BJP British Journal of Pharmacology

DOI:10.1111/bph.12678
www.brjpharmacol.org

INTERNATIONAL UNION OF BASIC AND CLINICAL PHARMACOLOGY REVIEW

Lysophospholipid receptor nomenclature review: IUPHAR Review 8

Yasuyuki Kihara[1], Michael Maceyka[2], Sarah Spiegel[2] and Jerold Chun[1]

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

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

Received
27 August 2013
Revised
3 February 2014
Accepted
12 February 2014

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).

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 LPA_1 – LPA_6 and italicized gene names *LPAR1-LPAR6* (human) and *Lpar1-Lpar6* (non-human). There are five sphingosine 1-phosphate (S1P) receptors: protein names $S1P_1$-$S1P_5$ 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 LPI_1 and gene name *LPIR1* (human) and *Lpir1* (non-human) – and three lysophosphatidyl serine receptors – protein names $LyPS_1$, $LyPS_2$, $LyPS_3$ 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

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 lysophospholipid 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-

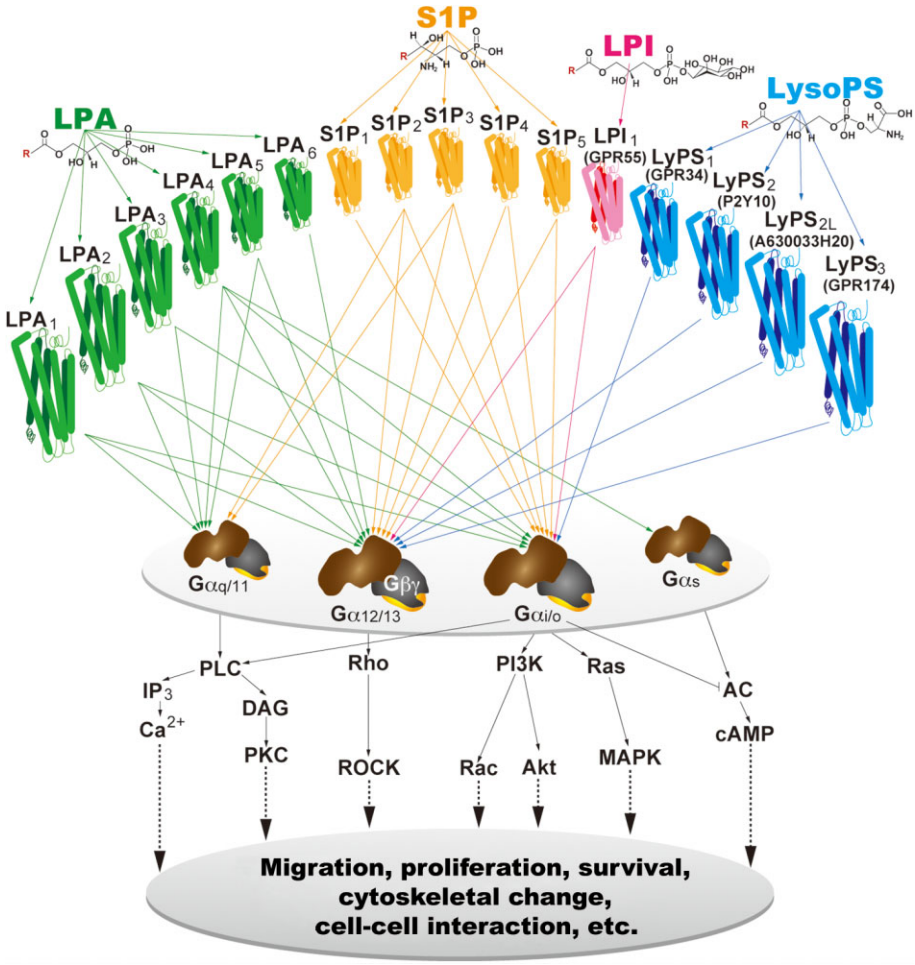

Figure 1

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, LPA_{1-6}. These 7-transmembrane GPCRs couple to one or more of the four classes of heterotrimeric G-proteins, commonly defined by their G_α proteins ($G_{\alpha12/13}$, $G_{\alpha q/11}$, $G_{\alpha i/o}$, 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.

LPA_1/*LPAR1*/*Lpar1*

The first receptor identified for any lysophospholipid came from studies on the brain, which identified LPA_1 (Hecht *et al.*, 1996), a receptor that mediates the effects of LPA. *LPAR1*

Table 2

Lysophospholipid receptors

			Human					Mouse/non-human				
Ligand	**Protein name[a]**	**G-proteins**	**Gene name**	**Chr**	**AA**	**MM[b]**	**Identity[c]**	**Gene name**	**Chr**	**AA**	**MM[a]**	**Previous orphan names[a]**
LPA	LPA_1	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*LPAR1*	9q31.3	364	41 109	97.3%	*Lpar1*	4	364	41 119	*vzg-1, edg-2, mrec1.3,* lp_{A1}
	LPA_2	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*LPAR2*	19p12	351	39 084	83.5%	*Lpar2*	8	348	38 777	*edg-4,* lp_{A2}
	LPA_3	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*LPAR3*	1p22.3-p31.1	353	40 128	91.2%	*Lpar3*	3	354	40 316	*edg-7,* lp_{A3}
	LPA_4	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*LPAR4*	Xq21.1	370	41 895	98.4%	*Lpar4*	X	370	41 899	*P2Y9/GPR23*
	LPA_5	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*LPAR5*	12p13.31	372	41 347	79.0%	*Lpar5*	6	372	41 394	*GPR92*
	LPA_6	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*LPAR6*	13q14	344	39 392	93.0%	*Lpar6*	14	344	39 439	*P2Y5*
S1P	$S1P_1$	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*S1PR1*	1p21	382	42 811	94.2%	*S1pr1*	3	382	42 639	*edg-1,* lp_{B1}
	$S1P_2$	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*S1PR2*	19p13.2	353	38 867	90.7%	*S1pr2*	9	352	38 829	*edg-5,* lp_{B2}, AGR16, H218
	$S1P_3$	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*S1PR3*	9q22.1-q22.2	378	42 250	87.3%	*S1pr3*	13	378	42 270	*edg-3,* lp_{B3}
	$S1P_4$	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*S1PR4*	19p13.3	384	41 623	81.1%	*S1pr4*	10	386	42 263	*edg-6,* lp_{C1}
	$S1P_5$	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*S1PR5*	19p13.2	398	41 775	83.8%	*S1pr5*	9	400	42 331	*edg-8,* lp_{B4}, *Nrg-1*
LPI	LPI_1	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*LPIR1*	2q37	319	36 637	74.4%	*Lpir1*	1	327	38 090	*GPR55*
LysoPS	$LysoPS_1$	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*LysoPSR1*	Xp11.4	381	43 860	89.0%	*Lypsr1*	X	375	43 173	*GPR34*
	$LysoPS_2$	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*LysoPSR2*	Xq21.1	339	38 774	82.9%	*Lypsr2*	X	328	37 244	*P2Y10*
	$LysoPS_3$	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	*LysoPSR3*	Xq21.1	333	38 503	87.8%	*Lypsr3*	X	335	38 761	*GPR174/FKSG79*
	$LysoPS_{2L}$	G_s, $G_{i/o}$, $G_{q/11}$, $G_{12/13}$	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.
[a]Hyperlinks are provided to online information in the IUPHAR/BPS Guide to PHARMACOLOGY.
[b]MMs were obtained from UniProt (UniprotConsortium, 2013).
[c]Identities between human and mouse lysophospholipid receptors were calculated in UniProt (UniprotConsortium, 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 *et al.*, 2009
	EC_{50}	64~200	9~10	75~321	26	11	1495	Ca^{2+}	Bandoh *et al.*, 2000; Yanagida *et al.*, 2013
2-Oleoyl-LPA	EC_{50}	~200	~10	~10	N/A	N/A	N/A	Ca^{2+}	Bandoh *et al.*, 2000
AGP	EC_{50}	1500	101	N/A	303	2	N/A	Ca^{2+}	Williams *et al.*, 2009
Alkyl OMPT	EC_{50}	794	N/A	62	N/A	N/A	N/A	Ca^{2+}	Qian *et al.*, 2006
VPC31143(*R*)	EC_{50}	59	16	130	341	126	1484	Ca^{2+}	Yanagida *et al.*, 2013
	EC_{50}	8	117	322	N/A	N/A	N/A	GTPγS	Heise *et al.*, 2001
VPC31144(*S*)	EC_{50}	461	2592	7123	18	16	4835	Ca^{2+}	Yanagida *et al.*, 2013
	EC_{50}	>5000	2645	4349	N/A	N/A	N/A	GTPγS	Heise *et al.*, 2001
Farnesyl diphosphate	IC_{50},EC_{50}	N/A	2100	4600	1980	40[b]	N/A	Ca^{2+}	Williams *et al.*, 2009
Farnesyl monophosphate	IC_{50},EC_{50}	N/A	161	517	1450	49[b]	N/A	Ca^{2+}	Williams *et al.*, 2009
Ki16425	(Ki)	(250)	(5600)	(360)	N/A	N/A	N/A	GTPγS	Ohta *et al.*, 2003
VPC12249	(Ki)	(137)	N/A	(428)	N/A	N/A	N/A	GTPγS	Heise *et al.*, 2001
	IC_{50} (Ki)	109 (18)	N/A	175	N/A	N/A	N/A	GTPγS	Heasley *et al.*, 2004
AM966	IC_{50}	17	1700	1600	7700	8600	N/A	Ca^{2+}	Swaney *et al.*, 2010

N/A, not applicable.
[a]Hyperlinks are provided to online information in the IUPHAR/BPS Guide to PHARMACOLOGY.
[b]Both farnesyl diphosphate and farnesyl monophosphate are reported to be antagonists for $LPA_{2,\ 3,\ 4}$, but agonist for LPA_5.

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 – $G_{\alpha i/o}$, $G_{\alpha q/11}$, and $G_{\alpha 12/13}$, 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 LPA_1 such as changes in cell shape through alterations in the actin cytoskeleton, cell migration, adhesion and cell–cell contact, and Ca^{2+} 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 background 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 LPA_1 signalling. Astrocytes express most LPA receptors (LPA_{1-5}; 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 LPA_1 and LPA_2 (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 LPA_1 and LPA_2 (Weiner *et al.*, 2001; Kobashi *et al.*, 2006) and Lpar1(–/–) mutants show increased survival via the $G_{\alpha i}$-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-P13K-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 LPA_5 (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). LPA_1 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). LPA_1 mutations have been reported in an osteosarcoma cell line (Okabe *et al.*, 2010) and in rat lung and liver tumours (Obo *et al.*, 2009).

