

INTERNATIONAL UNION OF BASIC AND CLINICAL PHARMACOLOGY REVIEW

Lysophospholipid receptor nomenclature review: IUPHAR Review 8

Yasuyuki Kihara¹, Michael Maceyka², Sarah Spiegel² and Jerold Chun¹

¹Molecular and Cellular Neuroscience Department, Dorris Neuroscience Center, The Scripps Research Institute, La Jolla, CA, USA, and ²Department of Biochemistry and Molecular Biology and the Massey Cancer Center, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA

Lysophospholipids encompass a diverse range of small, membrane-derived phospholipids that act as extracellular signals. The signalling properties are mediated by 7-transmembrane GPCRs, constituent members of which have continued to be identified after their initial discovery in the mid-1990s. Here we briefly review this class of receptors, with a particular emphasis on their protein and gene nomenclatures that reflect their cognate ligands. There are six lysophospholipid receptors that interact with lysophosphatidic acid (LPA): protein names LPA₁ – LPA₆ and italicized gene names *LPAR1-LPAR6* (human) and *Lpar1-Lpar6* (non-human). There are five sphingosine 1-phosphate (S1P) receptors: protein names S1P₁–S1P₅ and italicized gene names *S1PR1-S1PR5* (human) and *S1pr1-S1pr5* (non-human). Recent additions to the lysophospholipid receptor family have resulted in the proposed names for a lysophosphatidyl inositol (LPI) receptor – protein name LPI₁ and gene name *LPIR1* (human) and *Lpir1* (non-human) – and three lysophosphatidyl serine receptors – protein names LyPS₁, LyPS₂, LyPS₃ and gene names *LYPSR1-LYPSR3* (human) and *Lypsr1-Lypsr3* (non-human) along with a variant form that does not appear to exist in humans that is provisionally named LyPS_{2L}. This nomenclature incorporates previous recommendations from the International Union of Basic and Clinical Pharmacology, the Human Genome Organization, the Gene Nomenclature Committee, and the Mouse Genome Informatix.

Abbreviations

DRG, dorsal root ganglia; CNS, central nervous system; HGNC, Gene Nomenclature Committee; HUGO, Human Genome Organization; LPA, lysophosphatidic acid; LPI, lysophosphatidyl inositol; LysoPS, lysophosphatidyl serine; MGI, Mouse Genome Informatix; MS, multiple sclerosis; PSNL, partial sciatic nerve ligation; SC, Schwann cell; S1P, sphingosine 1-phosphate; VZ, ventricular zone

Correspondence

Sarah Spiegel, Department of Biochemistry and Molecular Biology and the Massey Cancer Center, School of Medicine, Virginia Commonwealth University, 1101 E. Marshall Street, Richmond, VA 23298, USA. E-mail: sspiegel@vcu.edu;
Jerold Chun, Molecular and Cellular Neuroscience Department, Dorris Neuroscience Center, The Scripps Research Institute, DNC-118, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA. E-mail: jchun@scripps.edu

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This paper, written by members of the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) subcommittees for the lysophospholipid (lysophosphatidic acid and S1P) receptors, confirms the existing nomenclature for these receptors and reviews our current understanding of their structure, pharmacology and functions, and their likely physiological roles in health and disease. More information on these receptor families can be found in the Concise Guide to PHARMACOLOGY (<http://onlinelibrary.wiley.com/doi/10.1111/bph.12445/abstract>) and for each member of the family in the corresponding database (<http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=36&familyType=GPCR>); and <http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=135&familyType=GPCR>).

Table 1

Links to online information in the IUPHAR/BPS Guide to PHARMACOLOGY

Targets	Ligands
Akt	[³ H]-LPA
Cannabinoid receptors	1-Oleoyl-LPA
COX-2	2-Oleoyl-LPA
EGF receptor	AFD (R)
ERK1/2	Alkyl OMPT
GPR34	AM966
GPR55	AUY954
GPR174	Bupivacaine
LPA ₁ receptor	CYM5181
LPA ₂ receptor	CYM-5442
LPA ₃ receptor	EGF
LPA ₄ receptor	Oestrogen
LPA ₅ receptor	Farnesyl diphosphate
LPA ₆ receptor	Farnesyl monophosphate
Lysophospholipid (LPA) receptors	Fingolimod
MAPK	FTY720
Metalloproteinases	FTY720-P
MMP9	IL-13
P2Y ₁₀	IL-17
PLC	IL-6
Protease-activated receptor 1	IL-2
ROCK	JTE-013
S1P receptors	Ki16425
Sphingosine kinase 1	LPA
S1P ₁ receptor	LP)
S1P ₂ receptor	LPC
S1P ₃ receptor	LysoPS
S1P ₄ receptor	S1P
S1P ₅ receptor	VEGF
Sodium/NHE3	VPC12249
Urokinase-type plasminogen activator	VPC23019
	VPC44116
	W146

This table lists protein targets and ligands that are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and the Concise Guide to PHARMACOLOGY 2013/14 (Alexander *et al.*, 2013a,b,d).

Introduction

The biological and pathophysiological functions of the small signalling lipids known as lysophospholipids continues to expand, with roles that involve virtually every vertebrate organ system (Fukushima *et al.*, 2001; Ishii *et al.*, 2004; Choi *et al.*, 2010; Mutoh *et al.*, 2012; Choi and Chun, 2013). The overwhelming majority of effects, and all activities that have led to actual medicines or to compounds that have entered late-stage clinical trials, rely mechanistically on lys-

ophospholipid receptors. All *bona fide* receptors are of the 7-transmembrane, GPCR class (Table 1 and Figure 1).

Various orphan receptor names have been used over the years; however, receptor identities have led to two nomenclatures: the first used in pharmacological fields and supported by the International Union of Basic and Clinical Pharmacologists (IUPHAR), and the second used in genetic or genomic fields, as represented by the Human Genome Organization (HUGO), Gene Nomenclature Committee (HGNC), and the Mouse Genome Informatix (MGI) Guide-

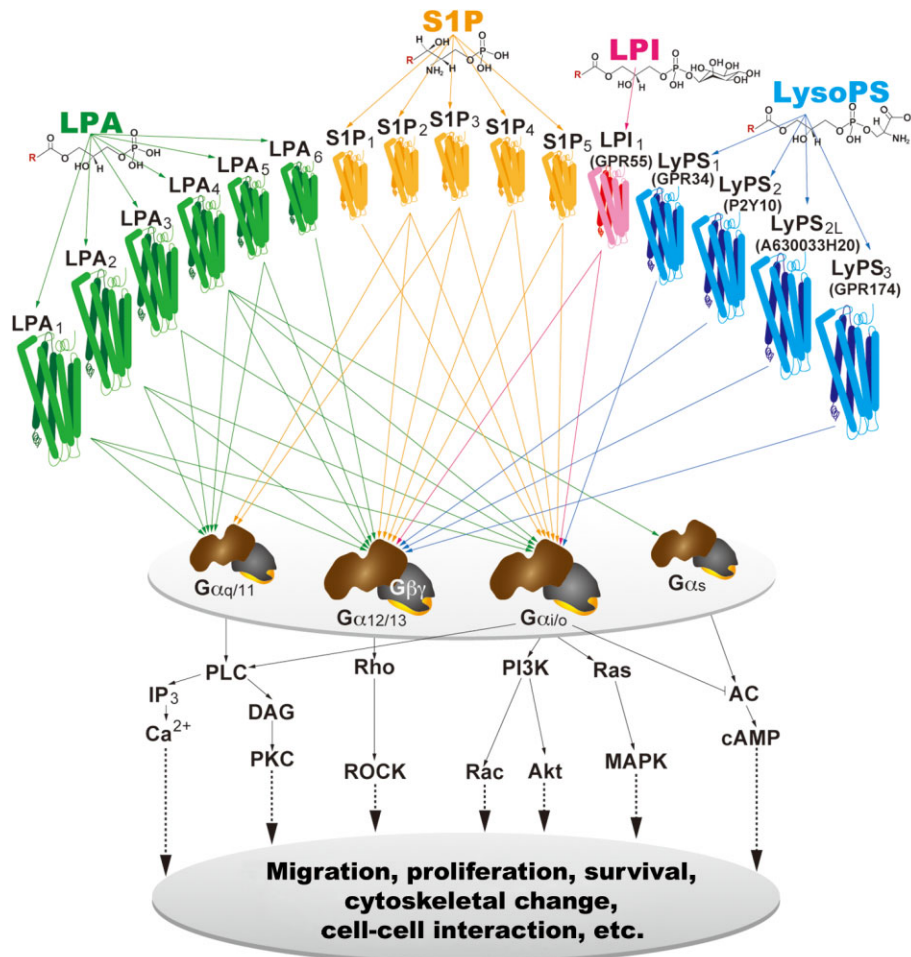


Figure 1

Lysophospholipid receptors and their intracellular signalling pathways. Lysophospholipid ligands (LPA, S1P, LPI and LysoPS) bind to their specific GPCRs, which activate heterotrimeric G-proteins (defined here by their α subunits) to initiate downstream signalling cascades. *R* in the chemical structures is a variable acyl side chain.

