$_1\beta$ produce LPA from PA by their PLA$_1$ activities. In contrast, S1P is produced intracellularly by phosphorylation

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Abbreviations: CHO, Chinese hamster ovary; D-LysoPS, lysophosphatidyl D-serine; GPCR, G protein-coupled receptor; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; LPG, lysophosphatidylglycerol; LPI, lysophosphatidylinositol; LysoGP, lysophospholipid; LPT, lysophosphatidylthreonine; LysoPS, lysophosphatidylserine; NGF, nerve growth factor; PA, phosphatidic acid; PLA, phospholipase A; S1P, sphingosine 1-phosphate; SPC, sphingosylphosphorylcholine; TGF, transforming growth factor.

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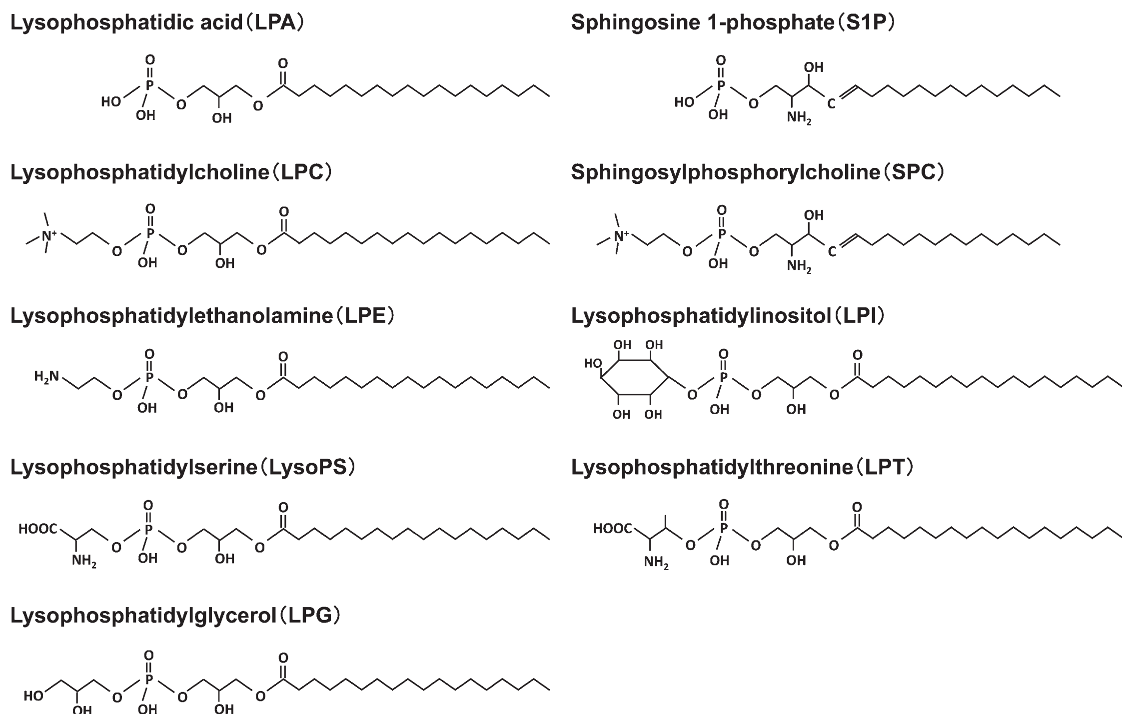


Fig. 1. Structures of lysophospholipids. For glycerophospholipids, the acyl chain can be linked to either the *sn*-1 or *sn*-2 position of the glycerol backbone. Each structure containing stearic acid (18:0) at the *sn*-1 position of glycerol is shown.

of sphingosine, which is catalyzed by sphingosine kinases (SphK1 and SphK2) (13).

While LPA and S1P have been extensively studied, other LysoGPs have received little attention. LPC is the most abundant LysoGP in humans, with a plasma concentration of several hundred micromoles (14). A number of in vitro studies have implicated LPC in the activation of macrophages and monocytes (15). However, there is no direct evidence that LPC has a role as a lipid mediator. Previously, several reports indicated that GPCRs, such as G2A, GPR4, and OGR1, reacted with LPC and SPC, a choline-containing lysosphingophospholipid (16, 17). However, several of these reports on the receptors for LPC and SPC have been retracted (18), so currently it is not clear if these GPCRs are real receptors for choline-containing LysoGPs (LPC and SPC). Other LysoGPs such as LPG, LPE, LPI, and LysoPS are present at low concentrations in vivo. Although their in vivo roles are unknown, they induce various cellular responses when applied to cells in vitro. **Table 1** summarizes the actions of LysoGPs obtained mainly through in vitro experiments, although some results from in vivo tests are also listed for LysoPS and lysophosphatidylthreonine (LPT).

