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Lysophospholipid signaling in the function and pathology of the reproductive system

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BACKGROUND: Lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P) are two prominent signaling lysophospholipids (LPs) exerting their functions through a group of G protein-coupled receptors (GPCRs). This review covers current knowledge of the LP signaling in the function and pathology of the reproductive system. METHODS: PubMed was searched up to May 2008 for papers on lysophospholipids/LPA/S1P/LPC/SPC in combination with each part of the reproductive system, such as testis/ovary/uterus. RESULTS: LPA and SIP are found in significant amounts in serum and other biological fluids. To date, 10 LP receptors have been identified, including LPA_{1-5} and $S1P_{1-5}$. *In vitro* and *in vivo* studies from the past three decades have demonstrated or suggested the physiological functions of LP signaling in reproduction, such as spermatogenesis, male sexual function, ovarian function, fertilization, early embryo development, embryo spacing, implantation, decidualization, pregnancy maintenance and parturition, as well as pathological roles in ovary, cervix, mammary gland and prostate cancers. CONCLUSIONS: Receptor knock-out and other studies indicate tissue-specific and receptor-specific functions of LP signaling in reproduction. More comprehensive studies are required to define mechanisms of LP signaling and explore the potential use as a therapeutic target.

Key words: cancer; LPA; lysophospholipid receptors; reproduction; S1P

Introduction

Lysophospholipids (LPs) were originally recognized as quantitatively minor lipid species produced during the biosynthesis of membrane phospholipids (Pieringer *et al.*, 1967). The signaling properties of LPs were initially noticed in the 1960s (Vogt, 1963). Later, more studies established LPs as signaling molecules (Tokumura *et al.*, 1978, 1980; van Corven *et al.*, 1989; Durieux *et al.*, 1993; Hill *et al.*, 1994a). LPs demonstrated to be involved in signaling include lysophosphatidic acid (LPA), sphingosine-1-phosphate (S1P), lysophosphatidylcholine (LPC) and sphingosylphosphorylcholine (SPC). Early studies revealed the effects of LPA on blood pressure, uterine smooth muscle contraction and platelet aggregation (Tokumura *et al.*, 1978, 1980; Gerrard *et al.*, 1979; Schumacher *et al.*, 1979). Subsequently, numerous studies identified a range of physiological processes in which LPs were involved, e.g. cell proliferation (van Corven *et al.*, 1989; Zhang *et al.*, 1991; Olivera and Spiegel, 1993; Goodemote *et al.*, 1995; Yoshida *et al.*, 1996), cell survival (Cuvillier *et al.*, 1996; Van Brocklyn *et al.*, 1998; Goetzl *et al.*, 1999; Weiner and Chun, 1999), cell differentiation (Piazza *et al.*, 1995; Sato *et al.*, 1998), cell morphological changes (Ridley and Hall, 1992; Jalink *et al.*, 1993, 1994; Bornfeldt *et al.*, 1995; Postma *et al.*, 1996; Sato *et al.*, 1997; Fukushima *et al.*, 1998), regulation of gap junctions (Hill *et al.*, 1994a), stimulation of the serum response element (Hill *et al.*, 1994b), induction of inward ion currents (Durieux *et al.*, 1993), etc. These broad biological effects have attracted increasing attention to LP signaling research in recent years. A significant portion of the recent discoveries are related to reproduction. This review will briefly introduce receptor-mediated LP signaling and comprehensively update the physiological and pathological functions of LP signaling in the reproductive system.

Materials and Methods

PubMed was searched up to May 2008 for papers on lysophospholipids/LPA/S1P/LPC/SPC in combination with each part of the reproductive system, such as testis/ovary/uterus.

Signaling LPs and LP signaling

Extracellular signaling LPs have simple chemical structures: a 3-carbon glycerol or a sphingoid backbone with a single acyl chain of varied

length and saturation (Ishii *et al.*, 2004). LPA and S1P are the most studied extracellular signaling LPs. Some LPs also have intracellular functions that are not covered here (Spiegel *et al.*, 1994, 1996; Spiegel and Milstien, 2003; Pebay *et al.*, 2007; Valentine *et al.*, 2007).

LPA has been detected in significant amounts in biological fluids such as serum (up to micromolar concentration) and plasma (Tokumura *et al.*, 1986; Baker *et al.*, 2000; Aoki *et al.*, 2002; Sano *et al.*, 2002), saliva (Sugiura *et al.*, 2002), blister fluid (Mazereeuw-Hautier *et al.*, 2005), tear (Liliom *et al.*, 1998), hen egg white (Nakane *et al.*, 2001), follicular fluid (Tokumura *et al.*, 1999), seminal plasma (Hama *et al.*, 2002) and ascites (Xu *et al.*, 1995b, 1998, 2003; Tokumura *et al.*, 2007). Evidence has shown that many cell types such as activated platelets (Mauco *et al.*, 1978; Gerrard and Robinson, 1989; Eichholtz *et al.*, 1993; Fourcade *et al.*, 1995), erythrocytes (Fourcade *et al.*, 1995), postmitotic neurons (Fukushima *et al.*, 2000), ovarian and cervical cancer cells (Shen *et al.*, 1998; Eder *et al.*, 2000; Luquain *et al.*, 2003), adipocytes (Gesta *et al.*, 2002) and mast cells (Mori *et al.*, 2007) are able to produce LPA.

The main pathways for LPA production may differ in various cell types and the metabolism of LPA in most cell types is still unclear (Aoki, 2004). Studies on the production of extracellular LPA in the serum have suggested two main pathways involving phospholipase D (PLD), phospholipase A1 (PLA1), phospholipase A2 (PLA2) and autotaxin/lysophospholipase D (ATX/lysoPLD) (Fig. 1). One main pathway is the cleavage of phospholipids (PLs) by PLD to form phosphatidic acids (PAs). LPA is generated from hydrolysis of PAs by PLA1 and PLA2, this process can be reversed by LPA acyltransferases (Leung, 2001). The other main pathway is the cleavage of LPs such as LPC, lysophosphatidylethanolamine and lysophosphatidylserine, by ATX/lysoPLD to free LPA. PLA1 and PLA2 are involved in the production of LPs from membrane PLs in this pathway. LPA is dephosphorylated to monoacylglycerol by a family of three membrane-bound lipid phosphate phosphatases (LPP1, LPP2 and LPP3). Extracellular LPA is normally bound to molecules, such as albumin, fatty acid binding proteins, gelsolin and lipoproteins, for transportation and stability (Gaits *et al.*, 1997; Pages *et al.*, 2001; Mills and Moolenaar, 2003; Aoki, 2004).