lines for Nomenclature of Genes, based upon the 2011 International Committee on Standardized Genetic Nomenclature for Mice. We briefly review these lysophospholipid receptors and their names, and suggest use of a hybrid nomenclature wherein protein names are referred to by their original IUPHAR names (Chun *et al.*, 2002; 2010; Davenport *et al.*, 2013), while HGNC nomenclatures are used to identify the human genes, and MGI nomenclatures for mice are extended to cover non-human genes (Table 2). In each subheading of this review, the protein name is followed by the human and non-human gene names. Recent additions to the lysophospholipid receptor family include glycerophospholipid species lysophosphatidyl inositol (LPI) and lysophosphatidyl serine (LysoPS); names for these newer receptors and genes have been proposed, which generally follow the receptor protein and gene for other lysophospholipid receptors and have been incorporated in this review. The names of established receptors and their human and non-human gene names start each subsection, while new receptors are treated under a separate heading.

Lysophosphatidic acid (LPA) receptors

The many effects of LPA are mediated through the six currently recognized LPA receptors, LPA₁₋₆. These 7-transmembrane GPCRs couple to one or more of the four classes of heterotrimeric G-proteins, commonly defined by their G_{α} proteins ($G_{\alpha 12/13}$, $G_{\alpha q/11}$, $G_{\alpha i/o}$, and $G_{\alpha s}$). Less explored is possible signalling through these receptors that do not require heterotrimeric G-proteins (Rajagopal *et al.*, 2005). Activation of these receptors and G-proteins can initiate myriad downstream pathways that in turn, produce a similarly diverse range of biological and pathological effects (Gilman, 1987). The agonists and antagonists for these receptors and their efficacy are summarized in Table 3.

LPA₁/LPAR1/*Lpar1*

The first receptor identified for any lysophospholipid came from studies on the brain, which identified LPA₁ (Hecht *et al.*, 1996), a receptor that mediates the effects of LPA. *LPAR1*

Table 2
Lysophospholipid receptors

Ligand	Protein name ^a	G-proteins	Human			Mouse/non-human						
			Gene name	Chr	AA	MM ^b	Identity ^c	Gene name	Chr	AA	MM ^a	Previous orphan names ^a
LPA	LPA ₁	G _s , G _{i/0} , G _{q/11} , G _{12/13}	LPAR1	9q31.3	364	41 109	97.3%	Lpar1	4	364	41 119	vzg-1, edg-2, mrecl.3, lpA1
	LPA ₂	G _s , G _{i/0} , G _{q/11} , G _{12/13}	LPAR2	19p12	351	39 084	83.5%	Lpar2	8	348	38 777	edg-4, lpA2
	LPA ₃	G _s , G _{i/0} , G _{q/11} , G _{12/13}	LPAR3	1p22.3-p31.1	353	40 128	91.2%	Lpar3	3	354	40 316	edg-7, lpA3
	LPA ₄	G _s , G _{i/0} , G _{q/11} , G _{12/13}	LPAR4	Xq21.1	370	41 895	98.4%	Lpar4	X	370	41 899	P2Y9/GPR23
	LPA ₅	G _s , G _{i/0} , G _{q/11} , G _{12/13}	LPAR5	12p13.31	372	41 347	79.0%	Lpar5	6	372	41 394	GPR92
	LPA ₆	G _s , G _{i/0} , G _{q/11} , G _{12/13}	LPAR6	13q14	344	39 392	93.0%	Lpar6	14	344	39 439	P2Y5
STP	STP ₁	G _s , G _{i/0} , G _{q/11} , G _{12/13}	STPR1	1p21	382	42 811	94.2%	STpr1	3	382	42 639	edg-1, lpB1
	STP ₂	G _s , G _{i/0} , G _{q/11} , G _{12/13}	STPR2	19p13.2	353	38 867	90.7%	STpr2	9	352	38 829	edg-5, lpB2, AGR16, H218
	STP ₃	G _s , G _{i/0} , G _{q/11} , G _{12/13}	STPR3	9q22.1-q22.2	378	42 250	87.3%	STpr3	13	378	42 270	edg-3, lpB3
	STP ₄	G _s , G _{i/0} , G _{q/11} , G _{12/13}	STPR4	19p13.3	384	41 623	81.1%	STpr4	10	386	42 263	edg-6, lpC1
	STP ₅	G _s , G _{i/0} , G _{q/11} , G _{12/13}	STPR5	19p13.2	398	41 775	83.8%	STpr5	9	400	42 331	edg-8, lpB4, Nrg-1
LPI	LPI ₁	G _s , G _{i/0} , G _{q/11} , G _{12/13}	LPIR1	2q37	319	36 637	74.4%	Lpir1	1	327	38 090	GPR55
LysoPS	LysoPS ₁	G _s , G _{i/0} , G _{q/11} , G _{12/13}	LysoPSR1	Xp11.4	381	43 860	89.0%	Lyprs1	X	375	43 173	GPR34
	LysoPS ₂	G _s , G _{i/0} , G _{q/11} , G _{12/13}	LysoPSR2	Xq21.1	339	38 774	82.9%	Lyprs2	X	328	37 244	P2Y10
	LysoPS ₃	G _s , G _{i/0} , G _{q/11} , G _{12/13}	LysoPSR3	Xq21.1	333	38 503	87.8%	Lyprs3	X	335	38 761	GPR174/FKSG79
	LysoPS _{2L}	G _s , G _{i/0} , G _{q/11} , G _{12/13}	N/A	N/A	N/A	N/A	N/A	pending	X	352	40 383	A630033H20

Chr, chromosome; AA, amino acids; MM, molecular mass. Utilized G-proteins are indicated in black.

^aHyperlinks are provided to online information in the IUPHAR/BPS Guide to PHARMACOLOGY.

^bMMs were obtained from UniProt (UniProt Consortium, 2013).

^cIdentities between human and mouse lysophospholipid receptors were calculated in UniProt (UniProt Consortium, 2013).

Table 3

Pharmacological tools for LPA receptors and their efficacy

Compounds ^a	Units (nM)	LPA ₁	LPA ₂	LPA ₃	LPA ₄	LPA ₅	LPA ₆	Assay	References
1-Oleoyl-LPA	Kd	69	64	N/A	100	89	N/A	Binding	Yanagida <i>et al.</i> , 2009
	EC ₅₀	64–200	9–10	75–321	26	11	1495	Ca ²⁺	Bandoh <i>et al.</i> , 2000; Yanagida <i>et al.</i> , 2013
2-Oleoyl-LPA	EC ₅₀	~200	~10	~10	N/A	N/A	N/A	Ca ²⁺	Bandoh <i>et al.</i> , 2000
AGP	EC ₅₀	1500	101	N/A	303	2	N/A	Ca ²⁺	Williams <i>et al.</i> , 2009
Alkyl OMPT	EC ₅₀	794	N/A	62	N/A	N/A	N/A	Ca ²⁺	Qian <i>et al.</i> , 2006
VPC31143(R)	EC ₅₀	59	16	130	341	126	1484	Ca ²⁺	Yanagida <i>et al.</i> , 2013
	EC ₅₀	8	117	322	N/A	N/A	N/A	GTPγS	Heise <i>et al.</i> , 2001
VPC31144(S)	EC ₅₀	461	2592	7123	18	16	4835	Ca ²⁺	Yanagida <i>et al.</i> , 2013
	EC ₅₀	>5000	2645	4349	N/A	N/A	N/A	GTPγS	Heise <i>et al.</i> , 2001
Farnesyl diphosphate	IC ₅₀ ,EC ₅₀	N/A	2100	4600	1980	40 ^b	N/A	Ca ²⁺	Williams <i>et al.</i> , 2009
Farnesyl monophosphate	IC ₅₀ ,EC ₅₀	N/A	161	517	1450	49 ^b	N/A	Ca ²⁺	Williams <i>et al.</i> , 2009
Ki16425	(Ki)	(250)	(5600)	(360)	N/A	N/A	N/A	GTPγS	Ohta <i>et al.</i> , 2003
VPC12249	(Ki)	(137)	N/A	(428)	N/A	N/A	N/A	GTPγS	Heise <i>et al.</i> , 2001
	IC ₅₀ (Ki)	109 (18)	N/A	175	N/A	N/A	N/A	GTPγS	Heasley <i>et al.</i> , 2004
AM966	IC ₅₀	17	1700	1600	7700	8600	N/A	Ca ²⁺	Swaney <i>et al.</i> , 2010

N/A, not applicable.