One of the reasons that these minor LysoGPs have not been carefully examined is that their receptors and synthetic enzymes have not been identified. However, GPCRs that react specifically with either LysoPS or LPI, have recently been reported. In this review we will summarize the receptors, especially GPCRs, for LysoPS and LPI, and their possible functions through their receptors.

LysoPS

Actions of LysoPS

LysoPS is known to induce several cellular responses both in vitro and in vivo (**Fig. 2**). The most characterized response has been the stimulatory response of mast cell degranulation (19, 20). In vitro, LysoPS enhances histamine release from peritoneal rodent mast cells triggered by the cross-linking of high-affinity IgE receptors (FcεRI). It also induces rapid degranulation of mast cells and consequent anaphylactic shock and hypothermia when administered intravenously in rodents (21, 22). The mast cell degranulation-stimulating activity is not induced by other LysoGPs including LPA, LPC, LPE, LPG, and LPI, and strictly requires the serine residue of LysoPS. It also strictly requires the overall structure of the serine residue of LysoPS, because modification of the serine residue completely abolishes the mast cell degranulation-stimulating activity. LysoPS directly acts on mast cells, because a deoxy analog of LysoPS (2-deoxy-LysoPS), which lacks the *sn*-2 hydroxyl group and is resistant to the reacylation reaction to PS, has activity similar to that of LysoPS.

LysoPS also enhances Nerve Growth Factor (NGF)-induced neurite outgrowth in PC12 cells (23), suppresses proliferation of isolated human T lymphocytes (24), stimulates migration of fibroblasts (25, 26), regulates cytochrome P450 activity (27), and enhances apoptotic cell-engulfment by macrophages (28) (Fig. 2). In the host-parasite interaction of schistosomes, LysoPS was identified as a Toll-like receptor 2 (TLR2)-activating molecule that prolonged the survival of the parasite and limited its pathology to the host (29).

TABLE 1. Action of LysoPS, LPT, LPG, LPE, and LPI

LysoGPs	Target Cells	Cellular or Pharmacological Responses	Receptor	References
LysoPS	Peritoneal mast cell (rodent)	Enhancement of degranulation	?	(19, 20)
	PC12	Enhancement of NGF-induced differentiation	?	(23)
	T lymphocyte	Growth inhibition	?	(24, 70)
	L2071 (fibroblast)	Migration	?	(26)
	U87 (glioma)	Migration	?	(25)
	Macrophage	Engulfment	G2A	(31, 32)
	Myotube 3T3-L1 (adipocyte)	Glucose uptake	?	(71)
	?	Depression, hypothermia (in vivo)	?	(22)
LPT	Peritoneal mast cell (rodent)	Enhancement of degranulation	?	(22)
	?	Depression, hypothermia (in vivo)	?	(22)
LPG	OVCAR-3 (ovarian cancer)	Intracellular calcium increase	?	(72)
	HUVEC	ERK phospholilation, migration, tube formation	?	(73)
	Natural killer cell	ERK phospholilation, migration	?	(74)
	Neutrophil, monocyte	Inhibition of chemokine-induced migration and IL-1β production, intracellular calcium increase	?	(75)
LPE	PC12	Activation of MAPK, neuronal differentiation	?	(76)
	SK-OV3 (ovarian cancer)	Intracellular calcium increase, migration, invasion	?	(77)
	MDA-MB-231 (breast cancer)	Intracellular calcium increase	LPA_1CD97	(78)
LPI	Pancreatic islet	Insulin release	?	(58)
	Hippocampal neuron	Prevention of ischemia-induced cell death (in vivo)	?	(60)
	Ras-transformed thyroid epithelial cell	Proliferation	?	(79)
	PC12	Intracellular calcium increase, exocytosis	?	(80)
	Endothelial cell	Wound healing	?	(81)

Recently, Bratton and colleagues showed that LysoPS was generated in neutrophils by an oxidation-dependent mechanism and served as an endogenous anti-inflammatory mediator by stimulating the clearance of recruited neutrophils by macrophages, contributing to the resolution of inflammation (30–32). In addition, their results suggest that a GPCR (G2A) on macrophages is responsible for the clearance of neutrophils by macrophages, raising the possibility that LysoPS is an endogenous ligand for G2A. G2A was once proposed as a receptor for LPC, but the proposal was later retracted (17). Now many reports have confirmed that G2A is a receptor for protons and for 9-HODE, a kind of oxidized fatty acid (linoleic acid) (33, 34). It is not clear if G2A directly recognizes LysoPS.