S1P also is found in significant levels in serum and plasma (Yatomi *et al.*, 2001). Major sources are platelets and erythrocytes (Yatomi *et al.*, 1995; English *et al.*, 2000; Hanel *et al.*, 2007; Ito *et al.*, 2007; Pappu *et al.*, 2007). Lung endothelial cells (Zhao *et al.*, 2007) and mast cells (Mitra *et al.*, 2006) can also produce this molecule. S1P is the product of sphingosine phosphorylation by sphingosine kinases (SphK1 and SphK2). Sphingosine is produced from ceramide, a pro-apoptotic factor. Specific dephosphorylation of S1P by S1P phosphohydrolases or non-specific dephosphorylation of S1P by LPPs can reverse this process. S1P is metabolized by S1P lyase to form phosphoethanolamine and hexadecenal (Brindley *et al.*, 2002; Le Stunff *et al.*, 2004). As with LPA, extracellular S1P is also bound to molecules, such as serum albumin and lipoproteins (Okajima 2002; Kobayashi *et al.*, 2006).

Previous debates about the mechanisms of extracellular LP signaling have been silenced by the identification of molecularly cloned receptors (Chun, 1999; Chun *et al.*, 2000; Fukushima *et al.*, 2001; Ishii *et al.*, 2004). While the majority of rigorous data supported the existence of specific receptors for extracellular LPA and S1P, other data, such as the reported lack of stereo-specific effects, the detergent-like chemical structures and the use of LPs at high concentrations were consistent with actions via non-receptor mechanisms such as membrane perturbation or disruption. The cloning of the first LPA receptor in 1996 (Hecht *et al.*, 1996) and the following identification of nine more LP receptors, as well as the establishement of receptor-specific functions, have clearly defined a receptor-mediated mechanism for the effects of extracellular LPs (Moolenaar, 2000; Spiegel and Milstien, 2003; Anliker and Chun, 2004; Ishii *et al.*, 2004; Birgbauer and Chun, 2006; Gardell *et al.*, 2006; Herr and Chun, 2007; Meyer zu Heringdorf and Jakobs, 2007; Watterson *et al.*, 2007).

The 10 so far identified LP receptors include LPA_{1-5} and $S1P_{1-5}$ (Table I). Suggested additional possible LP receptor candidates include: GPR87 and P2Y5 for LPA (Tabata *et al.*, 2007; Pasternack *et al.*, 2008); GPR3 and GPR12 for S1P and SPC (Uhlenbrock *et al.*, 2002, 2003; Hinckley *et al.*, 2005); G2A for LPC; OGR1 and GPR4 for SPC, etc (Xu 2002; Bektas *et al.*, 2003; Ishii *et al.*, 2004; Murakami *et al.*, 2004; Seuwen *et al.*, 2006). LPA_{1-5} and $S1P_{1-5}$ are transmembrane G protein-coupled receptors (GPCRs). They can differentially couple with $G_{12/13}$, G_q, $G_{i/o}$ or G_s to activate the downstream signaling cascades and eventually lead to LP-induced cellular functions, such as cell proliferation, cell survival, cell differentiation and cell morphological changes (Table I) (Fig. 1) (Ye *et al.*, 2002; Ishii *et al.*, 2004; Gardell *et al.*, 2006; Hannun and Obeid, 2008).

The LP receptors have overlapping expression patterns in specific tissues and each receptor has its unique expression profile. Based on data from northern analyses, the expression of LPA_1, $S1P_1$, $S1P_2$ and $S1P_3$ is ubiquitous although the expression levels in different tissues vary, whereas the expression of other receptors is more confined: LPA_2 is highly expressed in testis and kidney; LPA_3 in testis, kidney and lung; LPA_4 in heart and skin; LPA_5 in small intestine and stomach, with lower levels in skin, spleen and thymus; $S1P_4$ in lung, thymus and spleen; $S1P_5$ in brain and skin (Contos *et al.*, 2000b; Ishii *et al.*, 2001; Lee *et al.*, 2006a, 2007). The expression of LP receptors in the reproductive tissues are summarized in Table II. Moreover, LP receptors may have preferences for different ligands. For example, LPA_3 is not as responsive as LPA_1 and LPA_2 to LPA species with saturated acyl chains but has a relatively high affinity for 2-acyl-LPA containing unsaturated fatty acids (Bandoh *et al.*, 1999; Fischer *et al.*, 2001; Sonoda *et al.*, 2002). The differential coupling to G proteins, the differential receptor expression patterns and ligand specificity may contribute to LP receptor-specific functions.

The specific functions of LP receptors have been determined through molecular, biochemical, physiological, pharmacological and genetic approaches. Receptor-mediated LP signaling has broad implications in the nervous system. For example, LPA_1 is involved in neuropathic pain, suckling behavior, psychiatric disease such as schizophrenia, Schwann cell survival and morphological change, and astrocyte proliferation (Weiner and Chun, 1999; Contos *et al.*, 2000a; Renback *et al.*, 2000; Weiner *et al.*, 2001; Harrison *et al.*, 2003; Inoue *et al.*, 2004, 2006; Shano *et al.*, 2008), while LPA_1 and LPA_2 mediate brain formation (Kingsbury *et al.*, 2003; Estivill-Torrus *et al.*, 2008). $S1P_2$ plays a role in seizure and hearing (MacLennan *et al.*, 2001, 2006; Herr *et al.*, 2007; Kono *et al.*, 2007a), while $S1P_5$ is involved in development of oligodendroglial cells (Jaillard *et al.*, 2005) and S1P receptor(s) are implicated in multiple sclerosis (Webb *et al.*, 2004). LPA_1 and $S1P_{1-3}$ have crucial roles in cardiovascular system processes, such as angiogenesis, atherosclerosis and cardiac myocyte survival (Contos *et al.*, 2000a; Liu *et al.*, 2000; Siess, 2002; Allende *et al.*, 2003; Kono *et al.*, 2004; Siess and Tigyi, 2004; Maguire and Davenport, 2005; Zhang *et al.*, 2007). LPA_{1-3} and $S1P_{1-3}$ have been implicated in processes of the respiratory system: proinflammatory effects, acute respiratory distress syndrome and chronic inflammatory airway diseases (Ammit *et al.*, 2001; Jolly *et al.*, 2002; Konishi *et al.*, 2002; Gon *et al.*, 2005; Saatian *et al.*, 2006; Kono *et al.*, 2007b). LPA_{1-3}, $S1P_1$, $S1P_3$ and