LPA_2/*LPAR2/Lpar2*

LPA_2 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 LPA_1. *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). LPA_2 couples to the same heterotrimeric G-proteins as LPA_1: $G_{\alpha i/o}$, $G_{\alpha q/11}$, and $G_{\alpha 12/13}$ (Contos *et al.*, 2000b), and like LPA_1, can promote cell migration and survival (Goetzl *et al.*, 1999; Zheng *et al.*, 2000; 2001; Deng *et al.*, 2002; Panchatcharam *et al.*, 2008). LPA_2 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). LPA_2 signalling may inhibit EGF-induced migration of pancreatic cancer cells through $G_{\alpha 12/13}$/Rho (Komachi *et al.*, 2009). SCs up-regulate myelin markers like P0 protein via LPA_2, 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). LPA_2, in conjunction with LPA_1, 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 LPA_2 in promoting neoplasms based upon designed or observed overexpression (Kitayama *et al.*, 2004; Lee and Yun, 2010). LPA_2 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 LPA_2 generally appears to be protective against tumourgenesis (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). LPA_2 is expressed in unstimulated T-cells, as compared with LPA_1 that is predominantly within stimulated T-cells that can influence cell survival (Goetzl *et al.*, 1999). In unstimulated T-cells, LPA_2 is upregulated while LPA_1 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 LPA_1 and downregulate LPA_2, leading to inhibited chemotaxis, increased proliferation, and increased IL-2 and IL-13 production upon LPA stimulation (Zheng *et al.*, 2000; Rubenfeld *et al.*, 2006). LPA_2 is also expressed on dendritic cells (Panther *et al.*, 2002; Chen *et al.*, 2006).

LPA_3/*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 LPA_1 and LPA_2. LPA_3 couples to the heterotrimeric Gα proteins $G_{\alpha i/o}$ and $G_{\alpha q/11}$ to mediate downstream signalling pathways including adenyl cyclase activation, PLC activation and Ca^{2+} mobilization, and MAPK activation (Ishii *et al.*, 2000). LPA_3 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 LPA_3-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 LPA_3 loss (Ye *et al.*, 2005). Mechanistic studies demonstrated that LPA_3 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 $PLA_{2\alpha}$ ($cPLA_{2\alpha}$) 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 LPA_{1-3} 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).

LPA_4/*LPAR4*/*Lpar4*

LPA_4 is notable because it shares less than 20% amino acid sequence identity with LPA_{1-3} and $S1P_{1-5}$, and is phylogenetically far from them and located near the P2Y receptor family (Figure 2). Identification of LPA_4 was made by screening orphan receptors, including purine receptor families, using calcium mobilization as a readout for ligand-induced signals (Noguchi *et al.*, 2003). $P2Y_9$ has ~20% sequence identity to LPA_{1-3} (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

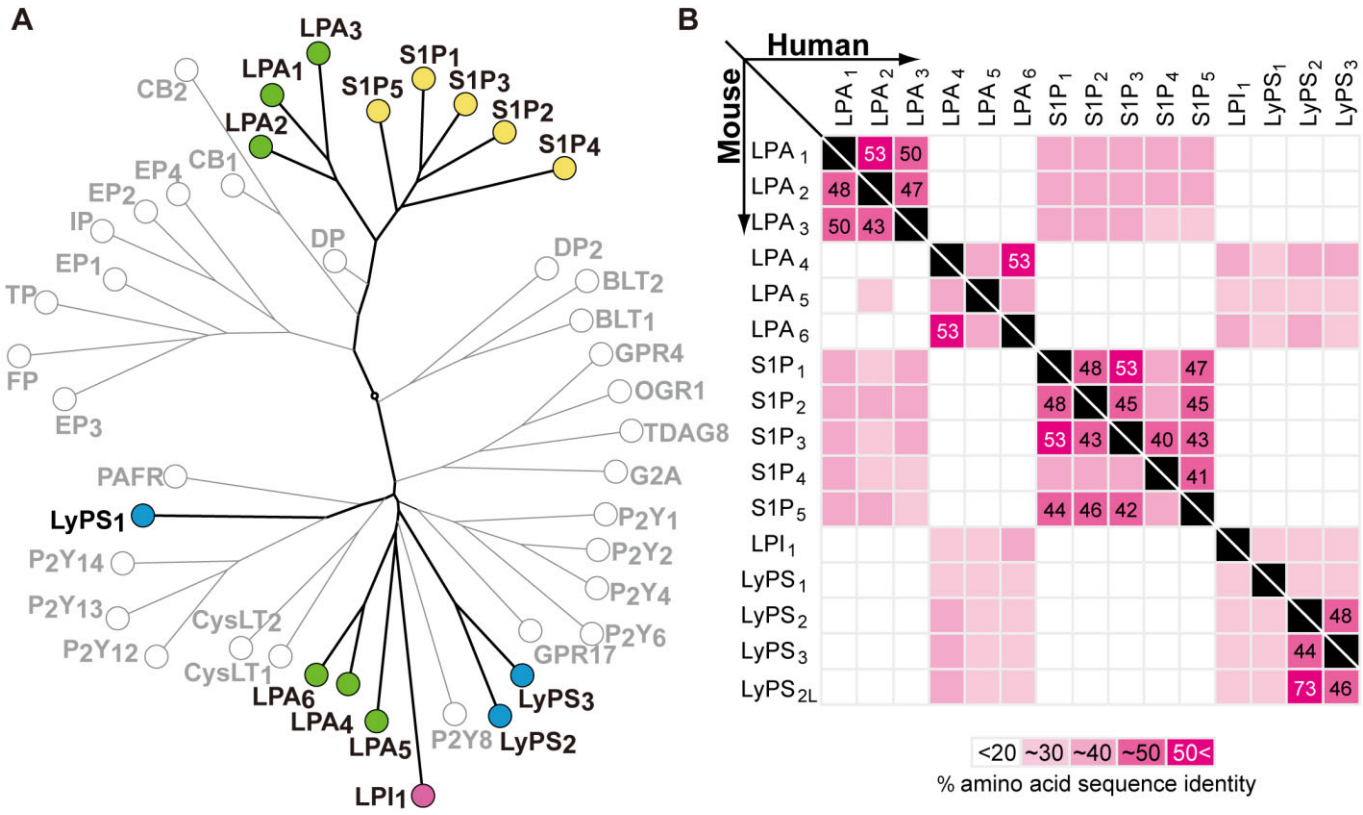

Figure 2

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).

LPA_4 couples to G_α-proteins $G_{\alpha s}$, $G_{\alpha i}$, $G_{\alpha q}$, and $G_{\alpha 12/13}$ (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 $G_{\alpha s}$ activity (Lee *et al.*, 2007) to promote intracellular cAMP accumulation. LPA_4 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).

LPA_5/*LPAR5*/*Lpar5*

LPA_5 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. LPA_5 couples to $G_{\alpha 12/13}$ and $G_{\alpha q}$ (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).

LPA_5-expressing cell lines can induce both neurite retraction and stress fibre formation in response to LPA via the $G_{\alpha 12/13}$ pathway, including clear receptor internalization (Lee *et al.*, 2006). It also activates $G_{\alpha q}$, Gai, leading to intracellular calcium levels (Lee *et al.*, 2006), while also increasing cAMP accumulation via a non-$G_{\alpha s}$ mechanism, based upon minigene experiments, which implicates other G-protein involvement (Kotarsky *et al.*, 2006; Lee *et al.*, 2006). LPA_5 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 LPA_1 (Lin *et al.*, 2012).

LPA_6/*LPAR6*/*Lpar6*

The latest member of the LPA receptor family is LPA_6. LPA_6 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 LPA_4, 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 $G_{\alpha 13}$ protein enabled detection of LPA_6-mediated cAMP accumulation and Rho-dependent morphological alterations, as well as [^{3}H]-LPA binding and LPA-induced [^{35}S]-guanosine 5′-3-*O*-(thio)triphosphate binding (Yanagida *et al.*, 2009). LPA_6 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 $G_{\alpha i}$, LPA_6 stimulated with LPA increased intracellular Ca^{2+}, reduced forskolin-stimulated cAMP and ERK1/2 activation (Lee *et al.*, 2009).

LPA_6 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 LPA_6 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 LPA_6 (Pasternack *et al.*, 2009; Shinkuma *et al.*, 2010). More recent analyses of this receptor by use of a TGFα 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 $S1P_1$-$S1P_5$ (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.

$S1P_1$/*S1PR1*/*S1pr1*

$S1P_1$ 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 $G_{\alpha i/o}$. 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 *et al.*, 2002; Sanna *et al.*, 2004; Pan *et al.*, 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 *et al.*, 2002; Pan *et al.*, 2006
AUY954	EC_{50}	1.2	N/A	1210	N/A	340	GTPγS	Pan *et al.*, 2006
SEW2781	EC_{50}	13–28.8	N/A	N/A	N/A	N/A	GTPγS	Sanna *et al.*, 2004; Gonzalez-Cabrera *et al.*, 2008
AFD (R)	EC_{50}	2.5	N/A	4	4	1.3	GTPγS	Brinkmann *et al.*, 2002
CYM5181	EC_{50}	3.4	N/A	N/A	N/A	N/A	GTPγS	Gonzalez-Cabrera *et al.*, 2008
CYM-5442	EC_{50}	1.2	N/A	N/A	N/A	N/A	GTPγS	Gonzalez-Cabrera *et al.*, 2008
W146	EC_{50} (K_i)	398 (77)	N/A	N/A	N/A	N/A	GTPγS	Sanna *et al.*, 2006
NIBR-0213	(K_i)	(2)	N/A	N/A	N/A	N/A	GTPγS	Quancard *et al.*, 2012
VPC03090-P	EC_{50} (K_i)	(21–24)	N/A	(51–58.7)	17.7[b]	2.4[b]	GTPγS	Kennedy *et al.*, 2011
VPC23019	(K_i)	(1)	N/A	(7.6)	N/A	N/A	Binding[c]	Davis *et al.*, 2005
VPC44116	EC_{50} (K_i)	(30)	N/A	(300)	6100[b]	33[b]	GTPγS	Foss *et al.*, 2007
JTE-013	IC_{50}	N/A	17	N/A	N/A	N/A	Binding[c]	Osada *et al.*, 2002

N/A, not applicable.
[a]Hyperlinks are provided to online information in the IUPHAR/BPS Guide to PHARMACOLOGY.
[b]Both VPC03090-P and VPC44116 are reported to be antagonists for $S1P_{1,\ 3,}$ but agonist for $S1P_{4,5}$.
[c]Ki and IC_{50} was estimated by determining the competitive binding of radioisotope-labelled S1P.

tal staining, have established that $S1P_1$ 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 $S1P_1$ 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 $G_{\alpha i}$-phosphatidylinositol-3-kinase pathway and the small GTPase Rac (Spiegel and Milstien, 2011; Cyster and Schwab, 2012). Down-regulation or desensitization of $S1P_1$ 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 $S1P_1$, $S1P_3$, $S1P_4$, and $S1P_5$. However, persistent activation of $S1P_1$ 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 $S1P_1$ 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 $S1P_1$ 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).