Because LysoPS induces various cellular responses in a LysoPS-specific manner, its actions may be mediated by LysoPS receptors. Recently, several orphan GPCRs were identified as LysoPS receptors. These include GPR34, P2Y10, A630033H20, and GPR174, all of which are P2Y family members (35, 36) (**Fig. 3**). Although new nomenclature for these LysoPS receptors was recently proposed by Kihara et al. (6), we propose that GPR34, P2Y10, A630033H20, and GPR174 be designated as LPS_1, LPS_2, LPS_2-like (LPS_{2L}), and LPS_3, respectively, according to the nomenclature of lysophospholipid receptors and the original report (36).

GPR34/LPS_1

GPR34 was first isolated from a human fetal brain cDNA library based on its sequence homology with the platelet-activating factor (PAF) receptor (37, 38). GPR34 is preserved among vertebrates and GPR34 sequences are found in fish including shark, fugu, zebrafish, and carp, suggesting that GPR34 has existed for at least 450 million years (39). GPR34 is thought to be a member of P2Y family (Fig. 3), because GPR34 has some amino acid residues that are characteristic of P2Y family members. The P2Y family includes receptors for nucleotide (P2Y1, P2Y2, P2Y12, and P2Y13), UDP-glucose (P2Y14), LPAs (P2Y9/LPA4, GPR92/LPA5, and P2Y5/LPA6), and the orphan GPCRs (GPR87, GPR171, and GPR82). Interestingly, GPR34 does not contain a charged basic residue within Transmembrane helix 7 (TM7) that other P2Y family members have and that is essential for the binding of nucleotide ligands such as ATP (40).

In 2006, in the course of a ligand fishing study for GPR34, Sugo et al. (35) found that LysoPS is a ligand for GPR34. They showed that LysoPS caused a dose-dependent inhibition of forskolin-stimulated cAMP accumulation in human GPR34-expressing Chinese hamster ovary (CHO) cells. They also showed that LysoPS induced phosphorylation of ERK in GPR34-expressing CHO cells. The response was completely abolished by treatment with pertussis toxin, indicating that GPR34 couples to a $G_{i/o}$-type G-protein. GPR34 did not respond to other lysophospholipids, including LPA, S1P, LPC, and LPE. Notably, lysophosphatidyl D-serine (D-LysoPS) as well as LPT were later shown to be poor agonists (22), indicating that GPR34 specifically and strictly recognizes the L-LysoPS moiety of LysoPS.

There is some controversy over whether LysoPS is a real ligand for mammalian GPR34 (41). On the one hand,

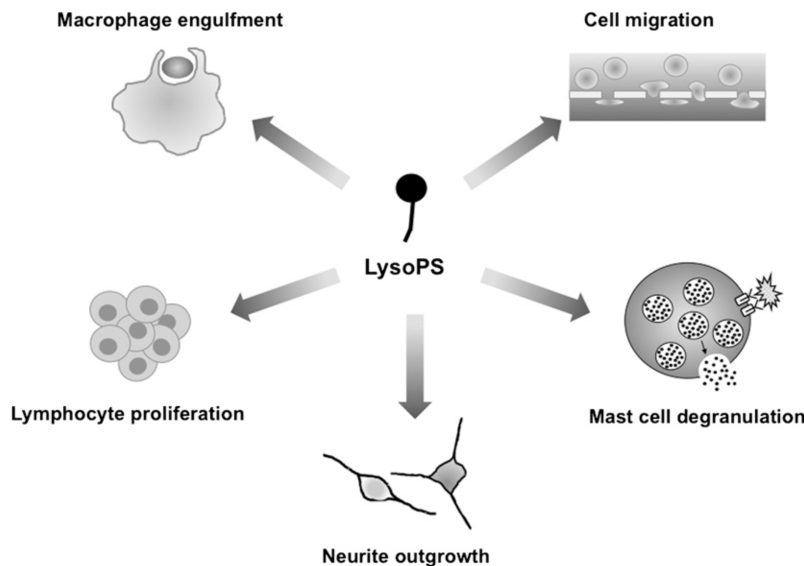


Fig. 2. Biological roles of LysoPS. LysoPS induces several cellular responses both in vitro and in vivo. LysoPS enhances antigen-triggered degranulation of mast cells and NGF-induced neurite outgrowth, suppresses T cell proliferation, stimulates migration of fibroblasts, and enhances apoptotic cell-engulfment by macrophages.