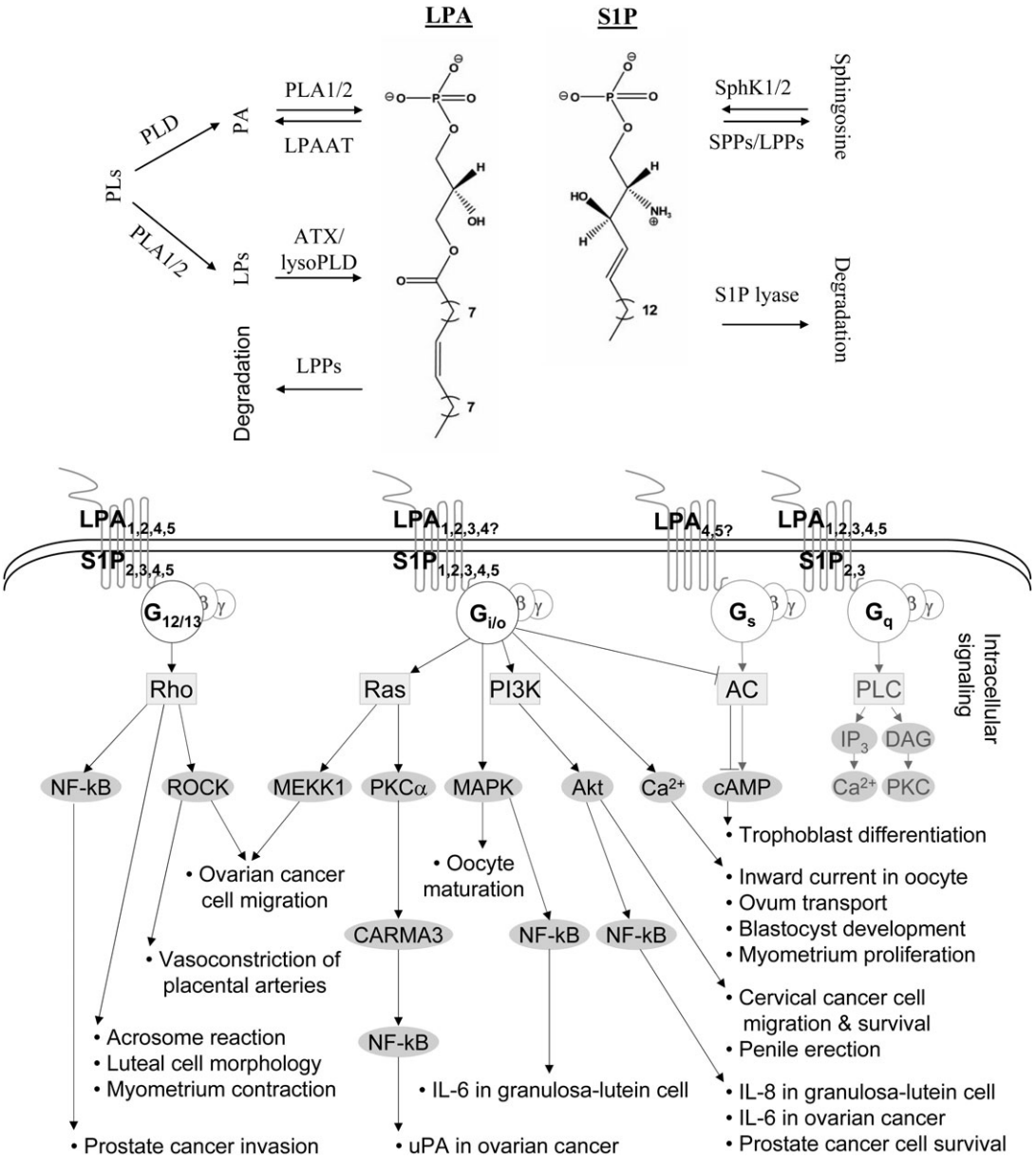

Figure 1: Metabolism of LPA and S1P (upper), differential coupling of their receptors to G proteins (middle), a few identified downstream signaling pathways in reproduction (lower).
(metabolism) ATX/lysoPLD, lysophospholipase D/Autotaxin; LPA, lysophosphatidic acid; LPAAT, LPA acyltransferases; LPPs, lipid phosphate phosphatases; LPs, lysophospholipids; PA, phosphatidic acids; PLD, phospholipase D; PLA1/2, phospholipase A1 and A2; PLs, phospholipids; S1P, sphingosine-1-phosphate; SphK1/2, sphingosine kinases 1 and 2; SPPs, S1P phosphohydrolases; (downstream signaling) AC, adenylyl cyclase; Akt, protein kinase B; Ca^{2+}, calcium; cAMP, cyclic AMP; CARMA3, CARD and MAGUK domain-containing protein 3; DAG, diacylglycerol; IP_3, inositol 1,4,5-trisphosphate; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; MEKK1, MEK kinase 1; NF-kB, nuclear factor kappaB; PI3K, phosphoinositol 3-kinase; PKCα, protein kinase C alpha; PLC, phospholipase C; ROCK, Rho-associated kinase; uPA, urokinase plasminogen activator. Note: the shown downstream signaling pathways are mediated through the specific G proteins but not all the LP receptors that activate these specific G proteins are necessarily involved in mediating these pathways.

$S1P_4$ can mediate LP functions in the immune system (Zheng *et al.*, 2001; Graler and Goetzl, 2002; Bagga *et al.*, 2004; Goetzl *et al.*, 2004; Matsuyuki *et al.*, 2006; Chan *et al.*, 2007; Czeloth *et al.*, 2007; Pappu *et al.*, 2007; Wang *et al.*, 2007b). In fact, FTY720, a broad-spectrum S1P receptor agonist, is in phase III studies for treating demyelinating diseases, specifically multiple sclerosis (Budde *et al.*, 2006; Chun and Rosen, 2006; Mullershausen *et al.*, 2007; Zhang and Schluesener, 2007). LPA_1 has a specific function in craniofacial formation (Contos *et al.*, 2000a). LPA_3 plays a critical role in embryo implantation and spacing (Ye *et al.*, 2005; Hama *et al.*, 2007). In addition, receptor-mediated LP signaling has been implicated in stem cells and wound healing (Pebay *et al.*, 2007; Watterson *et al.*, 2007), as well as multiple cancers including ovarian, prostate, renal, bladder, breast, liver and other forms (Azuma *et al.*, 2002, 2003; Mills and Moolenaar, 2003; Xu *et al.*, 2003; Lee *et al.*, 2005; Murph and Mills, 2007; Ng *et al.*, 2007; Ubai *et al.*, 2007; van Meeteren and Moolenaar, 2007). The roles of identified receptor-mediated LP signaling in reproduction are summarized in Table III.

Table I. LP receptors.