^aHyperlinks are provided to online information in the IUPHAR/BPS Guide to PHARMACOLOGY.^bBoth farnesyl diphosphate and farnesyl monophosphate are reported to be antagonists for LPA₂, ₃, ₄, but agonist for LPA₅.

encodes a receptor of 364 amino acids, with a molecular mass of ~41 kDa. The human gene is located on chromosome 9 (9q31.3), and consists of at least five exons. A gene variant of *Lpar1* (*Lpar1-mrec1.3*) lacks a predicted 18 amino acids from the amino terminus (Contos and Chun, 1998); however, its function and significance remain unclear. This receptor couples to three G_α proteins – G_{αi/o}, G_{αq/11}, and G_{α12/13}, which can result in the activation of a range of well-known, downstream pathways that include Akt, Rho, MAPK, and PLC. These pathways in turn can account for many of the cellular responses initiated by LPA₁ such as changes in cell shape through alterations in the actin cytoskeleton, cell migration, adhesion and cell–cell contact, and Ca²⁺ mobilization (reviewed in Contos *et al.*, 2000b; Fukushima *et al.*, 2001; Ishii *et al.*, 2004; Choi *et al.*, 2010; Mutoh *et al.*, 2012; Choi and Chun, 2013).

Expression of *Lpar1/LPAR1* is widespread, and can be found in most tissues at various stages of development albeit with non-uniform expression (An *et al.*, 1998; Contos *et al.*, 2000b; Ohuchi *et al.*, 2008; Ye, 2008), particularly within the developing nervous system (reviewed in Contos *et al.*, 2000b; Ishii *et al.*, 2004) where it is found in the neuroproliferative ventricular zone (VZ) as well as superficial marginal zone and meninges (Hecht *et al.*, 1996). By birth, the VZ dissipates as does the expression of *Lpar1* in this region; however, it reappears in oligodendrocytes that are involved in myelination.

Knockout mice have provided important insights for most of the lysophospholipid receptors, beginning with *Lpar1*^{-/-} mice that exhibit ~50% perinatal lethality (Contos *et al.*, 2000a) attributable to olfactory deficits that affect suckling as well as possible central mechanisms that show back-

ground strain dependence (Weiner *et al.*, 2001; Estivill-Torrús *et al.*, 2008; Matas-Rico *et al.*, 2008). The developing cerebral cortex in particular is affected by LPA signalling including overall organization (Kingsbury *et al.*, 2003), cell survival, migration, proliferation and process outgrowth (Contos *et al.*, 2000b; Fukushima *et al.*, 2000; 2002; Campbell and Holt, 2001; Kingsbury *et al.*, 2003; Yuan *et al.*, 2003).

Effects on the normal development and organization of the brain have pointed towards LPA influences on central nervous system (CNS) disorders. In particular, neuropsychiatric disorders that could arise prenatally and that could involve bleeding, hypoxia and immunological challenge, as proposed for autism and schizophrenia (Hultman *et al.*, 1999; Cannon *et al.*, 2002; Brimacombe *et al.*, 2007; Byrne *et al.*, 2007), could involve LPA signalling. Proof-of-concept for this idea comes from studies of congenital or fetal hydrocephalus (Yung *et al.*, 2011), one of the most common neurological disorders of newborns and young children, wherein models of FH can be rescued by removal of LPA signalling. Schizophrenia-relevant signals include *Lpar1*^{-/-} mutant mice that show deficits in pre-pulse inhibition 5-HT levels and glutamatergic synapses (Harrison *et al.*, 2003; Santin *et al.*, 2009; Musazzi *et al.*, 2010; Roberts *et al.*, 2005), while a variant mutant, *malPA1*^{-/-}, display a range of other defects (Harrison *et al.*, 2003; Estivill-Torrús *et al.*, 2008; Santin *et al.*, 2009; Castilla-Ortega *et al.*, 2010).

Glia are also influenced by LPA₁ signalling. Astrocytes express most LPA receptors (LPA₁₋₅; Shano *et al.*, 2008), and upon treatment with LPA, initiate a wide range of effects *in vitro* including morphological changes and stabilization of stress fibres (Manning and Sontheimer, 1997; Suidan *et al.*,

1997; de Sampaio *et al.*, 2008) that may contribute to astrogliosis (Sorensen *et al.*, 2003, reviewed in Noguchi *et al.*, 2009). Neuronal differentiation can also be influenced by LPA₁ and LPA₂ (Spohr *et al.*, 2008). Myelinating cells, oligodendrocytes (Allard *et al.*, 1998; Weiner *et al.*, 1998; Yu *et al.*, 2004) and Schwann cells (SCs) all, express LPA₁ and LPA₂ (Weiner *et al.*, 2001; Kobashi *et al.*, 2006) and *Lpar1*($-/-$) mutants show increased survival via the G_{ai}-PI3K-Akt pathway (Weiner and Chun, 1999) and higher levels of Schwann cell apoptosis within the sciatic nerves (Inoue *et al.*, 2004). Myelinating cells, oligodendrocytes, and Schwann cells all express LPA₁ and LPA₂, and *Lpar1*($-/-$) mutants show increased survival via the Gai-PI3K-Akt pathway and higher levels of Schwann cell apoptosis within the sciatic nerves.

LPA receptors have also been linked to neuropathic pain (Inoue *et al.*, 2004) using an animal model of partial sciatic nerve ligation (PSNL) in *Lpar1*^{-/-} mutants, which may involve demyelination (Inoue *et al.*, 2004; Fujita *et al.*, 2007). Other LPA receptors also appear to participate, including LPA₅ (Lin *et al.*, 2012). Moreover, autotaxin (gene name *ENPP2/Enpp2*) that converts lysophosphatidylcholine (LPC) into LPA (Inoue *et al.*, 2008a,b) also affects neuropathic pain animal models, such that *Enpp2*^{+/-} mice show protection in a PSNL model (Inoue *et al.*, 2008a). These observations support roles for LPA signalling in neuropathic pain.

LPA signalling is also found to play a role in obesity and fibrosis. LPA signalling can affect both proliferation and differentiation of pre-adipocytes (Valet *et al.*, 1998; Ferry *et al.*, 2003; Simon *et al.*, 2005; Nobusue *et al.*, 2010), and LPA's effects have been observed in adipocytes, including those from *db/db* mice (type II diabetes obese-diabetic mice; Ferry *et al.*, 2003; Boucher *et al.*, 2005). Fibrosis links to LPA include in the lung, kidney, and liver (Ikeda *et al.*, 1998; Wu and Zern, 2000; Pradere *et al.*, 2007; 2008; Watanabe *et al.*, 2007; Tager *et al.*, 2008). LPA₁ is expressed on both cancer cell lines and in tumours, where it can have a variety of effects, both cancer promoting and inhibiting (Yamada *et al.*, 2004; Yu *et al.*, 2008; Li *et al.*, 2009; Shin *et al.*, 2009). LPA₁ mutations have been reported in an osteosarcoma cell line (Okabe *et al.*, 2010) and in rat lung and liver tumours (Obo *et al.*, 2009).

LPA₂/LPAR2/*Lpar2*

LPA₂ is encoded by *LPAR2* on chromosome 19 (19p12) and encodes 348 amino acids for a calculated molecular mass of ~39 kDa (Contos and Chun, 2000). It is ~50% identical at the amino acid level to LPA₁. *Lpar2/LPAR2* is expressed at relatively high levels in leukocytes, kidney, testis, and uterus (An *et al.*, 1998; Contos and Chun, 2000). Relatively low levels are present in most other organs, including the brain (Ohuchi *et al.*, 2008). LPA₂ couples to the same heterotrimeric G-proteins as LPA₁: G_{ai/o}, G_{aq/11}, and G_{o12/13} (Contos *et al.*, 2000b), and like LPA₁, can promote cell migration and survival (Goetzl *et al.*, 1999; Zheng *et al.*, 2000; 2001; Deng *et al.*, 2002; Panchatcharam *et al.*, 2008). LPA₂ may also produce effects via TRIP6, a focal adhesion molecule (Lai *et al.*, 2005; 2007), and both zinc finger or PDZ-domain protein interactions have been reported (Lin and Lai, 2008), along with MAGI3 and Na⁺/H⁺ exchanger regulatory factor 2 (NHERF) interactions (Lee *et al.*, 2011). LPA₂ signalling may inhibit EGF-induced migration of pancreatic cancer cells through G_{o12/13}/Rho (Komachi *et al.*, 2009). SCs up-regulate myelin markers like P0

protein via LPA₂, including after insult by injury, nerve transection, and in PSNL models of neuropathic pain (Weiner *et al.*, 2001; Inoue *et al.*, 2004). It has also been reported to modulate hippocampal excitatory synaptic transmission (Trimbuch *et al.*, 2009). LPA₂, in conjunction with LPA₁, can also alter cerebral cortical architecture in *ex vivo* cultures after exposure to exogenous LPA (Kingsbury *et al.*, 2003), effects of which are lost in *Lpar1*^{-/-}/*Lpar2*^{-/-} mutant mouse cultures.