Liebscher et al. (41) demonstrated that GPR34 from carp, a kind of fish, did react strongly with LysoPS. On the other hand, the result of the initial study by Sugo et al. (35) was confirmed by Kitamura et al. (42), in which activation of GPR34 was evaluated by a Ca^{2+} mobilization assay and by a newly developed transforming growth factor (TGF)α shedding assay. In both assays, mammalian GPR34s from human, rat, and mouse origins reacted specifically with LysoPS, but not with other LysoGPs Notably, GPR34 reacted most strongly with LysoPS species with an unsaturated fatty acid at the *sn*-2 position. A similar ligand preference was observed using chemically synthesized LysoPS analogs. To confirm this result, GPR34 was activated by treating the cells with phosphatidylserine-specific PLA_1 (PS-PLA_1), which is capable of producing 2-acyl-LysoPS from PS on the cell surface. We also cloned two orthologs of GPR34 from zebrafish (zGPR34a and zGPR34b) and examined their reactivities with LysoPS. In the TGFα shedding assay, the two orthologs reacted much more strongly with LysoPS than did mammalian GPR34 (**Fig. 4**). All the experimental data strongly suggested that LysoPS, especially LysoPS with an unsaturated fatty acid at the *sn*-2 position, is the endogenous ligand for both mammalian and fish GPR34s.

GPR34 mRNA is expressed in many tissues, but is most highly expressed in mast cells (35). Thus, it was once proposed that LysoPS enhanced mast cell degranulation through GPR34. However, as stated above, LPT, a potent inducer of mast cell degranulation, did not activate GPR34 (22). In addition, peritoneal mast cells from GPR34-deficient mice still responded to LysoPS (41). Thus, it is likely that GPR34 is not involved in the mast cell degranulation response induced by LysoPS. Cuprizone, a demyelinating toxin, was found to upregulate the expression of GPR34 in activated microglia, which suggests that GPR34, and thus LysoPS, have roles in neuroinflammation (43). In addition, recent gene array analysis revealed that GPR34 is highly expressed in microglia in both humans and mice (44). Interestingly, other P2Y receptors, such as P2Y6, -12, and -13, are expressed in microglial cells and are involved in the chemotaxis of microglia (P2Y12 and -13) (45) and microglial phagocytosis (P2Y6) (46). GPR34 may have similar roles in microglial cells.

The in vivo role of LysoPS through GPR34 is not clear. GPR34 KO mice appeared healthy and normal but when GPR34 KO and WT mice were immunologically challenged with methylated BSA or bacterial infection, the KO mice showed fewer inflammatory cells and greater cytokine production than the WT mice (41) (**Table 2**). Because GPR34 is highly expressed in mononuclear cells of the immune system, LysoPS appears to serve as an immunomodulator through GPR34 in response to immunological challenges. Further studies are needed to elucidate the