Receptor (synonyms)	Agonist(s)	G protein(s)	References[a]
LPA_1 (EDG-2/VZG-1/LP_{A1})	LPA	$G_{12/13}$, $G_{i/o}$, G_q	Hecht *et al.* (1996)
LPA_2 (EDG-4/LP_{A2})	LPA	$G_{12/13}$, $G_{i/o}$, G_q	An *et al.* (1998)
LPA_3 (EDG-7/LP_{A3})	LPA	$G_{i/o}$, G_q	Bandoh *et al.* (1999), Im *et al.* (2000b)
LPA_4 (p2y_9/GPR23)	LPA	$G_{12/13}$, $G_{i/o}$?, G_s, G_q	Noguchi *et al.* (2003)
LPA_5 (GPR92)	LPA	$G_{12/13}$, G_s?, G_q	Kotarsky *et al.* (2006), Lee *et al.* (2006a)
$S1P_1$ (EDG-1/LP_{B1})	S1*P*>SPC	$G_{i/o}$	Lee *et al.* (1998), Zondag *et al.* (1998)
$S1P_2$ (EDG-5/AGR16/H218/LP_{B2})	S1*P*>SPC	$G_{12/13}$, $G_{i/o}$, G_q	Gonda *et al.* (1999)
$S1P_3$ (EDG-3/LP_{B3})	S1*P*>SPC	$G_{12/13}$, $G_{i/o}$, G_q	Okamoto *et al.* (1999)
$S1P_4$ (EDG-6/LP_{C1})	S1*P*>SPC	$G_{12/13}$, $G_{i/o}$	Van Brocklyn *et al.* (2000), Yamazaki *et al.* (2000)
$S1P_5$ (EDG-8/NRG-1/LP_{B4})	S1*P*>SPC	$G_{12/13}$, $G_{i/o}$	Im *et al.* (2000a)

[a]The listed references were the original ones describing the identification of LP receptors. Please refer to the following references for more complete information of each LP receptor (Moolenaar, 2000; Hla *et al.*, 2001; Mills and Moolenaar, 2003; Anliker and Chun, 2004; Ishii *et al.*, 2004; Birgbauer and Chun, 2006; Chun and Rosen, 2006; Gardell *et al.*, 2006; Lee *et al.*, 2006a; Milstien and Spiegel, 2006; Herr and Chun, 2007; Lee *et al.*, 2007; Meyer zu Heringdorf and Jakobs, 2007; Pebay *et al.*, 2007; Yanagida *et al.*, 2007).

Table II. The expression of LP receptors in the reproductive tissues.

Tissue	Testis	Penis	Ovary		Oviduct	Blastocyst	E3.5 uterus	Placenta		Mammary gland	Prostate
	M	H	H	M	M	M	M	H	M	H	H
LPA_1	+++	ND	√	√	√	√	+++	ND	√	++	√[a]
LPA_2	+++	ND	√[a]	√	√	√	+++	√[a]	ND	++[a]	√[a]
LPA_3	+++	ND	√[a]	x	√	x	+++ p	√[a]	√	+	√[a]
LPA_4	+/− h	ND	√	√	√	ND	+	ND	√	ND	ND
LPA_5	+/−	ND	ND	ND	ND	ND	+/−	ND	√	ND	ND
$S1P_1$	+	√	ND	ND	ND	ND	+++	√	√	ND	ND
$S1P_2$	++	√	ND	ND	ND	ND	+++	√	√	ND	ND
$S1P_3$	++	√	ND	√	ND	ND	++	√	√	ND	ND
$S1P_4$	+/−	ND	ND	ND	ND	ND	+++	ND	ND	ND	ND
$S1P_5$	+/−	ND	ND	ND	ND	ND	+	ND	ND	ND	ND

[a]Up-regulation in pathological conditions, such as hypertensive disorder and tumorigenesis. Quantitative or semi-quantitative result: +++, high level of expression; ++, medium level of expression; +, low level of expression; +/−, extremely low level of expression. Non-quantitative result: √, detectable; x, undetectable. h, LPA_4 is detectable in human testis; p, LPA_3 is detectable in pig uterus. M, mouse tissue; H, human tissue; E3.5, embryonic day 3.5; ND, no data. References: (X. Ye and J. Chun, unpublished data; Im *et al.*, 2000b; Ishii *et al.*, 2001; Noguchi *et al.*, 2003; Kitayama *et al.*, 2004; Liu and Armant, 2004; Hinckley *et al.*, 2005; Johnstone *et al.*, 2005; Nakamoto *et al.*, 2005; di Villa Bianca *et al.*, 2006; Guo *et al.*, 2006; Kotarsky *et al.*, 2006; Skaznik-Wikiel *et al.*, 2006; Kaminska *et al.*, 2007; Li *et al.*, 2007; Wang *et al.*, 2007a; Ye *et al.*, 2008).

LP signaling in testis

It was speculated for at least three reasons that LPA signaling had potential roles in male reproduction (Budnik and Mukhopadhyay, 2002b). First, LPA biosynthetic enzymes, including PLA1 and PLA2, and autotaxin/lysoPLD are present in the testis (Higgs and Glomset, 1996; Lee *et al.*, 1996; Ito *et al.*, 2002; Sonoda *et al.*, 2002; Hiramatsu *et al.*, 2003; Aoki, 2004; Xie and Meier, 2004). Second, LPA_1, LPA_2 and LPA_3 are highly expressed in the mouse testis (Contos *et al.*, 2000b), while LPA_4 was detected in the human testis (Noguchi *et al.*, 2003). Third, the transgenic mice overexpressing LPP1, which degrades LPA, showed severely impaired spermatogenesis (Yue *et al.*, 2004). *In situ* hybridization demonstrated that LPA_1, LPA_2 and LPA_3 are expressed in the male germ cells. Deletion of these receptors in mice led to a testosterone-independent reduction of mating activity and sperm counts, with an increased prevalence of azoospermia in aging animals. The physiological mechanism by which the deletion of these receptors led to reduced mating activity is not readily apparent. Increased germ cell apoptosis was responsible for the consequent reduction of germ cell proliferation and the diminished sperm counts, indicating LPA signaling as a germ cell survival factor in spermatogenesis (Ye *et al.*, 2008).

Northern analysis indicated $S1P_2$ and $S1P_3$ at medium expression levels, $S1P_1$ barely detectable, and $S1P_4$ and $S1P_5$ undetectable in the adult mouse testis (Ishii *et al.*, 2001). RT–PCR detected $S1P_1$, $S1P_2$ and $S1P_5$ in mouse spermatozoa (Matsumoto *et al.*, 2005). $S1P_1$ and $S1P_2$ were detected by immunohistochemistry in human Sertoli cells, with occasional and weak staining in the spermatogonia and early meiotic spermatocytes (Suomalainen *et al.*, 2005).

As with LPA, S1P seemed to be a survival factor for male germ cells. S1P partially protected mouse testicular germ cells against radiation-induced cell death (Otala *et al.*, 2004) and inhibited human germ cell apoptosis in a culture of human seminiferous tubules. Nuclear factor kappaB (NF-kappaB) and protein kinase B (Akt) phosphorylation were implicated in the effect in humans, but a receptor-independent mechanism was proposed (Suomalainen *et al.*, 2005). Furthermore, disruption of S1P lyase, which degrades S1P and regulates the ratio of pro-apoptotic ceramide and anti-apoptotic S1P, led to reduced testis size in *Drosophila* caused by increased apoptosis (Phan *et al.*, 2007). In addition, sphingolipid signaling is

critical for male gametophyte development in *Arabidopsis* (Teng *et al.*, 2008).