$S1P_1$ 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 $S1P_1$ 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 $S1P_1$ to maintain tight cell–cell junctions or alternatively, following entry of S1P into the sub-endothelial space via 'leaky' endothelium, dynamic $S1P_1$ signalling activates abluminal surface $S1P_1$ to close intercellular gaps. Furthermore, the S1P/$S1P_1$ 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 $S1P_1$ signalling pathway regulates endothelial barrier integrity will help our understanding and treatment of acute inflammatory diseases.

The vital role of $S1P_1$ 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 $S1P_1$ in angiogenesis, the development of new blood vessels, has been slightly revised. It was shown that $S1P_1$ in fact acts independently of mural cells in an endothelial cell-autonomous manner to inhibit sprouting angiogenesis (Shoham *et al.*, 2012). Endothelial $S1P_1$ stabilizes the primary vascular network during development and homeostasis (Gaengel *et al.*, 2012; Jung *et al.*, 2012).

Recently, the crystal structure of $S1P_1$ 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 $S1P_1$. 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 $S1P_1$-specific drugs as well as providing a basis for determining the structure of the other S1P receptors.

$S1P_2$/*S1PR2*/*S1pr2*

Now denoted as $S1P_2$, 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 $S1P_2$ 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 $G_{\alpha 12/13}$ to activate the small GTPase Rho. Thus, $S1P_2$ typically inhibits motility through inhibition of Rac. $S1P_2$ has been shown to be involved in S1P-induced cell proliferation, motility and transcriptional activation, usually acting in opposition to $S1P_1$ (Skoura and Hla, 2009; Chun *et al.*, 2010).

$S1P_2$ was initially shown to be required for heart development in zebrafish (Kupperman *et al.*, 2000). It was subsequently reported that $S1P_2$ signals through the $G_{\alpha 13}$/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 $S1P_2$ antagonist, JTE013, it was shown that $S1P_2$ 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 $S1P_2$ to vascular development and remodelling. $S1P_2$ 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).

$S1P_2$ has also been suggested to play a role in endothelial barrier integrity. In an LPS-induced model of acute lung injury, $S1P_2$ deletion reduced oedema while activation of $S1P_1$ with a specific agonist also reduced oedema (Sammani *et al.*, 2010), suggesting that $S1P_2$ reduces endothelial barrier function in contrast to $S1P_1$, which enhances it. In mice, $S1P_2$ 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 $S1P_2$ to increase clearance of histamine by the kidney through excretion.

$S1P_2$ 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 $S1P_1$ versus $S1P_2$. While $S1P_1$ promotes osteoclast migration from bone towards high blood levels of S1P (Ishii *et al.*, 2009a), migration away from bone is negatively controlled by $S1P_2$ (Ishii *et al.*, 2010). Insight into how the balance of S1P receptor expression controls bone remodelling was provided by the demonstration that calcetriol, the active form of vitamin D that promotes bone growth, reduces $S1P_2$ expression on osteoclasts (Kikuta *et al.*, 2013). This balance between $S1P_1$ and $S1P_2$ that controls traffic of cells into and out of tissues is becoming paradigmatic. Cyster and colleagues showed that $S1P_2$ 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, $S1P_2$ 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 $S1P_2$, but not $S1P_1$, 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, $S1P_2$ was not found to be involved in muscle regeneration (Danieli-Betto *et al.*, 2010). It was suggested that $S1P_3$ promoted, while $S1P_1$ 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.

$S1P_2$ 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 $S1P_2$, 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 $S1P_2$ signalling increased Brms1 expression suppressing lung metastasis (Ponnusamy *et al.*, 2012).

$S1P_3$/*S1PR3*/*S1pr3*

$S1P_3$, 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 $S1P_3$ receptor.

Like $S1P_2$, $S1P_3$ can couple to multiple G-proteins, including $G_{\alpha i/o}$, $G_{\alpha q}$, and $G_{\alpha 12/13}$ (Chun *et al.*, 2010), although in cells it most commonly couples to $G_{\alpha q}$, 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, $S1P_3$ 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 $S1P_3$ 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 $S1P_3$ (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, $S1P_3$ also activates Cdc42 and decreases degradation of, and increases signalling from, the EGF receptor (Sukocheva *et al.*, 2013). Interestingly, an $S1P_3$-blocking monoclonal antibody, 7H9, has been developed that blocks the growth of breast cancer tumours in a xenograft model (Harris *et al.*, 2012).

$S1P_3$ 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 $S1P_3$-specific antagonists, as well as $S1P_3$ deletion, protects from LPS-induced lethal sepsis (Niessen *et al.*, 2008; Sammani *et al.*, 2010). Although activation of $S1P_1$ increases endothelial barrier enhancement, $S1P_3$ disrupts it (Sammani *et al.*, 2010). Indeed, recent studies associate increased $S1P_3$ expression with sepsis and mortality of intensive care patients (Sun *et al.*, 2012). Finally, several studies indicate that $S1P_3$ is involved in liver fibrosis. S1P, acting through both $S1P_1$ and $S1P_3$, 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).

$S1P_4$/*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).

$S1P_4$ couples to $G_{\alpha i}$ and $G_{\alpha 12/13}$ and promotes cell migration (Graler *et al.*, 2003; Kohno *et al.*, 2003). $S1P_4$ 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 $S1P_1$, 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 $S1P_4$ agonist VPC23153 promoted vasoconstriction of both normotensive and hypertensive pulmonary arteries (Ota *et al.*, 2011). Moreover, expression of $S1P_4$ in ER-negative breast cancer cells correlated with poorer prognosis (Ohotski *et al.*, 2012).

$S1P_4$ is also important in megakaryocytes where it is highly induced upon differentiation. Although $S1P_4$ knockout mice have normal platelet levels, their ability to generate platelets after experimentally-induced thrombocytopenia is delayed, suggesting a role for $S1P_4$, in thrombopoiesis (Golfier *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).

$S1P_5$/*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 $G_{\alpha 12/13}$. $S1P_5$ knockout mice are viable and fertile. Intriguingly, they show greatly decreased numbers of circulating NK cells (Walzer *et al.*, 2007). Similar to the role $S1P_1$ plays in T and B cell trafficking, $S1P_5$ promotes the egress of NK cells from bone marrow and lymph nodes into blood and other tissues. Moreover, $S1P_5$ is required for NK recruitment to sites of inflammation (Walzer *et al.*, 2007; Jenne *et al.*, 2009). Furthermore, during NK cell differentiation, $S1P_5$ is expressed, allowing exit from the bone marrow (Mayol *et al.*, 2011). $S1P_5$ knockout mice also lack circulating Ly6C-negative peripheral monocytes, but have normal levels in the bone marrow (Debien *et al.*, 2013). Interestingly, although $S1P_5$ is required for egress of these cells, S1P is not a chemoattractant, suggesting that $S1P_5$ 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 TGFα shedding assay, are being developed and used successfully for both de-orphanization and correction or augmentation of lysophospholipid identities.

LPI receptor: LPI_1*/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 LPI_1 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 TGFα 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 TGFα 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 TGFα assay, its designation as $LysoPS_1$ appears to be warranted. $LysoPS_1$ 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 TGFα shedding assay as a screening tool, three other receptors were identified, the first of which was another P2Y orphan receptor, $P2Y_{10}$. *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 $LysoPS_1$, $LysoPS_2$ 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). $LysoPS_3$*/LyPSR3/Lypsr3*, another orphan receptor (formerly GPR174), was identified as a third LysoPS receptor by TGFα 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 $LysoPS_2$. *LyPSR3* has recently been reported as a genetic risk locus for Graves disease (Zhao *et al.*, 2013). During TGFα screening analyses of orphan GPCRs, a mouse cDNA not present in humans, A630033H20, was identified as a LysoPS receptor with predicted homology to $LysoPS_2$ (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 LPA_1 (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 LPI_1 and $LysoPS_{1-3}$, 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.

Acknowledgements

We thank Danielle Jones and Hope Mirendil for editorial assistance. This work was supported by the National Institutes of Health.

Conflict of interest

Jerold Chun has received honoraria, consulting fees and/or grant support from: Abbott, Amira Pharmaceuticals, Biogen-Idec, Celgene, GlaxoSmithKline, Johnson and Johnson, Merk, Mitsubishi Tanabe Pharma Corporation, Novaritis, Ono Pharmaceutical Co., Pfizer and Taisho Pharmaceutical Co. Yasuyuki Kihara has no conflict of interest.

References

Abbasi T, Garcia JG (2013). Sphingolipids in lung endothelial biology and regulation of vascular integrity. Handb Exp Pharmacol 216: 201–226.

Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL, McGrath JC *et al*. (2013a). The concise guide to PHARMACOLOGY 2013/14: overview. Br J Pharmacol 170: 1449–1458.

Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Spedding M *et al*. (2013b). The concise guide to PHARMACOLOGY 2013/14: G protein-coupled receptors. Br J Pharmacol 170: 1459–1581.

Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Spedding M *et al*. (2013c). The concise guide to PHARMACOLOGY 2013/14: Transporters. Br J Pharmacol 170: 1706–1796.

Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Spedding M *et al*. (2013d). The concise guide to PHARMACOLOGY 2013/14: enzymes. Br J Pharmacol 170: 1797–1867.

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

Allende ML, Yamashita T, Proia RL (2003). G-protein coupled receptor S1P1 acts within endothelial cells to regulate vascular maturation. Blood 102: 3665–3667.

Allende ML, Bektas M, Lee BG, Bonifacino E, Kang J, Tuymetova G *et al*. (2011). Sphingosine-1-phosphate lyase deficiency produces a pro-inflammatory response while impairing neutrophil trafficking. J Biol Chem 286: 7348–7358.

Amisten S, Braun OO, Bengtsson A, Erlinge D (2008). Gene expression profiling for the identification of G-protein coupled receptors in human platelets. Thromb Res 122: 47–57.

An S, Bleu T, Huang W, Hallmark OG, Coughlin SR, Goetzl EJ (1997). Identification of cDNAs encoding two G protein-coupled receptors for lysosphingolipids. FEBS Lett 417: 279–282.