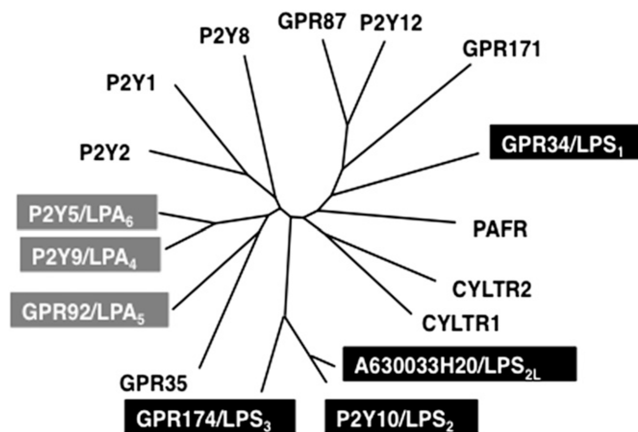
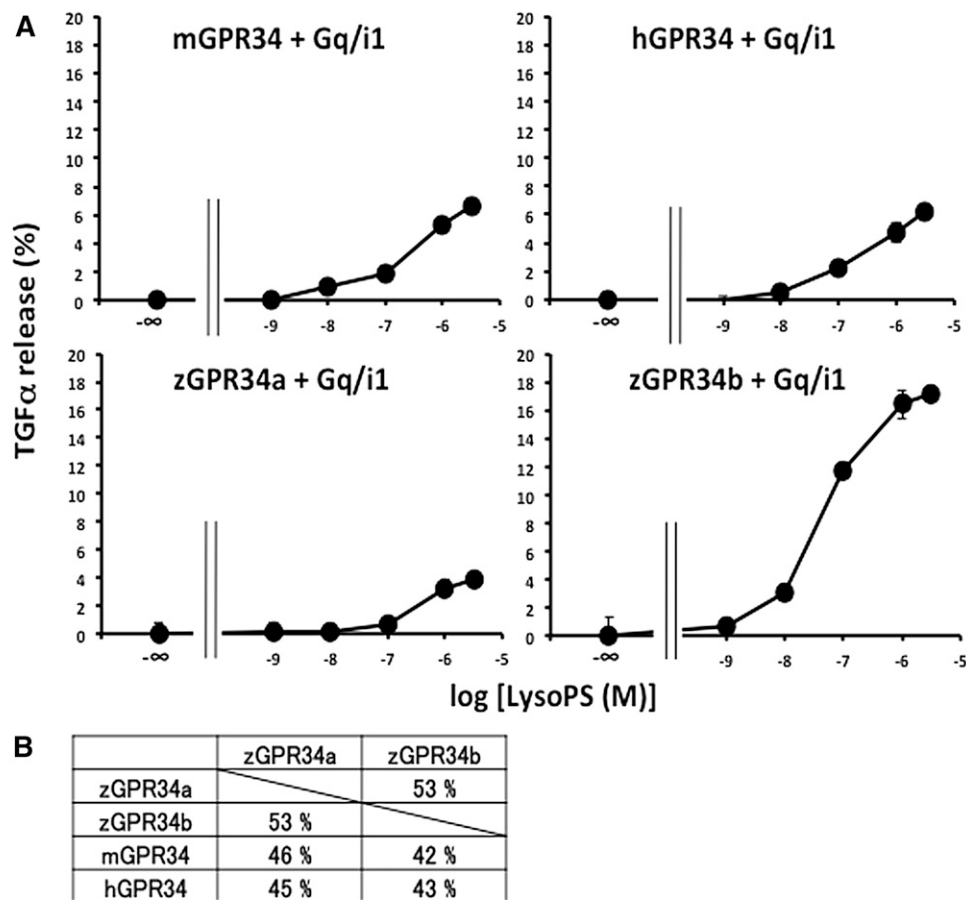


Fig. 3. Phylogenetic tree of the amino acid sequences of human P2Y family members.



	zGPR34a	zGPR34b
zGPR34a		53 %
zGPR34b	53 %	
mGPR34	46 %	42 %
hGPR34	45 %	43 %

Fig. 4. Reaction of two GPR34 orthologs in zebrafish to LysoPS. A: Reactivity of human, mouse, and zebrafish GPR34 to LysoPS (1-oleoyl-LysoPS) by TGFα shedding assay, in which activation of GPCR was monitored by ectodomain shedding of alkaline phosphatase (AP)-tagged TGFα downstream of G protein signaling. Note that zebrafish have two GPR34 orthologs (zGPR34a and zGPR34b). B: Comparison of GPR34 amino acid sequences from different species.

biological significance of LysoPS signaling via GPR34. Interestingly, ectopic expression of GPR34 was reported in clinical samples such as lymphoma and stomach cancer, indicating that aberrant GPR34 signaling is a cause or effect of tumor growth (47, 48).

P2Y10/LPS_2

Using our TGFα shedding assay (36), we found that LysoPS specifically reacted with 3 of 60 orphan GPCRs tested (P2Y10, A630033H20, and GPR174), all of which are P2Ys (Fig. 3). In the TGFα shedding assay, P2Y10-expressing cells reacted with LysoPS, but not with other LysoGPs Importantly, P2Y10 was not activated by D-LysoPS or LPT, demonstrating that P2Y10 strictly recognized the serine residue of LysoPS. The biological role of P2Y10 is not known at present. Expression of P2Y10 is restricted to lymphoid organs such as spleen, thymus, and lymph nodes. The expression of P2Y10 is dependent on PU.1 and Spi-B, two highly related Ets transcription factors (49). Ets transcription factors are involved in a variety of mammalian developmental processes at the cellular, tissue, and organ levels (50). In $PU.1^{+/-}$ Spi-$B^{-/-}$ mice, the expression of P2Y10 is dramatically reduced. These Ets transcription factors have a role in the signal transduction of B cell receptors (51), which suggests that P2Y10 has a role in regulating BCR signaling. A comprehensive expression analysis in the database (http://biogps.org/) indicated that P2Y10 is expressed in both B and T cells.