LP signaling in male sexual function

Reports have suggested that LP signaling may also participate in male sexual function. LPC is a major component of atherogenic oxidized low-density lipoproteins related to hypercholesterolemia, which can cause erectile dysfunction (Jung *et al.*, 2007; Xie *et al.*, 2008). It was suggested that LPC-induced intracellular calcium concentration $[Ca^{2+}]_i$ in human corporal smooth muscle cells might be involved in hypercholesterolemia-induced erectile function (So *et al.*, 2005). Coordinately, a tentative LPC receptor, G2A, may also provide pro-atherogenic stimulus to atherosclerotic lesions (Parks *et al.*, 2006). Therefore, the pro-atherogenic effect of LPC signaling might have negative impact on erectile function. LPA also has atherogenic activity (Siess and Tigyi, 2004). LPA activity was detected in the seminal plasma (Hama *et al.*, 2002). PLA2, an enzyme involved in LPA production, was down-regulated in the corpus cavernosum of hypercholesterolemic rats (Jung *et al.*, 2007). The significance of LPA signaling in male sexual function is unclear. S1P signaling, on the other hand, may have a positive effect on penile erection, which requires the coordinated arterial endothelium-dependent vasodilation and sinusoidal endothelium-dependent corporal smooth muscle relaxation. $S1P_1$, $S1P_2$ and $S1P_3$ were detected in the human penile artery and corpus cavernosum. S1P can dramatically boost the relaxation induced by acetylcholine in human corpus cavernosum strips. This effect was mediated through the Ca^{2+}-independent Akt-endothelial nitric oxide synthase pathway that led to the production of nitric oxide, the principle peripheral pro-erectile neurotransmitter (di Villa Bianca *et al.*, 2006).

LP signaling in ovary

The potential role of receptor-mediated LPA signaling in ovary was proposed before the identification of any LP receptor. Early studies demonstrated that LPA induced Ca^{2+}-activated Cl^- current in naked *Xenopus laevis* oocytes and a receptor-mediated G_i protein signaling mechanism was responsible for this effect (Durieux *et al.*, 1992, 1993). Since then more potential roles of LP signaling in the ovary have been explored.

More recently LPA was detected in follicular fluid and in hens' egg. LPA was present at significant levels in follicular fluid of the human pre-ovulatory follicle (Tokumura *et al.*, 1999). Ovarian stimulation in women may increase LPA levels since serum ATX/lysoPLD activity from patients receiving ovarian stimulation was higher than in women with natural cycles (Chen *et al.*, 2008). Concordantly, LPA was induced in incubated human follicular fluid by ATX/lysoPLD (Tokumura *et al.*, 1999). High amounts of acyl LPA (micromolar range) were present in hen egg yolk, predominantly saturated LPA, and hen egg white, predominantly polyunsaturated LPA produced from LPs, suggesting that egg yolk LPA and egg white LPA may play separate physiological roles in the development, differentiation and growth of embryos (Nakane *et al.*, 2001; Morishige *et al.*, 2007).

The transcripts of LPA_1, LPA_2 and LPA_4, but not LPA_3, are detectable in the mouse ovary (X. Ye and J. Chun, unpublished data) (Ye *et al.*, 2005). LPA_1, LPA_2 and LPA_3 mRNAs are detectable in the granulosa-lutein cells from women undergoing *in vitro* fertilization (IVF) (Chen *et al.*, 2008). LPA_4 has the highest mRNA expression level in the human ovary among all the human tissues that were examined (Noguchi *et al.*, 2003). The mRNA expression of LPA_5 in ovary has not been examined (Kotarsky *et al.*, 2006; Lee *et al.*, 2006a).

LPA signaling is involved in oocyte maturation *in vitro*. LPA, 10 μM, significantly increased the oocyte nuclear and cytoplasmic maturation rates in golden hamster immature oocytes via cumulus cells (Hinokio *et al.*, 2002). LPA receptor(s) (on cumulus cells), G_i and ERK (extracellular signal-regulated kinase)/p38 signaling pathways were involved in the closure or loosening of gap junctions between cumulus cells and the oocyte, leading to an early decrease of oocyte cAMP levels that may promote nuclear maturation of mouse oocytes *in vitro* (Komatsu *et al.*, 2006).

The role of LPA in granulosa-lutein cells from women undergoing IVF was recently reported. LPA enhanced the expression of angiogenic cytokines interleukin-6 (IL-6) and IL-8. LPA_1, G_i, MAPK (mitogen-activated protein kinase)/p38, PI3K (phosphoinositol 3-kinase)/Akt and NF-kappaB signaling pathways were involved in the LPA-induced IL-8 expression. LPA_2, G_i, MAPK/p38 and NF-kappaB signaling pathways were involved in the LPA-induced IL-6 expression. It was suggested that LPA in pre-ovulatory follicles may play a role in the angiogenesis of the corpus luteum and the excessive induction of IL-8 and IL-6 by LPA from multiple corpora luteae of stimulated ovaries may be a pathophysiological cause of ovarian hyperstimulation syndrome (Chen *et al.*, 2008). Results from LPA_2 transgenic ovaries suggested that the LPA-LPA_2 circuit may regulate ovarian cells both directly and through increases in protein growth factor systems (Huang *et al.*, 2004). A recent study demonstrated that deletion of PTEN (phosphatase and tensin homolog deleted on chromosome 10), a major negative regulator of PI3K-Akt signaling pathway, led to activation of entire primordial follicle pool and premature ovarian failure in mice (Reddy *et al.*, 2008). LP signaling regulates PI3K-Akt signaling pathway (Fig. 1), whether or not LP signaling is involved in follicle activation remains to be determined.

LPA induced Chinese hamster ovary (CHO) cell growth, migration and lamellipodium formation through G_i. LPA_1 may be the key LPA receptor in mediating these effects as LPA_2 and LPA_3, which also couple to G_i, are not expressed in CHO cells. LPA_4, which may couple to G_i, does not seem to be expressed in CHO cells at a significant level and LPA_5 does not couple to G_i (Noguchi *et al.*, 2003; Lee *et al.*, 2006a, 2007; Yanagida *et al.*, 2007). However, when G_i function was blocked by pertussis toxin pretreatment, LPA inhibited, rather than induced CHO cell migration in response to insulin-like growth factor I. LPA_1-G_{13}-Rho signaling pathway relayed this inhibitory effect (Yamaji *et al.*, 2004; Sugimoto *et al.*, 2006).

The effects of LPA signaling in bovine ovarian theca cells and luteal cells are quite complicated. In bovine ovarian theca cells LPA signaling has the following effects: induction of transient ERK phosphorylation through LPA_1-$G_{12/13}$ signaling pathway (Budnik *et al.*, 2003); redistribution of protein kinase C δ (PKCδ) from the cytosol to the perinuclear area; augmentation of luteinizing hormone (LH)-stimulated progesterone accumulation. LPA-induced nuclear localization of PKCδ might have a luteotropic function in the bovine ovary (Budnik and Mukhopadhyay, 2002a). In bovine luteal cells, LPA signaling regulated their morphology but its role in steroid synthesis was opposite to that observed in theca cells. During the development and rescue of the corpus luteum, LH induced major morphoregulatory effects such as formation of stellate processes. LPA inhibited these processes via Rho proteins (Budnik and Mukhopadhyay, 2001). LPA also dramatically inhibited LH-induced progesterone production on ovarian mid-cycle luteal cells presumably through LPA_2 and possibly associated with S1P production (Budnik and Brunswig-Spickenheier, 2005).