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

Ansell SM, Akasaka T, McPhail E, Manske M, Braggio E, Price-Troska T *et al*. (2012). t(X;14) (p11;q32) in MALT lymphoma involving GPR34 reveals a role for GPR34 in tumor cell growth. Blood 120: 3949–3957.

Bandoh K, Aoki J, Hosono H, Kobayashi S, Kobayashi T, Murakami-Murofushi K *et al*. (1999). Molecular cloning and characterization of a novel human G-protein-coupled receptor, EDG7, for lysophosphatidic acid. J Biol Chem 274: 27776–27785.

Bandoh K, Aoki J, Taira A, Tsujimoto M, Arai H, Inoue K (2000). Lysophosphatidic acid (LPA) receptors of the EDG family are differentially activated by LPA species. Structure–activity relationship of cloned LPA receptors. FEBS Lett 478: 159–165.

Bedard A, Tremblay P, Chernomoretz A, Vallieres L (2007). Identification of genes preferentially expressed by microglia and upregulated during cuprizone-induced inflammation. Glia 55: 777–789.

Berchtold S, Ogilvie AL, Bogdan C, Muhl-Zurbes P, Ogilvie A, Schuler G *et al*. (1999). Human monocyte derived dendritic cells express functional P2X and P2Y receptors as well as ecto-nucleotidases. FEBS Lett 458: 424–428.

Blaho VA, Hla T (2011). Regulation of mammalian physiology, development, and disease by the sphingosine 1-phosphate and lysophosphatidic acid receptors. Chem Rev 111: 6299–6320.

Boucher J, Quilliot D, Praderes JP, Simon MF, Gres S, Guigne C *et al*. (2005). Potential involvement of adipocyte insulin resistance in obesity-associated up-regulation of adipocyte lysophospholipase D/autotaxin expression. Diab Tologia 48: 569–577.

Brimacombe M, Ming X, Lamendola M (2007). Prenatal and birth complications in autism. Matern Child Health J 11: 73–79.

Brinkmann V, Davis MD, Heise CE, Albert R, Cottens S, Hof R *et al*. (2002). The immune modulator FTY720 targets sphingosine 1-phosphate receptors. J Biol Chem 277: 21453–21457.

Brinkmann V, Billich A, Baumruker T, Heining P, Schmouder R, Francis G *et al*. (2010). Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. Nat Rev Drug Discov 9: 883–897.

Byrne M, Agerbo E, Bennedsen B, Eaton WW, Mortensen PB (2007). Obstetric conditions and risk of first admission with schizophrenia: a Danish national register based study. Schizophr Res 97: 51–59.

Calise S, Blescia S, Cencetti F, Bernacchioni C, Donati C, Bruni P (2012). Sphingosine 1-phosphate stimulates proliferation and migration of satellite cells: role of S1P receptors. Biochim Biophys Acta 1823: 439–450.

Camerer E, Regard JB, Cornelissen I, Srinivasan Y, Duong DN, Palmer D *et al*. (2009). Sphingosine-1-phosphate in the plasma compartment regulates basal and inflammation-induced vascular leak in mice. J Clin Invest 119: 1871–1879.

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

Cannon M, Jones PB, Murray RM (2002). Obstetric complications and schizophrenia: historical and meta-analytic review. Am J Psychiatry 159: 1080–1092.

Castilla-Ortega E, Sánchez-López J, Hoyo-Becerra C, Matas-Rico E, Zambrana-Infantes E, Chun J *et al*. (2010). Exploratory, anxiety and spatial memory impairments are dissociated in mice lacking the LPA1 receptor. Neurobiol Learn Mem 94: 73–82.

Chan LC, Peters W, Xu Y, Chun J, Farese RV Jr, Cases S (2007). LPA3 receptor mediates chemotaxis of immature murine dendritic cells to unsaturated lysophosphatidic acid (LPA). J Leukoc Biol 82: 1193–1200.

Chen R, Roman J, Guo J, West E, McDyer J, Williams MA *et al*. (2006). Lysophosphatidic acid modulates the activation of human monocyte-derived dendritic cells. Stem Cells Dev 15: 797–804.

Choi JW, Chun J (2013). Lysophospholipids and their receptors in the central nervous system. Biochim Biophys Acta 1831: 20–32.

Choi JW, Herr DR, Noguchi K, Yung YC, Lee CW, Mutoh T *et al*. (2010). LPA receptors: subtypes and biological actions. Annu Rev Pharmacol Toxicol 50: 157–186.

Choi JW, Gardell SE, Herr DR, Rivera R, Lee CW, Noguchi K *et al*. (2011). FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte sphingosine 1-phosphate receptor 1 (S1P1) modulation. Proc Natl Acad Sci U S A 108: 751–756.

Chun J, Brinkmann V (2011). A mechanistically novel, first oral therapy for multiple sclerosis: the development of fingolimod (FTY720, Gilenya). Discov Med 12: 213–228.

Chun J, Hartung HP (2010). Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. Clin Neuropharmacol 33: 91–101.

Chun J, Goetzl EJ, Hla T, Igarashi Y, Lynch KR, Moolenaar W *et al*. (2002). International union of pharmacology. XXXIV. Lysophospholipid receptor nomenclature. Pharmacol Rev 54: 265–269.

Chun J, Hla T, Lynch KR, Spiegel S, Moolenaar WH (2010). International union of basic and clinical pharmacology. LXXVIII. Lysophospholipid receptor nomenclature. Pharmacol Rev 62: 579–587.

Cohen JA, Chun J (2011). Mechanisms of fingolimod's efficacy and adverse effects in multiple sclerosis. Ann Neurol 69: 759–777.

Contos JJ, Chun J (1998). Complete cDNA sequence, genomic structure, and chromosomal localization of the LPA receptor gene, lpA1/vzg-1/Gpcr26. Genomics 51: 364–378.

Contos JJ, Chun J (2000). Genomic characterization of the lysophosphatidic acid receptor gene, lp(A2)/Edg4, and identification of a frameshift mutation in a previously characterized cDNA. Genomics 64: 155–169.

Contos JJ, Fukushima N, Weiner JA, Kaushal D, Chun J (2000a). Requirement for the lpA1 lysophosphatidic acid receptor gene in normal suckling behavior. Proc Natl Acad Sci U S A 97: 13384–13389.

Contos JJ, Ishii I, Chun J (2000b). Lysophosphatidic acid receptors. Mol Pharmacol 58: 1188–1196.

Contos JJ, Ye X, Sah VP, Chun J (2002). Tandem genomic arrangement of a G protein (Gna15) and G protein-coupled receptor (s1p(4)/lp(C1)/Edg6) gene. FEBS Lett 531: 99–102.

Cyster JG, Schwab SR (2012). Sphingosine-1-phosphate and lymphocyte egress from lymphoid organs. Annu Rev Immunol 30: 69–94.

Danieli-Betto D, Peron S, Germinario E, Zanin M, Sorci G, Franzoso S *et al.* (2010). Sphingosine 1-phosphate signaling is involved in skeletal muscle regeneration. Am J Physiol Cell Physiol 298: C550–C558.

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE *et al.* (2013). International union of basic and clinical pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. Pharmacol Rev 65: 967–986.

Davis MD, Clemens JJ, Macdonald TL, Lynch KR (2005). Sphingosine 1-phosphate analogs as receptor antagonists. J Biol Chem 280: 9833–9841.

Debien E, Mayol K, Biajoux V, Daussy C, De Aguero MG, Taillardet M *et al.* (2013). S1PR5 is pivotal for the homeostasis of patrolling monocytes. Eur J Immunol 43: 1667–1675.

Deng W, Balazs L, Wang DA, Van Middlesworth L, Tigyi G, Johnson LR (2002). Lysophosphatidic acid protects and rescues intestinal epithelial cells from radiation- and chemotherapy-induced apoptosis. Gastroenterology 123: 206–216.

Estivill-Torrús G, Llebrez-Zayas P, Matas-Rico E, Santín L, Pedraza C, De Diego I *et al.* (2008). Absence of LPA1 signaling results in defective cortical development. Cereb Cortex 18: 938–950.

Estrella VC, Eder AM, Liu S, Pustilnik TB, Tabassam FH, Claret FX *et al.* (2007). Lysophosphatidic acid induction of urokinase plasminogen activator secretion requires activation of the p38MAPK pathway. Int J Oncol 31: 441–449.

Ferry G, Tellier E, Try A, Gres S, Naime I, Simon MF *et al.* (2003). Autotaxin is released from adipocytes, catalyzes lysophosphatidic acid synthesis, and activates preadipocyte proliferation. Up-regulated expression with adipocyte differentiation and obesity. J Biol Chem 278: 18162–18169.

Foss FW Jr, Snyder AH, Davis MD, Rouse M, Okusa MD, Lynch KR *et al.* (2007). Synthesis and biological evaluation of gamma-aminophosphonates as potent, subtype-selective sphingosine 1-phosphate receptor agonists and antagonists. Bioorg Med Chem 15: 663–677.

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

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

Fukushima N, Ishii I, Contos JJ, Weiner JA, Chun J (2001). Lysophospholipid receptors. Annu Rev Pharmacol Toxicol 41: 507–534.

Fukushima N, Weiner JA, Kaushal D, Contos JJ, Rehen SK, Kingsbury MA *et al.* (2002). Lysophosphatidic acid influences the morphology and motility of young, postmitotic cortical neurons. Mol Cell Neurosci 20: 271–282.

Gaengel K, Niaudet C, Hagikura K, Lavina B, Muhl L, Hofmann JJ *et al.* (2012). The sphingosine-1-phosphate receptor S1PR1 restricts sprouting angiogenesis by regulating the interplay between VE-cadherin and VEGFR2. Dev Cell 23: 587–599.

Gardell SE, Dubin AE, Chun J (2006). Emerging medicinal roles for lysophospholipid signaling. Trends Mol Med 12: 65–75.

Gilman AG (1987). G proteins: transducers of receptor-generated signals. Annu Rev Biochem 56: 615–649.

Goetzl EJ, Kong Y, Mei B (1999). Lysophosphatidic acid and sphingosine 1-phosphate protection of T cells from apoptosis in association with suppression of Bax. J Immunol 162: 2049–2056.

Goetzl EJ, Kong Y, Voice JK (2000). Cutting edge: differential constitutive expression of functional receptors for lysophosphatidic acid by human blood lymphocytes. J Immunol 164: 4996–4999.