P2Y10 couples with $G\alpha_{12/13}$ but not with other G proteins. $G\alpha_{12/13}$ signaling in T cells has a role to downregulate the cellular function of T cells. Genetic inactivation of both $G\alpha_{12}$ and $G\alpha_{13}$ genes enhanced the proliferation and adhesive properties of T cells (52). Interestingly, LysoPS suppressed the proliferation of activated T cells in vitro (24), which raises the possibility that LysoPS has its role in T cells through P2Y10.

It was reported that in CHO cells expressing human P2Y10, both LPA and S1P evoked a Ca^{2+} response (53). This suggested that P2Y10 is a receptor for both LPA and S1P. However, attempts to repeat the experiment were unsuccessful (36). As stated, P2Y10 was not activated by LysoPS analogs such as D-LysoPS and LPT. In addition, two other GPCRs that are close homologs of P2Y10 (GPR174 and A630033H20) are also activated specifically by LysoPS. Thus, it can safely be said that

TABLE 2. Receptors for LysoPS and LPI

LysoGPs	Receptor	Expression	Possible Functions	References
LysoPS	GPR34/LPS_1	Ubiquitous	Suppression of cytokine production upon infection	(41)
	P2Y10/LPS_2	Lymphoid organs	?	(49)
	A630033H20/LPS_{2L}	Lymphoid organs	?	—
	GPR174/LPS_3	Lymphoid organs	Autoimmune diseases (Basedow's disease)	(56)
LPI	GPR55	Ubiquitous	Bone morphogenesis, angiogenesis, cancer cell regulation, inflammation, pain, obesity	(66–68, 82, 83)

P2Y10 recognizes strictly the structure of the serine moiety of LysoPS. We thus propose to name the new LysoPS receptor P2Y10/LPS_2.

A630033H20/LPS_{2L}

A630033H20 was also shown to react specifically with LysoPS (36). A630033H20 is the closest homolog of P2Y10, with a 75% homology to P2Y10 at the amino acid level. The *A630033H20* locus is next to that of *P2Y10*, indicating that these two genes were generated by gene duplication. Interestingly, the human *A630033H20* gene identified in the database, has frame shift mutations that result in a shortened form composed of 114 amino acids. The product of the human gene does not function as a LysoPS receptor (A. Inoue, unpublished observations), indicating that the gene is a pseudogene. In rodents, however, A630033H20 is functional; and according to the public database, it is highly expressed in lymphoid organs such as spleen and lymph nodes. In mice, the expression patterns of A630033H20 and P2Y10 are similar, so that these receptors may have redundant roles. Like P2Y10, A630033H20 coupled with $G\alpha_{12/13}$ (36). Because of these properties, we propose to name A630033H20 as LPS_{2L} (LPS_2-like).

GPR174/LPS_3

GPR174 shows the highest homology to P2Y10 and A630033H20 with ~50% identity at the amino acid level. These three GPCRs seem to form a subfamily within the P2Y family (Fig. 3). Like P2Y10 and A630033H20, GPR174 is activated by LysoPS (54). The expression pattern of GPR174 is similar to the expression pattern of P2Y10 and A630033H20 with high expression in lymphoid tissues. However, GPR174 is also strongly expressed in some melanoma cells (55). GPR174 mainly coupled with both $G\alpha_s$ and $G\alpha_{13}$ (54). Given that $G\alpha_{13}$ signaling is induced by the three LysoPS receptors (P2Y10, A630033H20, and GPR174) which show similar expression patterns, it is likely that these three LysoPS receptors share redundant functions in activating the $G\alpha_{13}$ pathway. On the other hand, because there is only one LysoPS receptor (GPR174) that is coupled with $G\alpha_s$, GPR174 may have a unique role in regulating $G\alpha_s$ signaling. Like *P2Y10* and *A630033H20*, *GPR174* is on Xq21.1 in humans; and, interestingly, its locus is close to loci associated with the risk for Graves' disease, an autoimmune disease (56, 57) (Table 2). Thus, LysoPS may serve as an immunomodulator through GPR174.

LPI

Actions of LPI

The role of LPI was first demonstrated in 1986, when it was shown to stimulate the release of insulin from pancreatic cells (58). Subsequent studies found that LPI is produced in various cell systems and that it induces a number of cellular events (59). In addition, LPI is a biomarker for certain cancers (60) and gynecological diseases. LPI also has neuroprotective effects in a model of global cerebral ischemia and in a model of glutamate excitotoxicity in neuronal cultures (60). LPI was also identified as a ligand for GPR55 (61), which has roles in cancer progression, bone regulation, endothelial function, inflammation, and pain (**Fig. 5**, Table 1).