The function of LPA signaling in ovulation has not been fully determined. Superovulation data from $LPA_3^{(-/-)}$ females did not show any suppression of oocyte numbers released compared with

Table III. Receptor-mediated LP signaling in reproduction.

Site	Effect(s)	LPs	Identified receptor(s)	References[a]
Testis	Germ cell survival	LPA S1P	LPA_{1-3}	Otala *et al.* (2004), Ye *et al.* (2008)
Penis	Erectile function	LPC	$S1P^{b}_{1-3}$	di Villa Bianca *et al.* (2006), Parks *et al.* (2006), Jung *et al.* (2007)
		S1P		
Oocyte	Maturation	LPA S1P SPC	LPA^{b}_{1-2} $S1P_2$ $GPR^{b}_{3/12}$	Hinckley *et al.* (2005), Komatsu *et al.* (2006)
Ovary	IL-6, IL-8 and growth factor induction	LPA	LPA_{1-2}	Huang *et al.* (2004), Chen *et al.* (2008)
Blastocyst	Differentiation	LPA	LPA^{b}_{1-2}	Liu and Armant (2004)
Xenopus oocyte	Early embryo shape maintenance	LPA	$XLPA_{1-2}$	Lloyd *et al.* (2005)
Uterus	Uterine receptivity and embryo spacing		LPA_3	Ye *et al.* (2005), Hama *et al.* (2007)
	Decidualization	S1P	$S1P^{b}_{1-3}$	Ishii *et al.* (2002), Skaznik-Wikiel *et al.* (2006)
	Uterine contraction	LPA	LPA^{b}_{1-3}	Tokumura *et al.* (1980), Mikamo *et al.* (1998b), Nilsson and Svensson (2003), Hama *et al.* (2007), Leiber *et al.* (2007)
		LPC		
		S1P	$S1P^{b}_{2}$	
Placenta	Differentiation, vasoconstriction	S1P	$S1P_{1-3}$	Johnstone *et al.* (2005), Hudson *et al.* (2007)
Ovarian cancer cells	Cancer cell growth, survival, migration, and invasion	LPA	LPA_{2-3}	Pustilnik *et al.* (1999), Sengupta *et al.* (2003), Estrella *et al.* (2007), Park *et al.* (2007)
		S1P	$S1P_{1-3}$	
Cervical cancer cells	Cancer cell growth, survival, and migration	LPA		Xu *et al.* (2006), Rapizzi *et al.* (2007)
		S1P	$S1P_{1-3}$	
Breast cancer cells	Cancer cell migration and metastasis	LPA	LPA_{1-2}	Dolezalova *et al.* (2003), Stadler *et al.* (2006), Chen *et al.* (2007)
		S1P	$S1P_{2-3}$	

[a]Please refer to the related sections for more complete list of referencs; [b]Indicating proposed but not fully confirmed receptor(s).

the wild-type (WT) controls. This agreed with the result that LPA_3 was not detectable in the mouse ovary. LPA_1 and LPA_2 were expressed in the ovary. Preliminary data from $LPA_1^{(-/-)}$ $LPA_2^{(-/-)}$ females indicated that these females had comparable numbers of implantation sites to those of WT females, suggesting that LPA_1 and LPA_2 are not critical for ovulation (X. Ye and J. Chun, unpublished data; Ye *et al.*, 2005).

S1P was identified to be a heat-stable growth factor in the follicular fluid associated with follicular fluid high-density lipoproteins. The S1P concentration was ~170 nM (compared with ~900 nM in serum) in the human follicular fluid obtained from women undergoing ovarian hyperstimulation. S1P induced endothelial proliferation and angiogenesis through activation of ERK1/2, PKC and Akt signaling pathways, but it is unclear (i) which cell types produce the S1P in the follicular fluid, (ii) how S1P reaches the theca to affect angiogenesis and (iii) which S1P receptors are involved in these processes (von Otte *et al.*, 2006). Since angiogenesis plays an important role in the development of the ovarian follicle and its subsequent transition into the corpus luteum, the S1P in follicular fluid and its role in angiogenesis underscore S1P signaling as being important in ovarian function.

Indeed, the function of S1P signaling in oocytes, especially the protective role of S1P on oocytes, has been well documented. S1P at 50 μM induced Ca^{2+}-activated Cl^- inward currents in *X. laevis* oocytes and there was a complete cross-desensitization between LPA and S1P responses (Durieux *et al.*, 1993). The protective role of S1P on oocytes has at least two aspects. Extracellular S1P not only could protect bovine oocytes from a physiologically relevant heat shock, but also could affect oocyte maturation in the absence of heat shock. The blastocysts that arose from S1P-treated oocytes that survived heat shock had a normal developmental potential. It was suggested that S1P may be used to improve fertility in situations where developmental competence of the oocytes was compromised (Roth and Hansen, 2004). In addition, S1P-treated oocytes can resist developmental apoptosis, in which the oocyte reserve undergoes normal apoptotic depletion throughout post-natal life. Anti-cancer treatments can lead to premature ovarian failure and infertility. Promisingly, radiation-induced oocyte loss was completely prevented by *in vivo* therapy with S1P in mice (Morita *et al.*, 2000; Tilly and Kolesnick, 2002). Pre-administration of S1P into ovarian bursa had protective effects on whole-body irradiation-induced apoptosis of primordial follicles in rats (Kaya *et al.*, 2008). Local application of S1P in mice also protected ovarian follicles from chemotherapy-induced cell death (Hancke *et al.*, 2007). These studies provide promises to potentially preserve the fertility of female cancer patients.

$S1P_3$ and GPR3 are expressed in both oocytes and cumulus cells in mice. GPR12 is only detectable in oocytes. Both GPR3 and GPR12 are potential receptors for S1P and SPC. Incubation of mouse oocytes with

the GPR3/12 ligands SPC and S1P delayed spontaneous oocyte maturation, an effect that seemed to be opposite of LPA. It was suggested that the cAMP levels required for maintaining meiotic arrest in mouse and rat oocytes were dependent on the expression of GPR3 and/or GPR12 (Hinokio *et al.*, 2002; Hinckley *et al.*, 2005; Komatsu *et al.*, 2006).

The function of S1P signaling in ovary has also been indirectly demonstrated through studies of enzymes involved in S1P metabolism in different species: mutation of SphK2, which catalyzes S1P synthesis, led to diminished ovulation in *Drosophila* (Herr *et al.*, 2004); ovary degeneration was observed in *Drosophila* with disrupted S1P lyase, in which apoptosis was elevated (Phan *et al.*, 2007); when S1P lyase was knocked down in *Caenorhabditis elegans*, oocyte production and ovulation were impaired (Mendel *et al.*, 2003); dihydrosphingosine C4 hydroxylase (DSH) is a key enzyme for sphingolipid production in plants and yeasts and down-regulation of one of the five DSH genes, DSH1, caused sterility in rice plants (Imamura *et al.*, 2007).