Golfier S, Kondo S, Schulze T, Takeuchi T, Vassileva G, Achtman AH *et al.* (2010). Shaping of terminal megakaryocyte differentiation and proplatelet development by sphingosine-1-phosphate receptor S1P4. FASEB J 24: 4701–4710.

Gonzalez-Cabrera PJ, Jo E, Sanna MG, Brown S, Leaf N, Marsolais D *et al.* (2008). Full pharmacological efficacy of a novel S1P1 agonist that does not require S1P-like headgroup interactions. Mol Pharmacol 74: 1308–1318.

Gonzalez-Cabrera PJ, Cahalan SM, Nguyen N, Sarkisyan G, Leaf NB, Cameron MD *et al.* (2012). S1P(1) receptor modulation with cyclical recovery from lymphopenia ameliorates mouse model of multiple sclerosis. Mol Pharmacol 81: 166–174.

Graeler M, Goetzl EJ (2002). Activation-regulated expression and chemotactic function of sphingosine 1-phosphate receptors in mouse splenic T cells. FASEB J 16: 1874–1878.

Graler MH, Grosse R, Kusch A, Kremmer E, Gudermann T, Lipp M (2003). The sphingosine 1-phosphate receptor S1P4 regulates cell shape and motility via coupling to Gi and G12/13. J Cell Biochem 89: 507–519.

Green JA, Suzuki K, Cho B, Willison LD, Palmer D, Allen CD *et al.* (2011). The sphingosine 1-phosphate receptor S1P(2) maintains the homeostasis of germinal center B cells and promotes niche confinement. Nat Immunol 12: 672–680.

Groves A, Kihara Y, Chun J (2013). Fingolimod: direct CNS effects of sphingosine 1-phosphate (S1P) receptor modulation and implications in multiple sclerosis therapy. J Neurol Sci 328: 9–18.

Hama K, Aoki J, Bandoh K, Inoue A, Endo T, Amano T *et al.* (2006). Lysophosphatidic receptor, LPA3, is positively and negatively regulated by progesterone and estrogen in the mouse uterus. Life Sci 79: 1736–1740.

Hama K, Aoki J, Inoue A, Endo T, Amano T, Motoki R *et al.* (2007). Embryo spacing and implantation timing are differentially regulated by LPA3-mediated lysophosphatidic acid signaling in mice. Biol Reprod 77: 954–959.

Hanson MA, Roth CB, Jo E, Griffith MT, Scott FL, Reinhart G *et al.* (2012). Crystal structure of a lipid G protein-coupled receptor. Science 335: 851–855.

Harris GL, Creason MB, Brulte GB, Herr DR (2012). *In vitro* and *in vivo* antagonism of a G protein-coupled receptor (S1P3) with a novel blocking monoclonal antibody. PLoS ONE 7: e35129.

Harrison SM, Reavill C, Brown G, Brown JT, Cluderay JE, Crook B *et al.* (2003). LPA1 receptor-deficient mice have phenotypic changes observed in psychiatric disease. Mol Cell Neurosci 24: 1170–1179.

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

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

Heise CE, Santos WL, Schreihofer AM, Heasley BH, Mukhin YV, Macdonald TL *et al.* (2001). Activity of 2-substituted lysophosphatidic acid (LPA) analogs at LPA receptors: discovery of a LPA1/LPA3 receptor antagonist. Mol Pharmacol 60: 1173–1180.

Herr DR, Chun J (2007). Effects of LPA and S1P on the nervous system and implications for their involvement in disease. Curr Drug Targets 8: 155–167.

Herr DR, Grillet N, Schwander M, Rivera R, Muller U, Chun J (2007). Sphingosine 1-phosphate (S1P) signaling is required for maintenance of hair cells mainly via activation of S1P2. J Neurosci 27: 1474–1478.

Hope JM, Wang FQ, Whyte JS, Ariztia EV, Abdalla W, Long K *et al.* (2009). LPA receptor 2 mediates LPA-induced endometrial cancer invasion. Gynecol Oncol 112: 215–223.

Huang MC, Lee HY, Yeh CC, Kong Y, Zaloudek CJ, Goetzl EJ (2004). Induction of protein growth factor systems in the ovaries of transgenic mice overexpressing human type 2 lysophosphatidic acid G protein-coupled receptor (LPA2). Oncogene 23: 122–129.

Hultman CM, SparAcn P, Takei N, Murray RM, Cnattingius S (1999). Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case A – control study. BMJ 318: 421–426.

Ikeda H, Yatomi Y, Yanase M, Satoh H, Nishihara A, Kawabata M *et al.* (1998). Effects of lysophosphatidic acid on proliferation of stellate cells and hepatocytes in culture. Biochem Biophys Res Commun 248: 436–440.

Im DS, Heise CE, Ancellin N, O'Dowd BF, Shei GJ, Heavens RP *et al.* (2000a). Characterization of a novel sphingosine 1-phosphate receptor, Edg-8. J Biol Chem 275: 14281–14286.

Im DS, Heise CE, Harding MA, George SR, O'Dowd BF, Theodorescu D *et al.* (2000b). Molecular cloning and characterization of a lysophosphatidic acid receptor, Edg-7, expressed in prostate. Mol Pharmacol 57: 753–759.

Inoue A, Ishiguro J, Kitamura H, Arima N, Okutani M, Shuto A *et al.* (2012). TGFalpha shedding assay: an accurate and versatile method for detecting GPCR activation. Nat Methods 9: 1021–1029.

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

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

Inoue M, Ma L, Aoki J, Ueda H (2008b). Simultaneous stimulation of spinal NK1 and NMDA receptors produces LPC which undergoes ATX-mediated conversion to LPA, an initiator of neuropathic pain. J Neurochem 107: 1556–1565.

Ishii I, Contos JJ, Fukushima N, Chun J (2000). 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 58: 895–902.

Ishii I, Friedman B, Ye X, Kawamura S, McGiffert C, Contos JJ *et al.* (2001). Selective loss of sphingosine 1-phosphate signaling with no obvious phenotypic abnormality in mice lacking its G protein-coupled receptor, LP(B3)/EDG-3. J Biol Chem 276: 33697–33704.

Ishii I, Ye X, Friedman B, Kawamura S, Contos JJ, Kingsbury MA *et al.* (2002). Marked perinatal lethality and cellular signaling deficits in mice Null for the two sphingosine 1-phosphate receptors, S1P2/LPB2/EDG-5 and S1P3/LPB3/EDG-3. J Biol Chem 277: 25152–25159.

Ishii I, Fukushima N, Ye X, Chun J (2004). Lysophospholipid receptors: signaling and biology. Annu Rev Biochem 73: 321–354.

Ishii M, Egen JG, Klauschen F, Meier-Schellersheim M, Saeki Y, Vacher J *et al.* (2009a). Sphingosine-1-phosphate mobilizes osteoclast precursors and regulates bone homeostasis. Nature 458: 524–528.

Ishii M, Kikuta J, Shimazu Y, Meier-Schellersheim M, Germain RN (2010). Chemorepulsion by blood S1P regulates osteoclast precursor mobilization and bone remodeling *in vivo*. J Exp Med 207: 2793–2798.

Ishii S, Noguchi K, Yanagida K (2009b). Non-Edg family lysophosphatidic acid (LPA) receptors. Prostaglandins Other Lipid Mediat 89: 57–65.

Jacobi FK, Broghammer M, Pesch K, Zrenner E, Berger W, Meindl A *et al.* (2000). Physical mapping and exclusion of GPR34 as the causative gene for congenital stationary night blindness type 1. Hum Genet 107: 89–91.

Jenne CN, Enders A, Rivera R, Watson SR, Bankovich AJ, Pereira JP *et al.* (2009). T-bet-dependent S1P5 expression in NK cells promotes egress from lymph nodes and bone marrow. J Exp Med 206: 2469–2481.

Jeong KJ, Park SY, Seo JH, Lee KB, Choi WS, Han JW *et al.* (2008). Lysophosphatidic acid receptor 2 and Gi/Src pathway mediate cell motility through cyclooxygenase 2 expression in CAOV-3 ovarian cancer cells. Exp Mol Med 40: 607–616.

Jung B, Obinata H, Galvani S, Mendelson K, Ding BS, Skoura A *et al.* (2012). Flow-regulated endothelial S1P receptor-1 signaling sustains vascular development. Dev Cell 23: 600–610.

Kennedy PC, Zhu R, Huang T, Tomsig JL, Mathews TP, David M *et al.* (2011). Characterization of a sphingosine 1-phosphate receptor antagonist prodrug. J Pharmacol Exp Ther 338: 879–889.

Kikuta J, Kawamura S, Okiji F, Shirazaki M, Sakai S, Saito H *et al.* (2013). Sphingosine-1-phosphate-mediated osteoclast precursor monocyte migration is a critical point of control in antibone-resorptive action of active vitamin D. Proc Natl Acad Sci U S A 110: 7009–7013.

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

Kitamura H, Makide K, Shuto A, Ikubo M, Inoue A, Suzuki K *et al.* (2012). GPR34 is a receptor for lysophosphatidylserine with a fatty acid at the sn-2 position. J Biochem 151: 511–518.

Kitayama J, Shida D, Sako A, Ishikawa M, Hama K, Aoki J *et al.* (2004). Over-expression of lysophosphatidic acid receptor-2 in human invasive ductal carcinoma. Breast Cancer Res 6: R640–R646.

Kobashi H, Yaoi T, Oda R, Okajima S, Fujiwara H, Kubo T *et al.* (2006). Lysophospholipid receptors are differentially expressed in rat terminal Schwann cells, as revealed by a single cell RT-PCR and in situ hybridization. Acta Histochem Cytochem 39: 55–60.

Kohno T, Matsuyuki H, Inagaki Y, Igarashi Y (2003). Sphingosine 1-phosphate promotes cell migration through the activation of Cdc42 in Edg-6/S1P4-expressing cells. Genes Cells 8: 685–697.

Komachi M, Tomura H, Malchinkhuu E, Tobo M, Mogi C, Yamada T *et al.* (2009). LPA1 receptors mediate stimulation, whereas LPA2 receptors mediate inhibition, of migration of pancreatic cancer cells in response to lysophosphatidic acid and malignant ascites. Carcinogenesis 30: 457–465.

Kono M, Mi Y, Liu Y, Sasaki T, Allende ML, Wu YP *et al.* (2004). The sphingosine-1-phosphate receptors S1P1, S1P2, and S1P3 function coordinately during embryonic angiogenesis. J Biol Chem 279: 29367–29373.

Kono M, Belyantseva IA, Skoura A, Frolenkov GI, Starost MF, Dreier JL *et al.* (2007). Deafness and stria vascularis defects in $S1P_2$ receptor null mice. J Biol Chem 282: 10690–10696.