GPR55

Human GPR55 is 319 amino acids long and its gene maps to human chromosome 2q37. A database search for sequences similar to human GPR55 revealed that GPR55 is conserved among vertebrates from fish to mammals. The closest homologs to GPR55, as judged by amino acid homology, are LPA_6/P2Y5 (29%), LPA_4/GPR23 (30%), GPR35 (27%), and the chemokine receptor CCR4 (23%).

Two cannabinoid receptors (CB1 and CB2) have been identified. GPR55 has been proposed to be another cannabinoid receptor even though it has no similarity to CB1 and CB2. Classically, most cannabinoid ligands interact with CB1 and CB2. However, pharmacological data and studies using CB1 and CB2 KO mice have suggested that additional cannabinoid-sensitive targets exist. As a result, AstraZeneca and GlaxoSmithKline suggested that GPR55 was activated by a range of endogenous plant and synthetic cannabinoids (62, 63). However, to date, the most potent ligand identified for GPR55 is LPI (64). Although GPR55 clearly interacts with certain cannabinoid ligands, it is currently not clear whether CB1/CB2-independent cannabinoid actions are mediated by GPR55.

GPR55 appears primarily to couple to a $G\alpha_{13}$. In HEK293 cells, as well as in human neutrophils, activation of GPR55 by LPI led to the formation of filamentous actin, which was dependent on the presence of functional $G\alpha_{13}$, RhoA, and ROCK (65, 66). In a single-cell Ca^{2+} imaging approach, activation of GPR55 also led to an oscillatory Ca^{2+} response. In this response, phospholipase C-mediated inositol 1,4,5-triphosphate formation and

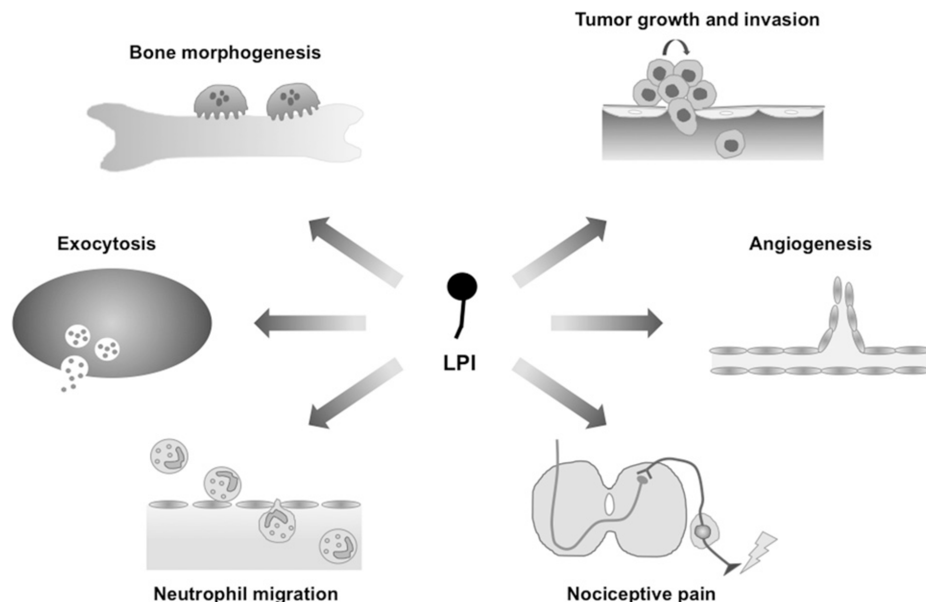
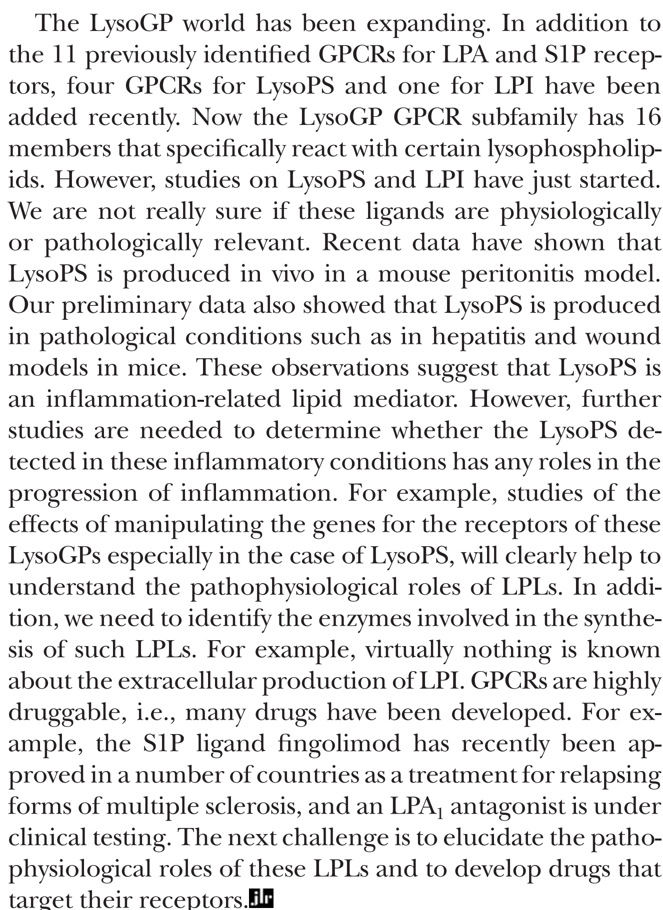