LP signaling in fertilization

Fertilization involves the binding and fusion of sperm and oocyte cells. A main step is acrosome reaction, an exocytotic process that exposes the zona-digesting enzymes around the anterior part of the sperm head and facilitates sperm penetration of the zona pellucida. LPA could activate sperm PKCα, which is implicated in the acrosome reaction, and could promote actin polymerization, a process necessary for spermatozoa incorporation deep into the oocyte cytoplasm. Rho GTPases are involved in the later process but the LPA receptor(s) mediating this process is (are) unknown (Garbi *et al.*, 2000; Delgado-Buenrostro *et al.*, 2005). However, LPA did not seem to affect bovine sperm motility (Garbi *et al.*, 2000). No change of sperm motility was observed in mice deficient of three LPA receptors, LPA_{1-3} (Ye *et al.*, 2008). LPC was able to induce the acrosome reaction in capacitated bovine sperm (Parrish *et al.*, 1988; Therien and Manjunath, 2003). LPC also accelerated and synchronized the acrosome reaction of hamster spermatozoa, as well as facilitating spermatozoa penetration of the zona pellucida, the fusion process and polyspermy (Riffo and Parraga, 1996). In addition, the detection of S1P receptors in mouse spermatozoa by RT–PCR led to a speculation that S1P might play a role in the acrosomal reaction (Matsumoto *et al.*, 2005). Deletion of acid sphingomyelinase, an enzyme regulating sphingolipid signaling, led to impaired sperm motility (Otala *et al.*, 2005).

LP signaling in oviduct

LPA_1, LPA_2, LPA_3 and LPA_4 mRNAs are expressed in the mouse oviduct (X. Ye and J. Chun, unpublished data). LPA at 10 μM could facilitate ovum transport in the mouse oviducts. Although serum LPA levels can reach the concentration effective for ovum transport, the LPA levels in mouse oviduct are unknown. The receptor-mediated G_i-Ca^{2+} signaling pathway was involved in LPA-induced mouse ovum transport (Kunikata *et al.*, 1999). Deletion of LPA_1, LPA_2 or LPA_3, the three G_i-coupled LPA receptors, did not seem to affect the transport of embryos to the mouse uterus (X. Ye and J. Chun, unpublished data; Ye *et al.*, 2005). This suggests that LPA signaling is not critical for embryo transport in the oviduct under physiological conditions, and/or other G_i-coupled LPA receptor(s) are present that compensated for the effect in the LPA receptor knockout mice.

LP signaling in early embryo development

LP signaling is involved in early stage embryo development and post-implantation embryo development processes such as vascular formation, vascular maturation and maintenance, heart development and brain formation (Kupperman *et al.*, 2000; Liu *et al.*, 2000; Allende and Proia, 2002; Contos *et al.*, 2002; Kingsbury *et al.*, 2003; Kono *et al.*, 2004; Mizugishi *et al.*, 2005; Tanaka *et al.*, 2006; van Meeteren *et al.*, 2006; Wendler and Rivkees, 2006). This section focuses on the LP signaling in early stage embryo development prior to implantation.

An early study revealed that the culture of embryos from the pronuclear stage in the presence of LPA could significantly increase the success rate of the development of 2-cell and 4-cell stage embryos to blastocysts via a G_i-protein-linked receptor mechanism (Kobayashi *et al.*, 1994). A more recent study found mRNA expression of LPA_1 in differentiating mouse blastocysts, expression of LPA_2 in late blastocysts and no expression of LPA_3. LPA could elevate $[Ca^{2+}]_i$ levels, which in turn accelerated murine blastocyst differentiation. LPA could also induce the transient accumulation of heparin-binding epidermal growth factor (EGF)-like growth factor (HB-EGF) on the embryo surface. Interfering with HB-EGF signaling through EGF receptors ErbB1 or ErbB4 could attenuate LPA-stimulated blastocyst differentiation (Liu and Armant, 2004).

A study of *Xenopus* also supported the importance of receptor-mediated LPA signaling in early embryo development (Lloyd *et al.*, 2005). During early embryo development, the maintenance of overall rigidity and shape of the whole embryo is required for embryogenesis to occur. A cortical actin network of filament bundles assembled in each cell is critical for maintaining embryo shape and rigidity during the egg-to-blastula stage in *Xenopus*. LPA could increase F-actin in the cortical actin network throughout the animal cap and in the purse-strings, leading to faster healing in the animal cap in early blastula stages in *Xenopus*. $XLPA_1$ was most abundant in oocytes (Kimura *et al.*, 2001) and expressed at lower levels throughout embryo development; the expression of $XLPA_2$ began in the mid-blastula stage and continued to at least stage 45, the swimming tadpole. Both $XLPA_1$ and $XLPA_2$ were necessary and sufficient for mediating LPA signaling in the correct pattern of cortical actin assembly in *Xenopus* embryos. Rho and Rac were the responsible downstream signaling molecules.

A recent study in mice demonstrated an anti-apoptotic role of S1P in early embryo development. Acid ceramidase hydrolyzes the pro-apoptotic ceramide into sphingosine, the precursor for the anti-apoptotic S1P (Fig. 1) (Morales and Fernandez-Checa, 2007). Acid ceramidase knockout embryos underwent apoptotic death and could not survive beyond the 2-cell stage. S1P treatment of early 2-cell embryos from the $Asah1^{(+/-)}$ intercrosses not only rescued $Asah1^{(-/-)}$ embryos, but also enabled their progression from the 2-cell to 4–8-cell stage (Eliyahu *et al.*, 2007).

LP signaling in embryo spacing and implantation

Embryo spacing is an event relevant to polytocous species in which embryos are implanted nearly equidistant from each other along the uterus. Implantation involves a competent embryo, a receptive uterus, and reciprocal interactions between them to achieve apposition and attachment of the embryo to the uterine luminal epithelium, invasion of the embryo into the stroma and establishment of a placenta (Carson *et al.*, 2000; Paria *et al.*, 2002; Genbacev *et al.*, 2003; Wang and Dey, 2006). Published reports and recent data have revealed the roles of LP signaling in both embryo spacing and implantation.

LPA signaling influences embryo spacing and uterine receptivity in mice (Ye *et al.*, 2005; Hama *et al.*, 2007). Deletion of LPA_3 in mice led to uneven embryo spacing, possibly contributed by defect in uterine contraction, and delayed implantation caused by defect in uterine receptivity. Embryo crowding and delayed implantation were two segregated events based on these observations: (i) restoration of on-time implantation in LPA_3-null females failed to correct embryo spacing and (ii) when single embryo, which cannot be subject to embryo crowding, was transferred into LPA_3-null uterus, delayed implantation persisted. Deletion of LPA_3 in mice also led to delayed embryonic development, prolonged pregnancy and ~50% embryonic lethality. Ovulation, fertilization, embryo transport, blastocyst development and decidualization were not adversely affected.