Links to cancer have been reported for LPA₂ in promoting neoplasms based upon designed or observed overexpression (Kitayama *et al.*, 2004; Lee and Yun, 2010). LPA₂ signalling has also been associated with cancer metastasis and colon endometrial, mesothelia, and ovarian cancer cells (Shida *et al.*, 2003; Jeong *et al.*, 2008; Hope *et al.*, 2009). Instances of cancer inhibition in pancreatic cells have also been reported (Komachi *et al.*, 2009). This influence may involve regulation of a range of factors including Akt/Erk1/2, COX-2, epithelial growth factor receptor, metalloproteinases, VEGF, and urokinase-type plasminogen activator (Huang *et al.*, 2004; Yun *et al.*, 2005; Estrella *et al.*, 2007; Jeong *et al.*, 2008; Shida *et al.*, 2008). Loss-of-function for LPA₂ generally appears to be protective against tumourigenesis (Masiello *et al.*, 2006; Estrella *et al.*, 2007; Yu *et al.*, 2008; Zhao *et al.*, 2013).

In the immune system, *Lpar2* (similar to *Lpar1*) is expressed in a variety of immunological organs like the spleen and thymus (Ishii *et al.*, 2004; Kotarsky *et al.*, 2006; Oh *et al.*, 2008), and in lymphocytes (Komachi *et al.*, 2009). LPA₂ is expressed in unstimulated T-cells, as compared with LPA₁ that is predominantly within stimulated T-cells that can influence cell survival (Goetzl *et al.*, 1999). In unstimulated T-cells, LPA₂ is upregulated while LPA₁ is downregulated, leading to LPA-induced chemotaxis and inhibition of (Goetzl *et al.*, 2000; Zheng *et al.*, 2000; 2001). In contrast, activated T-cells upregulate LPA₁ and downregulate LPA₂, leading to inhibited chemotaxis, increased proliferation, and increased IL-2 and IL-13 production upon LPA stimulation (Zheng *et al.*, 2000; Rubinfeld *et al.*, 2006). LPA₂ is also expressed on dendritic cells (Panther *et al.*, 2002; Chen *et al.*, 2006).

LPA₃/LPAR3/*Lpar3*

LPAR3/Lpar3 was identified based upon homology to defined LPA receptor genes and cloned using a degenerate, PCR-based cloning strategy (Bandoh *et al.*, 1999; Im *et al.*, 2000b). *LPAR3* (human chromosomal locus 1p22.3-p31.1) encodes a 353 amino acid, ~40 kDa GPCR, which in mice is ~50% identical in amino acid sequence to LPA₁ and LPA₂. LPA₃ couples to the heterotrimeric G_α proteins G_{ai/o} and G_{aq/11} to mediate downstream signalling pathways including adenyl cyclase activation, PLC activation and Ca²⁺ mobilization, and MAPK activation (Ishii *et al.*, 2000). LPA₃ appears to prefer 2-acyl-LPA containing unsaturated fatty acids (Bandoh *et al.*, 1999; Sonoda *et al.*, 2002).

LPAR3 is expressed in multiple human organs including the brain, heart, lung, ovary, pancreas, prostate, and testis (Bandoh *et al.*, 1999; Im *et al.*, 2000b), as well as mouse lung, testes, kidney, small intestine, spleen, stomach, and heart (Contos *et al.*, 2000b), and during development (Ohuchi *et al.*, 2008). While *Lpar3* null mice are viable, they have defects in the immune system reflecting in part LPA₃-specific dependent activation of chemotaxis of immature, but not mature, dendritic cells (Chan *et al.*, 2007). They also have

effects on zebra fish body asymmetry (Lai *et al.*, 2012) and probably are involved in effects of the nervous system including those involving pain (Ma *et al.*, 2009) and possibly other modalities. However, the most dramatic effect is on embryo implantation and fertility.

Lpar3^{-/-} null female mutants have a prominent reproductive system phenotype whereby normal embryo implantation is disrupted (Ye *et al.*, 2005). Within the uterus, *Lpar3* is specifically expressed in luminal endometrial epithelial cells where it is markedly up-regulated during the brief window of embryo implantation, following which its expression is rapidly down-regulated (Ye *et al.*, 2005). The hormones oestrogen and progesterone influence this expression pattern (Hama *et al.*, 2006), and may play a role in allowing embryos to implant within the uterus. *Lpar3* null mutant mice were found to have abnormal, delayed implantation of embryos that included crowding along the uterine horn and subsequent reductions in live births that could be attributed to maternal effects of LPA₃ loss (Ye *et al.*, 2005). Mechanistic studies demonstrated that LPA₃ promotes COX-2 expression; COX-2 is a rate-limiting enzyme for the production of PGs that are known to be important for fertility, although there is evidence that COX-2-independent functions are involved as well (Hama *et al.*, 2007). This may be relevant for the embryo

spacing phenotype in *Lpar3*^{-/-} mice that could interface with cytosolic PLA_{2α} (cPLA_{2α}) or Wnt/β-catenin signalling, in view of the reminiscent phenotypes in null-mutants for these genes (Song *et al.*, 2002; Mohamed *et al.*, 2005). In addition to this maternal phenotype, combined loss of LPA₁₋₃ that are expressed in the testis (Ishii *et al.*, 2004; Ye, 2008) results in loss of germ cells and progeric azoospermia (Ye, 2008), adding to the reproductive spectrum of effects produced by LPA receptor loss from reproductive tissues (reviewed in Ye, 2008).

LPA₄/LPAR4/*Lpar4*

LPA₄ is notable because it shares less than 20% amino acid sequence identity with LPA₁₋₃ and S1P₁₋₅, and is phylogenetically far from them and located near the P2Y receptor family (Figure 2). Identification of LPA₄ was made by screening orphan receptors, including purine receptor families, using calcium mobilization as a readout for ligand-induced signals (Noguchi *et al.*, 2003). P2Y₉ has ~20% sequence identity to LPA₁₋₃ (Noguchi *et al.*, 2003), yet it responds to LPA and not to assayed nucleosides or nucleotides (Noguchi *et al.*, 2003). *LPAR4* is located on chromosome Xq21.1 and encodes a 370 amino acid protein of ~42 kDa, with mouse *Lpar4* being present on the D-region of chromosome X. *Lpar4* gene expression is observed in the brain, heart, lung, skin, thymus, and