Fig. 5. Biological roles of LPI/GPR55. GPR55 KO mice show phenotypes in bone mass, inflammation, angiogenesis, and hyperalgesia.

subsequent release of Ca^{2+} from internal stores occur in a downstream signaling cascade involving $G\alpha_{13}$-RhoA-ROCK. Thus, GPR55 signaling evoked by LPI activates RhoA and ROCK and induces cytoskeletal change and prolonged and oscillatory Ca^{2+} release from intracellular stores, culminating in the induction of a variety of transcription factors with the potential to significantly alter cellular physiology.

At the cellular level, LPI induced many cellular responses through GPR55 (Tables 1, 2), which implicates the LPI-GPR55 axis in many pathophysiological processes. Male GPR55 KO mice exhibit a clear phenotype with high bone mass, although this is not observed in females (67). GPR55 is expressed in osteoclasts, and GPR55 activation in the cells results in osteoclastogenesis, cell polarization and bone resorption. In male GPR55 KO mice, osteoclast numbers were increased significantly. These findings indicate that the LPI-GPR55 axis affects differentiation and/or proliferation of osteoclasts and thus regulates bone metabolism. GPR55 KO mice were also reported to be resistant to mechanical hyperalgesia associated with Freund's complete adjuvant-induced inflammation or partial nerve ligation (68). In GPR55 KO female mice, the onset of experimentally autoimmune encephalomyelitis was delayed and the symptoms were less severe than those in WT mice (69).

Now new synthetic ligands selective for GPR55 and GPR55 KO mice are available, and these tools will clearly be helpful in uncovering the true significance of GPR55. Furthermore, emerging data suggest that other endogenous lipid ligands interact with GPR55. For example, *N*-arachidonoyl serine (ARA-S) and LPG can activate GPR55. Although the most potent known ligand for GPR55 is LPI, it should be kept in mind that some human lysophospholipids have sugar moieties other than inositol. Thus, the possibility that the major ligand of GPR55 is one of these lysophospholipids cannot be ruled out.



CONCLUSIONS AND FUTURE PROSPECTS

The LysoGP world has been expanding. In addition to the 11 previously identified GPCRs for LPA and S1P receptors, four GPCRs for LysoPS and one for LPI have been added recently. Now the LysoGP GPCR subfamily has 16 members that specifically react with certain lysophospholipids. However, studies on LysoPS and LPI have just started. We are not really sure if these ligands are physiologically or pathologically relevant. Recent data have shown that LysoPS is produced in vivo in a mouse peritonitis model. Our preliminary data also showed that LysoPS is produced in pathological conditions such as in hepatitis and wound models in mice. These observations suggest that LysoPS is an inflammation-related lipid mediator. However, further studies are needed to determine whether the LysoPS detected in these inflammatory conditions has any roles in the progression of inflammation. For example, studies of the effects of manipulating the genes for the receptors of these LysoGPs especially in the case of LysoPS, will clearly help to understand the pathophysiological roles of LPLs. In addition, we need to identify the enzymes involved in the synthesis of such LPLs. For example, virtually nothing is known about the extracellular production of LPI. GPCRs are highly druggable, i.e., many drugs have been developed. For example, the S1P ligand fingolimod has recently been approved in a number of countries as a treatment for relapsing forms of multiple sclerosis, and an LPA_1 antagonist is under clinical testing. The next challenge is to elucidate the pathophysiological roles of these LPLs and to develop drugs that target their receptors.

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