Kotarsky K, Boketoft A, Bristulf J, Nilsson NE, Norberg A, Hansson S *et al.* (2006). Lysophosphatidic acid binds to and activates GPR92, a G protein-coupled receptor highly expressed in gastrointestinal lymphocytes. J Pharmacol Exp Ther 318: 619–628.

Kotsikorou E, Lynch DL, Abood ME, Reggio PH (2011). Lipid bilayer molecular dynamics study of lipid-derived agonists of the putative cannabinoid receptor, GPR55. Chem Phys Lipids 164: 131–143.

Kupperman E, An S, Osborne N, Waldron S, Stainier DY (2000). A sphingosine-1-phosphate receptor regulates cell migration during vertebrate heart development. Nature 406: 192–195.

Lai SL, Yao WL, Tsao KC, Houben AJ, Albers HM, Ovaa H *et al.* (2012). Autotaxin/Lpar3 signaling regulates Kupffer's vesicle formation and left-right asymmetry in zebrafish. Development 139: 4439–4448.

Lai YJ, Chen CS, Lin WC, Lin FT (2005). c-Src-mediated phosphorylation of TRIP6 regulates its function in lysophosphatidic acid-induced cell migration. Mol Cell Biol 25: 5859–5868.

Lai YJ, Lin WC, Lin FT (2007). PTPL1/FAP-1 negatively regulates TRIP6 function in lysophosphatidic acid-induced cell migration. J Biol Chem 282: 24381–24387.

Lauckner JE, Jensen JB, Chen HY, Lu HC, Hille B, Mackie K (2008). GPR55 is a cannabinoid receptor that increases intracellular calcium and inhibits M current. Proc Natl Acad Sci U S A 105: 2699–2704.

Lee CW, Rivera R, Gardell S, Dubin AE, Chun J (2006). GPR92 as a new G12/13- and Gq-coupled lysophosphatidic acid receptor that increases cAMP, LPA5. J Biol Chem 281: 23589–23597.

Lee CW, Rivera R, Dubin AE, Chun J (2007). 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 282: 4310–4317.

Lee M, Choi S, Hallden G, Yo SJ, Schichnes D, Aponte GW (2009). P2Y5 is a G(alpha)i, G(alpha)12/13 G protein-coupled receptor activated by lysophosphatidic acid that reduces intestinal cell adhesion. Am J Physiol Gastrointest Liver Physiol 297: G641–G654.

Lee MJ, Thangada S, Liu CH, Thompson BD, Hla T (1998a). Lysophosphatidic acid stimulates the G-protein-coupled receptor EDG-1 as a low affinity agonist. J Biol Chem 273: 22105–22112.

Lee MJ, Van Brocklyn JR, Thangada S, Liu CH, Hand AR, Menzeleev R *et al.* (1998b). Sphingosine-1-phosphate as a ligand for the G protein-coupled receptor EDG-1. Science 279: 1552–1555.

Lee SJ, Yun CC (2010). Colorectal cancer cells – proliferation, survival and invasion by lysophosphatidic acid. Int J Biochem Cell Biol 42: 1907–1910.

Lee SJ, Ritter SL, Zhang H, Shim H, Hall RA, Yun CC (2011). MAGI-3 competes with NHERF-2 to negatively regulate LPA2 receptor signaling in colon cancer cells. Gastroenterology 140: 924–934.

Lee Z, Cheng CT, Zhang H, Subler MA, Wu J, Mukherjee A *et al.* (2008). Role of LPA4/p2y9/GPR23 in negative regulation of cell motility. Mol Biol Cell 19: 5435–5445.

Li TT, Alemayehu M, Aziziyeh AI, Pape C, Pampillo M, Postovit LM *et al.* (2009). Beta-arrestin/Ral signaling regulates lysophosphatidic acid-mediated migration and invasion of human breast tumor cells. Mol Cancer Res 7: 1064–1077.

Liebscher I, Muller U, Teupser D, Engemaier E, Engel KM, Ritscher L *et al.* (2011). Altered immune response in mice deficient for the G protein-coupled receptor GPR34. J Biol Chem 286: 2101–2110.

Lin FT, Lai YJ (2008). Regulation of the LPA2 receptor signaling through the carboxyl-terminal tail-mediated protein–protein interactions. Biochim Biophys Acta 1781: 558–562.

Lin ME, Rivera RR, Chun J (2012). Targeted deletion of LPA5 identifies novel roles for lysophosphatidic acid signaling in development of neuropathic pain. J Biol Chem 287: 17608–17617.

Lin S, Yeruva S, He P, Singh AK, Zhang H, Chen M *et al.* (2010). Lysophosphatidic acid stimulates the intestinal brush border Na(+)/H(+) exchanger 3 and fluid absorption via LPA(5) and NHERF2. Gastroenterology 138: 649–658.

Liu X, Yue S, Li C, Yang L, You H, Li L (2011). Essential roles of sphingosine 1-phosphate receptor types 1 and 3 in human hepatic stellate cells motility and activation. J Cell Physiol 226: 2370–2377.

Liu Y, Wada R, Yamashita T, Mi Y, Deng CX, Hobson JP *et al.* (2000). Edg-1, the G protein-coupled receptor for sphingosine-1-phosphate, is essential for vascular maturation. J Clin Invest 106: 951–961.

Liu YB, Kharode Y, Bodine PV, Yaworsky PJ, Robinson JA, Billiard J (2010). LPA induces osteoblast differentiation through interplay of two receptors: LPA1 and LPA4. J Cell Biochem 109: 794–800.

Loh KC, Leong WI, Carlson ME, Oskouian B, Kumar A, Fyrst H *et al.* (2012). Sphingosine-1-phosphate enhances satellite cell activation in dystrophic muscles through a S1PR2/STAT3 signaling pathway. PLoS ONE 7: e37218.

Ma L, Uchida H, Nagai J, Inoue M, Chun J, Aoki J *et al.* (2009). Lysophosphatidic acid-3 receptor-mediated feed-forward production of lysophosphatidic acid: an initiator of nerve injury-induced neuropathic pain. Mol Pain 5: 64.

Maceyka M, Harikumar KB, Milstien S, Spiegel S (2012). Sphingosine-1-phosphate signaling and its role in disease. Trends Cell Biol 22: 50–60.

Maher B (2012). ENCODE: the human encyclopaedia. Nature 489: 46–48.

Makide K, Aoki J (2013). GPR34 as a lysophosphatidylserine receptor. J Biochem 153: 327–329.

Malek RL, Toman RE, Edsall LC, Wong S, Chiu J, Letterle CA *et al.* (2001). Nrg-1 belongs to the endothelial differentiation gene family of G protein-coupled sphingosine-1-phosphate receptors. J Biol Chem 276: 5692–5699.

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

Masiello LM, Fotos JS, Galileo DS, Karin NJ (2006). Lysophosphatidic acid induces chemotaxis in MC3T3-E1 osteoblastic cells. Bone 39: 72–82.

Matas-Rico E, García-Diaz B, Llebrez-Zayas P, López-Barroso D, Santín L, Pedraza C *et al.* (2008). Deletion of lysophosphatidic acid receptor LPA1 reduces neurogenesis in the mouse dentate gyrus. Mol Cell Neurosci 39: 342–355.

Matloubian M, Lo CG, Cinamon G, Lesneski MJ, Xu Y, Brinkmann V *et al.* (2004). Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature 427: 355–360.

Mayol K, Biajoux V, Marvel J, Balabanian K, Walzer T (2011). Sequential desensitization of CXCR4 and S1P5 controls natural killer cell trafficking. Blood 118: 4863–4871.

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

Mendelson K, Zygmunt T, Torres-Vazquez J, Evans T, Hla T (2013). Sphingosine 1-phosphate receptor signaling regulates proper embryonic vascular patterning. J Biol Chem 288: 2143–2156.

Mohamed OA, Jonnaert M, Labelle-Dumais C, Kuroda K, Clarke HJ, Dufort D (2005). Uterine Wnt/beta-catenin signaling is required for implantation. Proc Natl Acad Sci U S A 102: 8579–8584.

Musazzi L, Di Daniel E, Maycox P, Racagni G, Popoli M (2010). Abnormalities in alpha/beta-CaMKII and related mechanisms suggest synaptic dysfunction in hippocampus of LPA1 receptor knockout mice. Int J Neuropsychopharmacol 14: 941–953.

Mutoh T, Rivera R, Chun J (2012). Insights into the pharmacological relevance of lysophospholipid receptors. Br J Pharmacol 165: 829–844.

Nahum S, Morice-Picard F, Taieb A, Sprecher E (2011). A novel mutation in LPAR6 causes autosomal recessive hypotrichosis of the scalp. Clin Exp Dermatol 36: 188–194.

Niessen F, Schaffner F, Furlan-Freguia C, Pawlinski R, Bhattacharjee G, Chun J *et al.* (2008). Dendritic cell PAR1-S1P3 signalling couples coagulation and inflammation. Nature 452: 654–658.

Nobusue H, Kondo D, Yamamoto M, Kano K (2010). Effects of lysophosphatidic acid on the *in vitro* proliferation and differentiation of a novel porcine preadipocyte cell line. Comp Biochem Physiol B Biochem Mol Biol 157: 401–407.

Noguchi K, Chun J (2011). Roles for lysophospholipid S1P receptors in multiple sclerosis. Crit Rev Biochem Mol Biol 46: 2–10.

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

Noguchi K, Herr D, Mutoh T, Chun J (2009). Lysophosphatidic acid (LPA) and its receptors. Curr Opin Pharmacol 9: 15–23.

Obo Y, Yamada T, Furukawa M, Hotta M, Honoki K, Fukushima N *et al.* (2009). Frequent mutations of lysophosphatidic acid receptor-1 gene in rat liver tumors. Mutat Res/Fundam Mol Mech Mutagen 660: 47–50.

Oh DY, Yoon JM, Moon MJ, Hwang JI, Choe H, Lee JY *et al.* (2008). Identification of farnesyl pyrophosphate and N-arachidonylglycine as endogenous ligands for GPR92. J Biol Chem 283: 21054–21064.

Ohotski J, Long JS, Orange C, Elsberger B, Mallon E, Doughty J *et al.* (2012). Expression of sphingosine 1-phosphate receptor 4 and sphingosine kinase 1 is associated with outcome in oestrogen receptor-negative breast cancer. Br J Cancer 106: 1453–1459.

Ohta H, Sato K, Murata N, Damirin A, Malchinkhuu E, Kon J *et al.* (2003). Ki16425, a subtype-selective antagonist for EDG-family lysophosphatidic acid receptors. Mol Pharmacol 64: 994–1005.