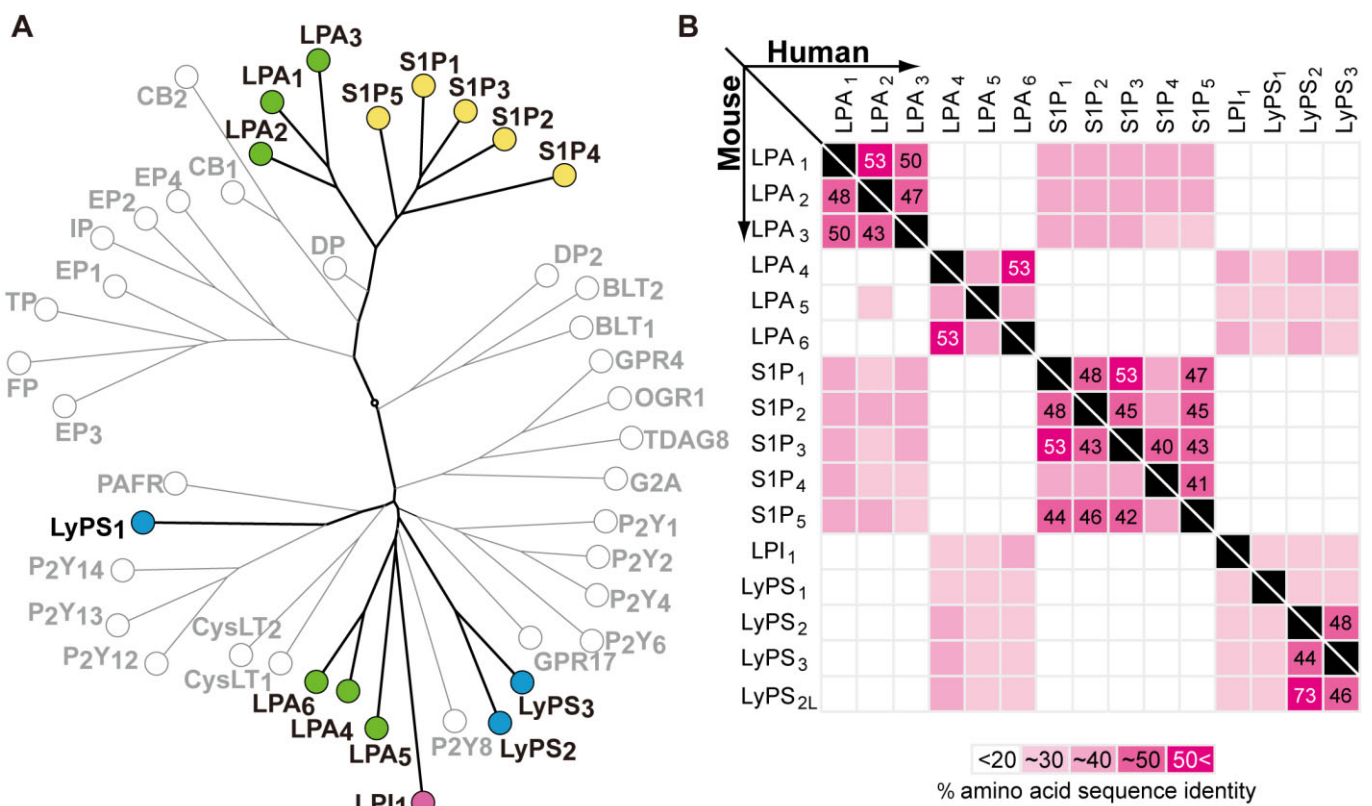


Figure 2

Phylogenetic tree of related GPCRs and amino acid sequence identities. (A) A molecular phylogenetic tree of human GPCRs. The selected GPCR protein sequences were analysed for the phylogenetic reconstruction by the 'All against All' sequence programme at the Computational Biochemistry Research Group server of the ETH Zürich. (B) Pair-wise matrices comparing amino acid sequences of lysophospholipid receptors. The upper and lower matrices specify identities among lysophospholipid receptors in human and mouse respectively. The amino acid sequence identities are shown in a gray-to-white gradient. The numbers in the boxes were calculated by Clustal Omega (Sievers *et al.*, 2011).

uterus (Ishii *et al.*, 2009b). It is also developmentally expressed within the embryonic brain branchial arches, limb buds, liver, maxillary processes, and somites (Ohuchi *et al.*, 2008).

LPA₄ couples to G_α-proteins G_{αs}, G_{αi}, G_{αq}, and G_{α12/13} (Lee *et al.*, 2007), the latter of which activates Rho/ROCK to induce neurite retraction and stress fibre formation seen with activation of other LPA receptors (Lee *et al.*, 2007; Yanagida *et al.*, 2007). It can also induce cell aggregation and adhesion through N-cadherin (Yanagida *et al.*, 2007) and was the first LPA receptor activating G_{αs} activity (Lee *et al.*, 2007) to promote intracellular cAMP accumulation. LPA₄ can transform cells when co-expressed with oncogenic-promoting genes like c-Myc or Tbx2 (Taghavi *et al.*, 2008). It has also been reported to affect immortalized hippocampal progenitor cells (Rhee *et al.*, 2006).

Null mutant mice for *Lpar4* do not show overt abnormalities (Lee *et al.*, 2008) aside from some prenatal loss, probably produced by blood vessel defects that result in abnormal haemorrhage (Sumida *et al.*, 2010). Lymphatic vessels and lymph sacs are also affected during development of the circulatory system (Sumida *et al.*, 2010). Osteoblast differentiation is also inhibited based on cell culture analyses in experiments that knocked down *LPAR4* (Liu *et al.*, 2010). Cells from *Lpar4*^{-/-} mice show reduced cell motility (Lee *et al.*, 2008).

LPA₅/LPAR5/*Lpar5*

LPA₅ was the fifth LPA receptor to be reported (Kotarsky *et al.*, 2006; Lee *et al.*, 2006), sharing ~35% homology with *LPAR4*, while being more dissimilar to *LPAR1-3* (Lee *et al.*, 2006). *LPAR5* has a chromosomal location of 12p13.31 and encodes a 372-amino acid protein with a molecular mass of ~41 kDa, and *Lpar5* is located on chromosome 6. LPA₅ couples to G_{α12/13} and G_{αq} (Lee *et al.*, 2006) and is expressed broadly, with high expression in dorsal root ganglia (DRG), gastrointestinal lymphocytes, heart, platelets, and spleen (Kotarsky *et al.*, 2006; Lee *et al.*, 2006; Amisten *et al.*, 2008). It is also expressed developmentally in the embryonic mouse brain (Ohuchi *et al.*, 2008).

LPA₅-expressing cell lines can induce both neurite retraction and stress fibre formation in response to LPA via the G_{α12/13} pathway, including clear receptor internalization (Lee *et al.*, 2006). It also activates G_{αq}, G_{ai}, leading to intracellular calcium levels (Lee *et al.*, 2006), while also increasing cAMP accumulation via a non-G_{αs} mechanism, based upon mini-gene experiments, which implicates other G-protein involvement (Kotarsky *et al.*, 2006; Lee *et al.*, 2006). LPA₅ signalling also appears to affect intestinal water absorption (Lin *et al.*, 2010) through effects on intestinal epithelial cells, whereby LPA induces Na⁺-dependent water absorption via Na⁺/H⁺ exchanger 3 (NHE3; see Alexander *et al.*, 2013c) and the NHERF2 that recruits NHE3 to intestinal microvilli (Lin *et al.*, 2010). This receptor has also been implicated in neuropathic pain models through mechanisms that appear to be distinct from effects mediated by LPA₁ (Lin *et al.*, 2012).

LPA₆/LPAR6/*Lpar6*

The latest member of the LPA receptor family is LPA₆. LPA₆ is encoded by *LPAR6* on chromosome 13 (13q14) and encodes 344 amino acids for a calculated molecular mass of ~39 kDa.

It is a member of the P2Y receptor family like LPA₄, and was known originally by its orphan name P2Y5, which was identified as a human mutation affecting hair growth (Pasternack *et al.*, 2008). Use of a chimeric G_{α13} protein enabled detection of LPA₆-mediated cAMP accumulation and Rho-dependent morphological alterations, as well as [³H]-LPA binding and LPA-induced [³⁵S]-guanosine 5'-3-O-(thio)triphosphate binding (Yanagida *et al.*, 2009). LPA₆ has some preference for 2-acyl-LPA rather than 1-acyl-LPA. The receptor is distinct from the other five in being somewhat refractory to many cell-based tests, as evidenced by the much higher concentrations of LPA required to get a signal (Yanagida *et al.*, 2009). When co-expressed with a promiscuous G_α protein, which activates G_{αi}, LPA₆ stimulated with LPA increased intracellular Ca²⁺, reduced forskolin-stimulated cAMP and ERK1/2 activation (Lee *et al.*, 2009).

LPA₆ was initially identified as being an autosomal dominant genetic factor for hypotrichosis simplex, a complex of rare diseases characterized by familial hair loss in humans. Independent studies identified LPA₆ mutations in hypotrichosis patients (Pasternack *et al.*, 2008; Shimomura *et al.*, 2009; Nahum *et al.*, 2011). Conceptually linked reports have implicated lipase member H, associated with decreased LPA production in culture studies that then fail to activate LPA₆ (Pasternack *et al.*, 2009; Shinkuma *et al.*, 2010). More recent analyses of this receptor by use of a TGF α shedding assay (Inoue *et al.*, 2012) validate it as an atypical, but legitimate, LPA receptor.

Sphingosine 1-phosphate (S1P) receptors

S1P is a pleiotropic bioactive lipid that is an important regulator of many physiological processes including proliferation, migration, survival, and differentiation and plays important roles in disorders of the immune system and CNS (Maceyka *et al.*, 2012). Most of the actions of S1P are mediated by five specific cognate GPCRs, designated S1P₁-S1P₅ (Chun *et al.*, 2010; Blaho and Hla, 2011). These receptors bind S1P and dihydro-S1P with high affinity and there is very little evidence for additional endogenous ligands. We have summarized the experimental pharmacological tools for S1P receptors in Table 4.

S1P₁/S1PR1/*S1pr1*

S1P₁ was one of the first S1P receptors to be functionally identified (Lee *et al.*, 1998b) and it is the most well studied. Early studies suggested that it might mediate actions of LPA based on its sequence and function (Lee *et al.*, 1998a); however, it is now known to be a selective S1P receptor. *S1PR1* is located on chromosome 1 (1p21) and encodes a 382-amino acid of ~43 kDa that is highly conserved and has 94% sequence identity with the murine receptor. *S1PR1* is the only S1PR that couples exclusively to G_{αi/o}. Although *S1PR1* is ubiquitously expressed (Zhang *et al.*, 1999; McGiffert *et al.*, 2002), its most important functions are in the regulation of trafficking of lymphocytes and other haematopoietic cells and vascular development and integrity. Genetic and pharmacological approaches, together with sophisticated intravi-

Table 4

Pharmacological tools for S1P receptors and their efficacy

Compounds ^a	Units (nM)	S1P ₁	S1P ₂	S1P ₃	S1P ₄	S1P ₅	Assay	References
S1P	EC ₅₀	0.4–79	3.8–8.9	0.16–2	8.6–794	0.5–20	GTPγS	Brinkmann <i>et al.</i> , 2002; Sanna <i>et al.</i> , 2004; Pan <i>et al.</i> , 2006
FTY720-P	EC ₅₀	0.3–6.3	N/A	3.1–4.0	0.6–63.1	0.3–6.3	GTPγS	Brinkmann <i>et al.</i> , 2002; Pan <i>et al.</i> , 2006
AUY954	EC ₅₀	1.2	N/A	1210	N/A	340	GTPγS	Pan <i>et al.</i> , 2006
SEW2781	EC ₅₀	13–28.8	N/A	N/A	N/A	N/A	GTPγS	Sanna <i>et al.</i> , 2004; Gonzalez-Cabrera <i>et al.</i> , 2008
AFD (R)	EC ₅₀	2.5	N/A	4	4	1.3	GTPγS	Brinkmann <i>et al.</i> , 2002
CYM5181	EC ₅₀	3.4	N/A	N/A	N/A	N/A	GTPγS	Gonzalez-Cabrera <i>et al.</i> , 2008
CYM-5442	EC ₅₀	1.2	N/A	N/A	N/A	N/A	GTPγS	Gonzalez-Cabrera <i>et al.</i> , 2008
W146	EC ₅₀ (K _i)	398 (77)	N/A	N/A	N/A	N/A	GTPγS	Sanna <i>et al.</i> , 2006
NIBR-0213	(K _i)	(2)	N/A	N/A	N/A	N/A	GTPγS	Quancard <i>et al.</i> , 2012
VPC03090-P	EC ₅₀ (K _i)	(21–24)	N/A	(51–58.7)	17.7 ^b	2.4 ^b	GTPγS	Kennedy <i>et al.</i> , 2011
VPC23019	(K _i)	(1)	N/A	(7.6)	N/A	N/A	Binding ^c	Davis <i>et al.</i> , 2005
VPC44116	EC ₅₀ (K _i)	(30)	N/A	(300)	6100 ^b	33 ^b	GTPγS	Foss <i>et al.</i> , 2007
JTE-013	IC ₅₀	N/A	17	N/A	N/A	N/A	Binding ^c	Osada <i>et al.</i> , 2002

N/A, not applicable.

^aHyperlinks are provided to online information in the IUPHAR/BPS Guide to PHARMACOLOGY.^bBoth VPC03090-P and VPC44116 are reported to be antagonists for S1P₁, ₃, but agonist for S1P_{4,5}.^cK_i and IC₅₀ was estimated by determining the competitive binding of radioisotope-labelled S1P.

tal staining, have established that S1P₁ controls the trafficking and migration of numerous types of haematopoietic cells, including T and B lymphocytes, NK T-cells, dendritic cells, macrophages, neutrophils, haematopoietic progenitors, mast cells, and osteoclasts (Matloubian *et al.*, 2004; Spiegel and Milstien, 2011; Cyster and Schwab, 2012), in both homeostatic and disease settings. Blood and lymph contain high nM levels of S1P, which form a gradient between the much lower levels in tissues (Pappu *et al.*, 2007; Pham *et al.*, 2010). When S1P₁ on lymphocytes recognizes high levels of S1P in the blood and lymph, egress of the cells from lymphoid organs into the blood is promoted through activation of the G_α-phosphatidylinositol-3-kinase pathway and the small GTPase Rac (Spiegel and Milstien, 2011; Cyster and Schwab, 2012). Down-regulation or desensitization of S1P₁ enables lymphocytes to subsequently migrate from the blood into tissues (Schwab and Cyster, 2007).

The immunomodulatory drug FTY720/fingolimod, which has been approved by the Food and Drug Administration for the treatment of relapsing forms of multiple sclerosis (MS) (Chun and Hartung, 2010; Chun and Brinkmann, 2011; Cohen and Chun, 2011), is phosphorylated *in vivo* to FTY720-P, producing the active form of the drug (Brinkmann *et al.*, 2010). FTY720-P is a structural analogue of S1P and an agonist of S1P₁, S1P₃, S1P₄, and S1P₅. However, persistent activation of S1P₁ by FTY720-P causes its internalization and degradation and thus it acts as a functional antagonist (Graeler and Goetzl, 2002; Matloubian *et al.*, 2004; Oo *et al.*, 2007; Brinkmann *et al.*, 2010; Gonzalez-Cabrera *et al.*, 2012). Down-regulating surface expression of S1P₁ on lymphocytes prevents their egress from lymphoid organs and reduces

peripheral blood lymphocyte levels (Brinkmann *et al.*, 2010; Gonzalez-Cabrera *et al.*, 2012). Concomitantly, direct CNS actions may be relevant to MS through S1P₁ expressed on astrocytes, since conditional removal of this receptor reduces MS-like disease in animals and attenuates FTY720 activity (Choi *et al.*, 2011). Expression of this and other S1P receptors in the CNS supports other activities relevant to MS, and perhaps other CNS disorders (Gardell *et al.*, 2006; Herr and Chun, 2007; Noguchi and Chun, 2011; Soliven *et al.*, 2011; Mutoh *et al.*, 2012; Choi and Chun, 2013; Groves *et al.*, 2013).

S1P₁ maintains the integrity of the vascular system (Liu *et al.*, 2000; Camerer *et al.*, 2009; Wang and Dudek, 2009; Abbasi and Garcia, 2013), which is critical for homeostasis and to prevent extravasation of plasma during infections, sepsis and anaphylactic shock, which can be life threatening. Blood S1P enhances vascular barrier function by ligation of S1P₁ with subsequent downstream activation of the Rho family of small GTPases, cytoskeletal reorganization, adherens junction and tight junction assembly, and focal adhesion formation (Wang and Dudek, 2009; Abbasi and Garcia, 2013). Depletion of blood S1P in mice induces basal vascular leak and increases lethal responses in anaphylaxis induced by administration of platelet-activating factor or histamine (Camerer *et al.*, 2009). It has been suggested that either S1P continuously activates luminal endothelial S1P₁ to maintain tight cell–cell junctions or alternatively, following entry of S1P into the sub-endothelial space via 'leaky' endothelium, dynamic S1P₁ signalling activates abluminal surface S1P₁ to close intercellular gaps. Furthermore, the S1P/S1P₁ axis also attenuates LPS-induced acute lung injury in murine and

canine models (Wang and Dudek, 2009; Abbasi and Garcia, 2013). Deciphering the mechanisms by which the S1P₁ signalling pathway regulates endothelial barrier integrity will help our understanding and treatment of acute inflammatory diseases.

The vital role of S1P₁ in vascular maturation and development was demonstrated by knockout of the *S1pr1* gene in mice that die *in utero* because of a defect in the association of mural cells with nascent vessels and incomplete coverage (Liu *et al.*, 2000; Allende *et al.*, 2003). More recently, the role of S1P₁ in angiogenesis, the development of new blood vessels, has been slightly revised. It was shown that S1P₁ in fact acts independently of mural cells in an endothelial cell-autonomous manner to inhibit sprouting angiogenesis (Shoham *et al.*, 2012). Endothelial S1P₁ stabilizes the primary vascular network during development and homeostasis (Gaengel *et al.*, 2012; Jung *et al.*, 2012).

Recently, the crystal structure of S1P₁ fused to T4-lysozyme in complex with an antagonist was solved to 2.8 Å resolution (Hanson *et al.*, 2012). Intriguingly, this receptor has a novel N-terminal fold that blocks access of S1P to the binding pocket from the extracellular environment. Therefore, S1P must gain access by entering laterally between helices I and VII within the transmembrane region of S1P₁. This work provides the first view of the molecular recognition of S1P (Hanson *et al.*, 2012; Rosen *et al.*, 2013) and may aid in the development of S1P₁-specific drugs as well as providing a basis for determining the structure of the other S1P receptors.