Ohuchi H, Hamada A, Matsuda H, Takagi A, Tanaka M, Aoki J *et al.* (2008). Expression patterns of the lysophospholipid receptor genes during mouse early development. Dev Dyn 237: 3280–3294.

Okabe K, Hayashi M, Fujii M, Honoki K, Mori T, Fukushima N *et al.* (2010). Mutations of lysophosphatidic acid receptor genes in human osteosarcoma cells. Pathobiology 77: 278–282.

Olivera A, Eisner C, Kitamura Y, Dillahunt S, Allende L, Tuymetova G *et al.* (2010). Sphingosine kinase 1 and sphingosine-1-phosphate receptor 2 are vital to recovery from anaphylactic shock in mice. J Clin Invest 120: 1429–1240.

Olivera A, Dillahunt SE, Rivera J (2013). Interrogation of sphingosine-1-phosphate receptor 2 function *in vivo* reveals a prominent role in the recovery from IgE and IgG-mediated anaphylaxis with minimal effect on its onset. Immunol Lett 150: 89–96.

Oo ML, Thangada S, Wu MT, Liu CH, Macdonald TL, Lynch KR *et al.* (2007). Immunosuppressive and anti-angiogenic sphingosine 1-phosphate receptor-1 agonists induce ubiquitinylation and proteasomal degradation of the receptor. J Biol Chem 282: 9082–9089.

Osada M, Yatomi Y, Ohmori T, Ikeda H, Ozaki Y (2002). Enhancement of sphingosine 1-phosphate-induced migration of vascular endothelial cells and smooth muscle cells by an EDG-5 antagonist. Biochem Biophys Res Commun 299: 483–487.

Ota H, Beutz MA, Ito M, Abe K, Oka M, McMurtry IF (2011). S1P(4) receptor mediates S1P-induced vasoconstriction in normotensive and hypertensive rat lungs. Pulm Circ 1: 399–404.

Pan S, Mi Y, Pally C, Beerli C, Chen A, Guerini D *et al.* (2006). A monoselective sphingosine-1-phosphate receptor-1 agonist prevents allograft rejection in a stringent rat heart transplantation model. Chem Biol 13: 1227–1234.

Panchatcharam M, Miriyala S, Yang F, Rojas M, End C, Vallant C *et al.* (2008). Lysophosphatidic acid receptors 1 and 2 play roles in regulation of vascular injury responses but not blood pressure. Circ Res 103: 662–670.

Panther E, Idzko M, Corinti S, Ferrari D, Herouy Y, Mockenhaupt M *et al.* (2002). The influence of lysophosphatidic acid on the functions of human dendritic cells. J Immunol 169: 4129–4135.

Pappu R, Schwab SR, Cornelissen I, Pereira JP, Regard JB, Xu Y *et al.* (2007). Promotion of lymphocyte egress into blood and lymph by distinct sources of sphingosine-1-phosphate. Science 316: 295–298.

Pasternack SM, von Kugelgen I, Aboud KA, Lee Y-A, Ruschendorf F, Voss K *et al.* (2008). G protein-coupled receptor P2Y5 and its ligand LPA are involved in maintenance of human hair growth. Nat Genet 40: 329–334.

Pasternack SM, von Kugelgen I, Muller M, Oji V, Traupe H, Sprecher E *et al.* (2009). *In vitro* analysis of LIPH mutations causing hypotrichosis simplex: evidence confirming the role of lipase H and lysophosphatidic acid in hair growth. J Invest Dermatol 129: 2772–2776.

Pawson AJ, Sharman JL, Benson HE, Faccenda E, Alexander SP, Buneman OP *et al.* (2014). The IUPHAR/BPS Guide to

PHARMACOLOGY: an expert-driven knowledgebase of drug targets and their ligands. Nucleic Acids Res 42 (Database Issue): D1098–D1106.

Pham TH, Baluk P, Xu Y, Grigorova I, Bankovich AJ, Pappu R *et al.* (2010). Lymphatic endothelial cell sphingosine kinase activity is required for lymphocyte egress and lymphatic patterning. J Exp Med 207: 17–27.

Ponnusamy S, Selvam SP, Mehrotra S, Kawamori T, Snider AJ, Obeid LM *et al.* (2012). Communication between host organism and cancer cells is transduced by systemic sphingosine kinase 1/sphingosine 1-phosphate signalling to regulate tumour metastasis. EMBO Mol Med 4: 761–775.

Pradere JP, Klein J, Gres S, Guigne C, Neau E, Valet P *et al.* (2007). LPA1 receptor activation promotes renal interstitial fibrosis. J Am Soc Nephrol 18: 3110–3118.

Pradere JP, Gonzalez J, Klein J, Valet P, Gres S, Salant D *et al.* (2008). Lysophosphatidic acid and renal fibrosis. Biochim Biophys Acta 1781: 582–587.

Qian L, Xu Y, Simper T, Jiang G, Aoki J, Umezu-Goto M *et al.* (2006). Phosphorothioate analogues of alkyl lysophosphatidic acid as LPA3 receptor-selective agonists. Chem Med Chem 1: 376–383.

Quancard J, Bollbuck B, Janser P, Angst D, Berst F, Buehlmayer P *et al.* (2012). A potent and selective S1P(1) antagonist with efficacy in experimental autoimmune encephalomyelitis. Chem Biol 19: 1142–1151.

Rajagopal K, Lefkowitz RJ, Rockman HA (2005). When 7 transmembrane receptors are not G protein-coupled receptors. J Clin Invest 115: 2971–2974.

Rao S, Garrett-Sinha LA, Yoon J, Simon MC (1999). The Ets factors PU.1 and Spi-B regulate the transcription *in vivo* of P2Y10, a lymphoid restricted heptahelical receptor. J Biol Chem 274: 34245–34252.

Rapizzi E, Donati C, Cencetti F, Nincheri P, Bruni P (2008). Sphingosine 1-phosphate differentially regulates proliferation of C2C12 reserve cells and myoblasts. Mol Cell Biochem 314: 193–199.

Rhee HJ, Nam JS, Sun Y, Kim MJ, Choi HK, Han DH *et al.* (2006). Lysophosphatidic acid stimulates cAMP accumulation and cAMP response element-binding protein phosphorylation in immortalized hippocampal progenitor cells. Neuroreport 17: 523–526.

Ritscher L, Engemaier E, Staubert C, Liebscher I, Schmidt P, Hermsdorf T *et al.* (2012). The ligand specificity of the G-protein-coupled receptor GPR34. Biochem J 443: 841–850.

Roberts C, Winter P, Shilliam CS, Hughes ZA, Langmead C, Maycox PR *et al.* (2005). Neurochemical changes in LPA1 receptor deficient mice – a putative model of schizophrenia. Neurochem Res 30: 371–377.

Rosen H, Stevens RC, Hanson M, Roberts E, Oldstone MB (2013). Sphingosine-1-phosphate and its receptors: structure, signaling, and influence. Annu Rev Biochem 82: 637–662.

Rubenfeld J, Guo J, Sookrung N, Chen R, Chaicumpa W, Casolaro V *et al.* (2006). Lysophosphatidic acid enhances interleukin-13 gene expression and promoter activity in T cells. Am J Physiol Lung Cell Mol Physiol 290: L66–L74.

Sammani S, Moreno-Vinasco L, Mirzapoiazova T, Singleton PA, Chiang ET, Evenoski CL *et al.* (2010). Differential effects of sphingosine 1-phosphate receptors on airway and vascular barrier function in the murine lung. Am J Respir Cell Mol Biol 43: 394–402.

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

Sanna MG, Liao J, Jo E, Alfonso C, Ahn MY, Peterson MS *et al.* (2004). Sphingosine 1-phosphate (S1P) receptor subtypes S1P1 and S1P3, respectively, regulate lymphocyte recirculation and heart rate. J Biol Chem 279: 13839–13848.

Sanna MG, Wang SK, Gonzalez-Cabrera PJ, Don A, Marsolais D, Matheu MP *et al.* (2006). Enhancement of capillary leakage and restoration of lymphocyte egress by a chiral S1P1 antagonist *in vivo*. Nat Chem Biol 2: 434–441.

Santin LJ, Bilbao A, Pedraza C, Matas-Rico E, Lopez-Barroso D, Castilla-Ortega E *et al.* (2009). Behavioral phenotype of maLPA1-null mice: increased anxiety-like behavior and spatial memory deficits. Genes Brain Behav 8: 772–784.

Schulze T, Golfier S, Tabeling C, Rabel K, Graler MH, Witzenrath M *et al.* (2011). Sphingosine-1-phospate receptor 4 (S1P(4)) deficiency profoundly affects dendritic cell function and TH17-cell differentiation in a murine model. FASEB J 25: 4024–4036.

Schwab SR, Cyster JG (2007). Finding a way out: lymphocyte egress from lymphoid organs. Nat Immunol 8: 1295–1301.

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

Shida D, Kitayama J, Yamaguchi H, Okaji Y, Tsuno NH, Watanabe T *et al.* (2003). Lysophosphatidic acid (LPA) enhances the metastatic potential of human colon carcinoma DLD1 cells through LPA1. Cancer Res 63: 1706–1711.

Shida D, Fang X, Kordula T, Takabe K, Lepine S, Alvarez SE *et al.* (2008). Cross-talk between LPA1 and epidermal growth factor receptors mediates up-regulation of sphingosine kinase 1 to promote gastric cancer cell motility and invasion. Cancer Res 68: 6569–6577.

Shimomura Y, Garzon MC, Kristal L, Shapiro L, Christiano AM (2009). Autosomal recessive woolly hair with hypotrichosis caused by a novel homozygous mutation in the P2RY5 gene. Exp Dermatol 18: 218–221.

Shin KJ, Kim YL, Lee S, Kim DK, Ahn C, Chung J *et al.* (2009). Lysophosphatidic acid signaling through LPA receptor subtype 1 induces colony scattering of gastrointestinal cancer cells. J Cancer Res Clin Oncol 135: 45–52.

Shinkuma S, Akiyama M, Inoue A, Aoki J, Natsuga K, Nomura T *et al.* (2010). Prevalent LIPH founder mutations lead to loss of P2Y5 activation ability of PA-PLA1alpha in autosomal recessive hypotrichosis. Hum Mutat 31: 602–610.

Shoham AB, Malkinson G, Krief S, Shwartz Y, Ely Y, Ferrara N *et al.* (2012). S1P1 inhibits sprouting angiogenesis during vascular development. Development 139: 3859–3869.