S1P₂/S1PR2/S1pr2

Now denoted as S1P₂, this receptor was previously known as *Edg-5*, *H218*, *AGR16*, and *lp_{B2}* and was one of the first to be identified as an S1P receptor (An *et al.*, 1997). The human gene, *S1PR2*, is located on chromosomal locus 19p13.2 and its sequence is highly conserved across species, with the human receptor containing 353 amino acids and a receptor of ~39 kDa compared with the murine transcript with 352 (also ~39 kDa). The S1P₂ gene is expressed in a variety of tissues (Zhang *et al.*, 1999; McGiffert *et al.*, 2002) and can couple to multiple G-proteins, although it most efficiently utilizes G_{α12/13} to activate the small GTPase Rho. Thus, S1P₂ typically inhibits motility through inhibition of Rac. S1P₂ has been shown to be involved in S1P-induced cell proliferation, motility and transcriptional activation, usually acting in opposition to S1P₁ (Skoura and Hla, 2009; Chun *et al.*, 2010).

S1P₂ was initially shown to be required for heart development in zebrafish (Kupperman *et al.*, 2000). It was subsequently reported that S1P₂ signals through the G_{α13}/RhoGEF pathway to promote the migration of myocardial precursor cells (Ye and Lin, 2013), although *S1pr2* knockout mice are viable (Ishii *et al.*, 2002), demonstrating species differences. However, these null mutants have multiple severe inner ear defects, leading to deafness and balance problems (Herr *et al.*, 2007; Kono *et al.*, 2007). Using an S1P₂ antagonist, JTE013, it was shown that S1P₂ promotes vasoconstriction of the spiral modiolar artery, which protects the stria vascularis capillary bed of the inner ear from high perfusion pressure. Several other studies have linked S1P₂ to vascular development and remodelling. S1P₂ is induced in endothelial cells undergoing hypoxic stress and mice lacking both *S1pr1* and *S1pr2* exhibit substantially more vascular defects than *S1pr1* knockout

alone, suggesting that the two receptors may act coordinately during vascular development (Kono *et al.*, 2004). Experiments in developing zebrafish, which have *S1PR* homologues and S1P levels in the blood that are higher than the *K_D* of the receptors, showed similar results. *S1pr1* knockdown interfered with the development of the intersegmental vessels, and this phenotype was enhanced when *S1pr2* was suppressed (Mendelson *et al.*, 2013).

S1P₂ has also been suggested to play a role in endothelial barrier integrity. In an LPS-induced model of acute lung injury, S1P₂ deletion reduced oedema while activation of S1P₁ with a specific agonist also reduced oedema (Sammani *et al.*, 2010), suggesting that S1P₂ reduces endothelial barrier function in contrast to S1P₁, which enhances it. In mice, S1P₂ can also promote the recovery from anaphylactic shock, at least in part through counteracting the histamine-induced vasodilatation responsible for hypotension (Olivera *et al.*, 2010; 2013). Accordingly, histamine initiates a negative feedback loop, stimulating production of S1P that acts through S1P₂ to increase clearance of histamine by the kidney through excretion.

S1P₂ also plays a role in bone maintenance. Bone is remodelled throughout life, with osteoblasts forming bone and osteoclasts resorbing it. Osteoclast precursor cells migrate dynamically between bone and blood, which is controlled by the balance between S1P signalling through S1P₁ versus S1P₂. While S1P₁ promotes osteoclast migration from bone towards high blood levels of S1P (Ishii *et al.*, 2009a), migration away from bone is negatively controlled by S1P₂ (Ishii *et al.*, 2010). Insight into how the balance of S1P receptor expression controls bone remodelling was provided by the demonstration that calcitriol, the active form of vitamin D that promotes bone growth, reduces S1P₂ expression on osteoclasts (Kikuta *et al.*, 2013). This balance between S1P₁ and S1P₂ that controls traffic of cells into and out of tissues is becoming paradigmatic. Cyster and colleagues showed that S1P₂ promotes the retention of B cells in the germinal centres of lymphoid follicles at the low end of an S1P gradient (Green *et al.*, 2011). Moreover, S1P₂ also plays a role in controlling growth and apoptosis of germinal centre B cells through inhibition of Akt (Green *et al.*, 2011).

S1P also has an important role in muscle regeneration through activation of muscle stem cells called satellite cells (Rapizzi *et al.*, 2008). Saba and colleagues demonstrated that S1P biosynthesis is up-regulated following muscle injury (Loh *et al.*, 2012) and activation of S1P₂, but not S1P₁, promoted muscle regeneration by activating STAT3, which in turn down-regulates the cell cycle inhibitors p21 and p27 allowing for satellite cell growth (Loh *et al.*, 2012). Moreover, Mdx mice, a model for muscular dystrophy, have higher levels of S1P-metabolizing enzymes and lower circulating levels of S1P. However, using a different model of muscle injury induced by bupivacaine, S1P₂ was not found to be involved in muscle regeneration (Danieli-Betto *et al.*, 2010). It was suggested that S1P₃ promoted, while S1P₁ inhibited, muscle regeneration. The conflicting data concerning the specific S1P receptors involved may be due to the different models used or the timing of S1P receptor activation.

S1P₂ has also recently been implicated in promoting metastasis. Using genetic and pharmacological approaches, it was shown that bladder cancer xenografts increased systemic

S1P levels. This S1P in turn activated S1P₂, leading to the down-regulation of Brms1, a known suppressor of metastasis (Ponnusamy *et al.*, 2012). Thus, inhibition of systemic sphingosine kinase 1 and production of S1P and/or S1P₂ signalling increased Brms1 expression suppressing lung metastasis (Ponnusamy *et al.*, 2012).

S1P₃/S1PR3/S1pr3

S1P₃, previously known as *Edg-3* and *lp_{B3}*, was also an early identified S1P receptor (An *et al.*, 1997), with human *S1PR3* located at chromosomal locus 9q22.1-q22.2, encoding a 378-amino acid protein of ~42 kDa, with seven predicted transmembrane domains. It shares 87% identity with the murine S1P₃ receptor.

Like S1P₂, S1P₃ can couple to multiple G-proteins, including G_{αi/o}, G_{αq}, and G_{α12/13} (Chun *et al.*, 2010), although in cells it most commonly couples to G_{αq}, leading to the generation of inositol trisphosphate and diacylglycerol with subsequent calcium mobilization and activation of PKC respectively.

Despite fairly broad gene expression (Zhang *et al.*, 1999; McGiffert *et al.*, 2002), global deletion of *S1pr3* in mice did not reveal an obvious phenotype or developmental defects (Ishii *et al.*, 2001), although the *S1pr2/3* double knockouts have reduced fertility (Ishii *et al.*, 2002). Initially, S1P₃ was reported to be highly expressed in breast cancer models where it plays a positive role in cell migration (Chun *et al.*, 2010). Moreover, increased expression of S1P₃ in oestrogen receptor (ER)-positive tumour samples correlated with decreased disease-free survival times (Watson *et al.*, 2010). One possible explanation for this is the intriguing finding that in breast cancer cells, oestrogen stimulates S1P release and activation of S1P₃ (Sukocheva *et al.*, 2006). This then increases the activity of MMP9, resulting in the release of EGF to signal in an autocrine manner. Additionally, in this system, S1P₃ also activates Cdc42 and decreases degradation of, and increases signalling from, the EGF receptor (Sukocheva *et al.*, 2013). Interestingly, an S1P₃-blocking monoclonal antibody, 7H9, has been developed that blocks the growth of breast cancer tumours in a xenograft model (Harris *et al.*, 2012).

S1P₃ has also been implicated in sepsis. Signalling of the protease-activated receptor 1 on dendritic cells promotes the inflammatory response in sepsis syndrome. Treatment with S1P₃-specific antagonists, as well as S1P₃ deletion, protects from LPS-induced lethal sepsis (Niessen *et al.*, 2008; Sammani *et al.*, 2010). Although activation of S1P₁ increases endothelial barrier enhancement, S1P₃ disrupts it (Sammani *et al.*, 2010). Indeed, recent studies associate increased S1P₃ expression with sepsis and mortality of intensive care patients (Sun *et al.*, 2012). Finally, several studies indicate that S1P₃ is involved in liver fibrosis. S1P, acting through both S1P₁ and S1P₃, promotes the motility of hepatic stellate cells and their differentiation into hepatic myofibroblasts (Liu *et al.*, 2011), and enhances liver angiogenesis associated with fibrosis (Yang *et al.*, 2013).

S1P₄/S1PR4/S1pr4

S1PR4 is located at chromosomal locus 19p13.3, previously known as *Edg-6* and *lp_{C1}* (Contos *et al.*, 2002) and encodes a 384-amino acid protein of ~42 kDa in humans that is highly homologous across mammalian species (Van Brocklyn *et al.*, 2000).

S1P₄ couples to G_{αi} and G_{α12/13} and promotes cell migration (Graler *et al.*, 2003; Kohno *et al.*, 2003). S1P₄ has a restricted tissue distribution and is expressed mainly in haematopoietic tissue, though it was recently reported to be in other tissues, such as the muscle satellite cells, where together with S1P₁, it promotes migration in response to S1P (Calise *et al.*, 2012). Expression of *S1pr4* has also been reported in rat lungs, but not in renal or mesenteric arteries, and the S1P₄ agonist VPC23153 promoted vasoconstriction of both normotensive and hypertensive pulmonary arteries (Ota *et al.*, 2011). Moreover, expression of S1P₄ in ER-negative breast cancer cells correlated with poorer prognosis (Ohotski *et al.*, 2012).

S1P₄ is also important in megakaryocytes where it is highly induced upon differentiation. Although S1P₄ knockout mice have normal platelet levels, their ability to generate platelets after experimentally-induced thrombocytopenia is delayed, suggesting a role for S1P₄ in thrombopoiesis (Golfer *et al.*, 2010). Also in these mice, T-cell proliferation and cytokine secretion are not significantly altered (Schulze *et al.*, 2011). Interestingly, *S1pr4* knockout mice also have differential responses in various models of inflammation with exacerbated Th2-mediated responses, but reduced Th1-mediated responses. These changes were linked to altered dendritic cell functions, including decreased IL-6 production and IL-17 secretion. *S1pr4* deletion also decreased neutrophilia, suggesting a potential role for this receptor in neutrophil migration (Allende *et al.*, 2011).

S1P₅/S1PR5/S1pr5

Previously known as *Edg-8*, *lp_{B4}*, and *Nrg-1*, *S1PR5* is located at chromosomal locus 19p13.2 and encodes a highly conserved 398-amino acid protein with a calculated molecular mass of ~39 kD with tissue expression primarily restricted to brain and spleen (Im *et al.*, 2000a; Malek *et al.*, 2001). Like other S1P receptors, it couples to multiple G-proteins, although in its common role of inhibiting migration and promoting cell retraction, it couples to G_{α12/13}. S1P₅ knockout mice are viable and fertile. Intriguingly, they show greatly decreased numbers of circulating NK cells (Walzer *et al.*, 2007). Similar to the role S1P₁ plays in T and B cell trafficking, S1P₅ promotes the egress of NK cells from bone marrow and lymph nodes into blood and other tissues. Moreover, S1P₅ is required for NK recruitment to sites of inflammation (Walzer *et al.*, 2007; Jenne *et al.*, 2009). Furthermore, during NK cell differentiation, S1P₅ is expressed, allowing exit from the bone marrow (Mayol *et al.*, 2011). S1P₅ knockout mice also lack circulating Ly6C-negative peripheral monocytes, but have normal levels in the bone marrow (Debien *et al.*, 2013). Interestingly, although S1P₅ is required for egress of these cells, S1P is not a chemoattractant, suggesting that S1P₅ may act during their differentiation.

New lysophospholipid receptors

Efforts to de-orphanize GPCRs led to the identification of putative new members of the lysophospholipid receptor family. These receptors interact with two distinct glycerophospholipids: LPI and LysoPS. Newer technologies to identify receptors, such as the TGF α shedding assay, are being developed and used successfully for both de-orphanization and correction or augmentation of lysophospholipid identities.

LPI receptor: LPI₁/LPIR1/Lpir1 (orphan GPR55)

Orphan receptor GPR55 had originally been reported to be a novel cannabinoid receptor (Lauckner *et al.*, 2008); however, it appears that this receptor may in fact act as a LPI receptor based upon recent evaluations (Kotsikorou *et al.*, 2011; Inoue *et al.*, 2012; Aoki, Inoue and colleagues, unpublished). In view of these data, we consider GPR55 as a provisional LPI receptor with receptor name LPI₁ and gene names *LPIR1/Lpir1* for human and non-human genes respectively. *LPIR1* is located on human chromosome 2 (2q37) and encodes a 319-amino acid protein (~37 kDa). It is currently unclear whether this receptor genuinely acts as a cannabinoid receptor, and efforts are underway to better determine the ligand specificity of this GPCR.

Proposed LysoPS receptors

The following receptors have shown activity using a TGF α shedding assay (Inoue *et al.*, 2012), which strongly support their identity as LysoPS receptors; however, this identity should be considered provisional. In addition, the name of the receptors may require future modification: LysoPS_x is utilized here to avoid confusion with lipopolysaccharide that is commonly referred to as LPS. The lysophospholipid LysoPS, has been known as an immune cell stimulus, leading to identification of the first LysoPS receptor from mast cells via de-orphanization of the P2Y family of GPCRs known as GPR34 (Sugo *et al.*, 2006). *LyPSR1* is located at chromosomal locus Xp11.4 and encodes a 381-amino acid protein for a calculated molecular mass of ~44 kD. Receptor identity was confirmed using the TGF α shedding assay (Inoue *et al.*, 2012; Kitamura *et al.*, 2012; Makide and Aoki, 2013), although there is some disagreement in the literature on the veracity of this identity (Ritscher *et al.*, 2012). Genetic deletion of GPR34 does result in immunological dysfunction (Liebscher *et al.*, 2011), consistent with the immunological effects of LysoPS, and combined with positivity in the TGF α assay, its designation as LysoPS₁ appears to be warranted. LysoPS₁ has been implicated in other cell types such as microglia in the brain (Bedard *et al.*, 2007), and has been linked to diseases or disorders, including a form of night blindness (Jacobi *et al.*, 2000) and cancers of both immune (Ansell *et al.*, 2012) and non-immune origin (Yu *et al.*, 2013). Through the use of the TGF α shedding assay as a screening tool, three other receptors were identified, the first of which was another P2Y orphan receptor, P2Y₁₀. *LyPSR2* is located on human chromosome X (Xq21.1) and encodes a 339 amino acid protein (~39 kDa). Consistent with the biological effects of LysoPS on the immune system and data from analyses of LysoPS₁, LysoPS₂ also influences the immune system, and appears to show restricted expression in dendritic cells derived from monocytes (Berchtold *et al.*, 1999) and lymphoid lineages (Rao *et al.*, 1999). LysoPS₃/*LyPSR3/LyPSR3*, another orphan receptor (formerly GPR174), was identified as a third LysoPS receptor by TGF α assay (Inoue *et al.*, 2012) and independently supported by classical assays (Sugita *et al.*, 2013). *LyPSR3* is located near the *LPAR4* and *LyPSR2* genes (Xq21.1) and encodes a 333 amino acid protein of ~39 kDa, which shares about 45% identity with LysoPS₂. *LyPSR3* has recently been reported as a genetic risk locus for Graves disease (Zhao *et al.*,

2013). During TGF α screening analyses of orphan GPCRs, a mouse cDNA not present in humans, A630033H20, was identified as a LysoPS receptor with predicted homology to LysoPS₂ (Inoue *et al.*, 2012). This gene is located between *LyPSR2/p2ry10* and *LyPSR3/GPR174* on mouse chromosomal locus Xq21.1, which corresponds to the human *P2RY10P2* pseudogene. Therefore, nomenclature for a mouse-specific receptor and consequent gene names is neither proposed nor discouraged. A number of lysophospholipid receptor mutants or variants have been reported, such as the mRec1.3 mutant of LPA₁ (Contos *et al.*, 2000b; Fukushima *et al.*, 2001) or the original sequence for *S1pr3* (*Edg-3*) that was a variant form present in a cancer cell line (An *et al.*, 1997), and there is currently no uniform recommendation for naming these receptor variants, which could be a topic for future nomenclature efforts.

Concluding remarks

This nomenclature review for lysophospholipid receptors incorporates the recommended, as well as the most common uses of protein and gene names. For receptor proteins, the simple use of the cognate ligand immediately followed by a subscript to designate a receptor subtype is easily extended to receptors for other lysophospholipid ligands, as illustrated by the additions of LPI₁ and LysoPS₁₋₃, as was first used for this family based upon IUPHAR recommendations. To easily differentiate proteins from genes and provide an accurate interface with sequence databases such as ENCODE (Maher, 2012; Skipper *et al.*, 2012), the italicized use of the HGNC and MGI nomenclatures are recommended for human and non-human genes respectively. This nomenclature will accommodate the likely addition of new members to the lysophospholipid receptor family via both de-orphanization and revised receptor identities.

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Conflict of interest

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