Sievers F, Wilm A, Dineen D, Gibson TJ, Karplus K, Li W *et al.* (2011). Fast, scalable generation of high-quality protein multiple sequence alignments using Clustal Omega. Mol Syst Biol 7: 539.

Simon MF, Daviaud D, Pradere JP, Gres S, Guigne C, Wabitsch M *et al.* (2005). Lysophosphatidic acid inhibits adipocyte differentiation via lysophosphatidic acid 1 receptor-dependent down-regulation of peroxisome proliferator-activated receptor gamma2. J Biol Chem 280: 14656–14662.

Skipper M, Dhand R, Campbell P (2012). Presenting ENCODE. Nature 489: 45.

Skoura A, Hla T (2009). Regulation of vascular physiology and pathology by the S1P2 receptor subtype. Cardiovasc Res 82: 221–228.

Soliven B, Miron V, Chun J (2011). The neurobiology of sphingosine 1-phosphate signaling and sphingosine 1-phosphate receptor modulators. Neurology 76: S9–S14.

Song H, Lim H, Paria BC, Matsumoto H, Swift LL, Morrow J *et al.* (2002). Cytosolic phospholipase A2alpha is crucial [correction of A2alpha deficiency is crucial] for 'on-time' embryo implantation that directs subsequent development. Development 129: 2879–2889.

Sonoda H, Aoki J, Hiramatsu T, Ishida M, Bandoh K, Nagai Y *et al.* (2002). A novel phosphatidic acid-selective phospholipase A1 that produces lysophosphatidic acid. J Biol Chem 277: 34254–34263.

Sorensen SD, Nicole O, Peavy RD, Montoya LM, Lee CJ, Murphy TJ *et al.* (2003). Common signaling pathways link activation of murine PAR-1, LPA, and S1P receptors to proliferation of astrocytes. Mol Pharmacol 64: 1199–1209.

Spiegel S, Milstien S (2011). The outs and the ins of sphingosine-1-phosphate in immunity. Nat Rev Immunol 11: 403–415.

Spohr TC, Choi JW, Gardell SE, Herr DR, Rehen SK, Gomes FC *et al.* (2008). Lysophosphatidic acid receptor-dependent secondary effects via astrocytes promote neuronal differentiation. J Biol Chem 283: 7470–7479.

Sugita K, Yamamura C, Tabata K, Fujita N (2013). Expression of orphan G-protein coupled receptor GPR174 in CHO cells induced morphological changes and proliferation delay via increasing intracellular cAMP. Biochem Biophys Res Commun 430: 190–195.

Sugo T, Tachimoto H, Chikatsu T, Murakami Y, Kikukawa Y, Sato S *et al.* (2006). Identification of a lysophosphatidylserine receptor on mast cells. Biochem Biophys Res Commun 341: 1078–1087.

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

Sukocheva O, Wadham C, Holmes A, Albanese N, Verrier E, Feng F *et al.* (2006). Estrogen transactivates EGFR via the sphingosine 1-phosphate receptor Edg-3: the role of sphingosine kinase-1. J Cell Biol 173: 301–310.

Sukocheva O, Wadham C, Xia P (2013). Estrogen defines the dynamics and destination of transactivated EGF receptor in breast cancer cells: role of S1P(3) receptor and Cdc42. Exp Cell Res 319: 455–465.

Sumida H, Noguchi K, Kihara Y, Abe M, Yanagida K, Hamano F *et al.* (2010). LPA4 regulates blood and lymphatic vessel formation during mouse embryogenesis. Blood 116: 5060–5070.

Sun X, Singleton PA, Letsiou E, Zhao J, Belvitch P, Sammani S *et al.* (2012). Sphingosine-1-phosphate receptor-3 is a novel biomarker in acute lung injury. Am J Respir Cell Mol Biol 47: 628–636.

Swaney JS, Chapman C, Correa LD, Stebbins KJ, Bundey RA, Prodanovich PC *et al.* (2010). A novel, orally active LPA(1) receptor antagonist inhibits lung fibrosis in the mouse bleomycin model. Br J Pharmacol 160: 1699–1713.

Tager AM, LaCamera P, Shea BS, Campanella GS, Selman M, Zhao Z *et al.* (2008). The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. Nat Med 14: 45–54.

Taghavi P, Verhoeven E, Jacobs JJ, Lambooij JP, Stortelers C, Tanger E *et al.* (2008). *In vitro* genetic screen identifies a cooperative role for LPA signaling and c-Myc in cell transformation. Oncogene 27: 6806–6816.

Trimbuch T, Beed P, Vogt J, Schuchmann S, Maier N, Kintscher M *et al.* (2009). Synaptic PRG-1 modulates excitatory transmission via lipid phosphate-mediated signaling. Cell 138: 1222–1235.

UniprotConsortium (2013). Update on activities at the Universal Protein Resource (UniProt) in 2013. Nucleic Acids Res 41: D43–D47.

Valet P, Pages C, Jeanneton O, Daviaud D, Barbe P, Record M *et al.* (1998). Alpha2-adrenergic receptor-mediated release of lysophosphatidic acid by adipocytes. A paracrine signal for preadipocyte growth. J Clin Invest 101: 1431–1438.

Van Brocklyn JR, Graler MH, Bernhardt G, Hobson JP, Lipp M, Spiegel S (2000). Sphingosine-1-phosphate is a ligand for the G protein-coupled receptor EDG-6. Blood 95: 2624–2629.

Walzer T, Chiossone L, Chaix J, Calver A, Carozzo C, Garrigue-Antar L *et al.* (2007). Natural killer cell trafficking *in vivo* requires a dedicated sphingosine 1-phosphate receptor. Nat Immunol 8: 1337–1344.

Wang L, Dudek SM (2009). Regulation of vascular permeability by sphingosine 1-phosphate. Microvasc Res 77: 39–45.

Watanabe N, Ikeda H, Nakamura K, Ohkawa R, Kume Y, Aoki J *et al.* (2007). Both plasma lysophosphatidic acid and serum autotaxin levels are increased in chronic hepatitis C. J Clin Gastroenterol 41: 616–623.

Watson C, Long JS, Orange C, Tannahill CL, Mallon E, McGlynn LM *et al.* (2010). High expression of sphingosine 1-phosphate receptors, S1P1 and S1P3, sphingosine kinase 1, and extracellular signal-regulated kinase-1/2 is associated with development of tamoxifen resistance in estrogen receptor-positive breast cancer patients. Am J Pathol 177: 2205–2215.

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

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

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

Williams JR, Khandoga AL, Goyal P, Fells JI, Perygin DH, Siess W *et al.* (2009). Unique ligand selectivity of the GPR92/LPA5 lysophosphatidate receptor indicates role in human platelet activation. J Biol Chem 284: 17304–17319.

Wu J, Zern MA (2000). Hepatic stellate cells: a target for the treatment of liver fibrosis. J Gastroenterol 35: 665–672.

Yamada T, Sato K, Komachi M, Malchinkhuu E, Tobo M, Kimura T *et al.* (2004). Lysophosphatidic acid (LPA) in malignant ascites stimulates motility of human pancreatic cancer cells through LPA1. J Biol Chem 279: 6595–6605.

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

Yanagida K, Masago K, Nakanishi H, Kihara Y, Hamano F, Tajima Y *et al.* (2009). Identification and characterization of a novel lysophosphatidic acid receptor, p2y5/LPA6. J Biol Chem 284: 17731–17741.

Yanagida K, Kurikawa Y, Shimizu T, Ishii S (2013). Current progress in non-Edg family LPA receptor research. Biochim Biophys Acta 1831: 33–41.

Yang L, Yue S, Liu X, Han Z, Zhang Y, Li L (2013). Sphingosine kinase/sphingosine 1-phosphate (S1P)/S1P receptor axis is involved in liver fibrosis-associated angiogenesis. J Hepatol 59: 114–123.

Ye D, Lin F (2013). S1pr2/Galpha13 signaling controls myocardial migration by regulating endoderm convergence. Development 140: 789–799.

Ye X (2008). Lysophospholipid signaling in the function and pathology of the reproductive system. Hum Reprod Update 14: 519–536.

Ye X, Hama K, Contos JJ, Anliker B, Inoue A, Skinner MK *et al*. (2005). LPA3-mediated lysophosphatidic acid signalling in embryo implantation and spacing. Nature 435: 104–108.

Yu N, Lariosa-Willingham KD, Lin FF, Webb M, Rao TS (2004). Characterization of lysophosphatidic acid and sphingosine-1-phosphate-mediated signal transduction in rat cortical oligodendrocytes. Glia 45: 17–27.

Yu S, Murph MM, Lu Y, Liu S, Hall HS, Liu J *et al*. (2008). Lysophosphatidic acid receptors determine tumorigenicity and aggressiveness of ovarian cancer cells. J Natl Cancer Inst 100: 1630–1642.

Yu W, Ma S, Wang L, Zuo B, Li M, Qiao Z *et al*. (2013). Upregulation of GPR34 expression affects the progression and prognosis of human gastric adenocarcinoma by PI3K/PDK1/AKT pathway. Histol Histopathol 28: 1629–1638.

Yuan XB, Jin M, Xu X, Song YQ, Wu CP, Poo MM *et al*. (2003). Signalling and crosstalk of Rho GTPases in mediating axon guidance. Nat Cell Biol 5: 38–45.

Yun CC, Sun H, Wang D, Rusovici R, Castleberry A, Hall RA *et al*. (2005). LPA2 receptor mediates mitogenic signals in human colon cancer cells. Am J Physiol Cell Physiol 289: C2–C11.

Yung Y, Mutoh T, Lin ME, Noguchi K, Rivera RR, Choi JW *et al*. (2011). Lysophosphatidic acid signaling may initiate fetal hydrocephalus. Sci Transl Med 3: 99ra87.

Zhang G, Contos JJ, Weiner JA, Fukushima N, Chun J (1999). Comparative analysis of three murine G-protein coupled receptors activated by sphingosine-1-phosphate. Gene 227: 89–99.

Zhao SX, Xue LQ, Liu W, Gu ZH, Pan CM, Yang SY *et al*. (2013). Robust evidence for five new Graves' disease risk loci from a staged genome-wide association analysis. Hum Mol Genet 22: 3347–3362.

Zheng Y, Voice JK, Kong Y, Goetzl EJ (2000). Altered expression and functional profile of lysophosphatidic acid receptors in mitogen-activated human blood T lymphocytes. FASEB J 14: 2387–2389.

Zheng Y, Kong Y, Goetzl EJ (2001). Lysophosphatidic acid receptor-selective effects on Jurkat T cell migration through a Matrigel model basement membrane. J Immunol 166: 2317–2322.