Prostaglandins (PGs) were identified to be at least partially responsible for the phenotypes of $LPA_3^{(-/-)}$ females. Expression of cycloxygenase 2 (COX-2), the rate-limiting enzyme for PG synthesis, as well as PGE_2 and PGI_2 levels were suppressed in the preimplantation embryonic day 3.5 (E3.5) $LPA_3^{(-/-)}$ uteri. Exogenous PGE_2 and PGI_2 could rescue delayed implantation in the $LPA_3^{(-/-)}$ females. These results reinforced the importance of PGs in embryo implantation (Kennedy, 1977; Kinoshita *et al.*, 1985; Song *et al.*, 2002). However, PGE_2 and PGI_2 failed to correct embryo spacing, suggesting that different PGs that control uterine contraction or possible non-PG mechanisms may be responsible for embryo spacing (Ye *et al.*, 2005; Hama *et al.*, 2007). Limited studies have identified several other factors that influence embryo spacing: nicotine, phenoxybenzamine and prazosin caused crowding of implantation sites near the utero-tubal junction in rats (Yoshinaga *et al.*, 1979; Legrand *et al.*, 1987); estrogen (E_2) and histamine increased intrauterine migration of porcine embryos (Pope *et al.*, 1982); whereas relaxin reduced intrauterine embryo migration in rat (Pusey *et al.*, 1980); deletion of cPLA2α (Song *et al.*, 2002) and inhibition of Wnt/β-catenin signaling (Mohamed *et al.*, 2005) led to aberrant embryo spacing. COX-2/PG pathways were suggested to be involved in the effects of cPLA2α. It is unknown if other factors act through PG pathways and/or if LPA_3-mediated LPA signaling pathways cross-talk with these factors in regulating embryo spacing.

The embryo implantation defects present in $LPA_3^{(-/-)}$ females have not been observed in other LP receptor-null females, e.g. $LPA_1^{(-/-)}$, $LPA_2^{(-/-)}$, $S1P_2^{(-/-)}$ and $S1P_3^{(-/-)}$ mice. Among the 10 LP receptors, only LPA_3 was almost exclusively expressed in the luminal endometrial epithelium, while the remaining nine LP receptors were indistinguishably expressed in the luminal endometrial epithelium, stroma and myometrium at E3.5 mouse uterus. In addition, only LPA_3 was up-regulated by progesterone (P4) treatment. The data suggest that the differential expression of LPA_3 in luminal endometrial epithelium and up-regulation of LPA_3 by P4 may distinguish it from other LP receptors for its role in uterine receptivity (X. Ye and J. Chun, unpublished data; Ye *et al.*, 2005; Hama *et al.*, 2006).

The expression pattern of LPA_3 in pig uterus suggests that LPA_3 may play a role in pigs during early pregnancy. The highest expression level of LPA_3 was detected in the uterus on Day 10–12 of gestation, when an embryo undergoes a dramatic elongation process prior to implantation (Waclawik and Ziecik, 2007). The presence of embryos also induced pig uterine LPA_3 expression (Kaminska *et al.*, 2007). This was different from the expression pattern in mice, in which LPA_3 had similar expression patterns in uteri from early pregnant and pseudopregnant mice (Ye *et al.*, 2005; Hama *et al.*, 2006). Biomarkers for uterine receptivity have clinical applications, especially in IVF programs. It will be of great interest to examine the expression pattern of LPA_3 in human endometrium to ascertain if it can serve as a potential biomarker for uterine receptivity as can some other potential biomarkers (Campbell and Rockett, 2006).

LPA, acting on decidual cells, can increase embryo outgrowth and induce actin stress fiber formation in human decidual cells. The RhoA signaling pathway mediated the LPA effects in the decidual cells that may regulate embryo development and differentiation after attachment (Shiokawa *et al.*, 2000).

Preliminary observations indicated comparable numbers of on-time implanted implantation sites and normal embryo spacing in $S1P_2^{(-/-)}$ $S1P_3^{(-/-)}$ female mice (X. Ye and J. Chun, unpublished data), suggesting no obvious defects in ovulation, fertilization, embryo transport or uterine receptivity in $S1P_2^{(-/-)}$ $S1P_3^{(-/-)}$ females. However, the litter sizes from $S1P_2^{(-/-)}$ $S1P_3^{(-/-)}$ females were significantly lower (23–33% reduction) than that from WT females mated with WT, $S1P_2^{(+/-)}$ or $S1P_3^{(+/-)}$ control males (Ishii *et al.*, 2002). These results suggest maternal defects beyond implantation. $S1P_1$, $S1P_2$ and $S1P_3$ had co-operative functions in mediating S1P signaling in angiogenesis during embryonic development (Liu *et al.*, 2000; Kono *et al.*, 2004). They were up-regulated during decidualization, suggesting that these three receptors may play co-operative roles in decidual angiogenesis as well (Skaznik-Wikiel *et al.*, 2006). Enzymes involved in sphingolipid metabolism were also up-regulated in the uterus during decidualization (Kaneko-Tarui *et al.*, 2007). The importance of this regulation was confirmed in $SphK1^{(-/-)}SphK2^{(+/-)}$ females that showed decidualization defects. There is a link between S1P and PG signaling in early pregnancy, but PG signaling did not seem to be critical for the decidualization defects in the $SphK1^{(-/-)}SphK2^{(+/-)}$ females (Mizugishi *et al.*, 2007).

LP signaling in pregnancy and parturition

The involvement of LP signaling in pregnancy beyond implantation could be multi-faceted. First, LPA signaling has been suggested in the maintenance of human pregnancy as serum ATX/lysoPLD activity, a key enzyme for LPA production, and LPA levels were shown to increase during pregnancy (Tokumura *et al.*, 2002). High lysophospholipase activity was present in the human placental tissues with the highest in the amnion (Jarvis *et al.*, 1984). Although amnion has been heavily implicated in the initiation of labor presumably through the release of arachidonic acid, the high lysophospholipase activity in amnion suggests that its products, including LPs, might also involve in the regulation of labor.

Second, LP signaling has potential functions in placental and vascular tone during pregnancy. High levels of LPA_2 and LPA_3 expression in the placentas of patients with hypertensive disorder suggest that LPA signaling might be involved in this complication (Li *et al.*, 2007). Hypertensive disorder can worsen with the progress of pregnancy. LPA levels increase during pregnancy. It is unknown whether even higher levels of LPA are present in the pregnant patients complicated with hypertensive disorder. LPA_1, LPA_3, LPA_4 and LPA_5 mRNAs were also detectable in mouse placenta (X. Ye and J. Chun, unpublished data; Noguchi *et al.*, 2003; Kotarsky *et al.*, 2006). The functions of LPA signaling in placenta await further exploration.

Several reports show the roles of S1P signaling in placental trophoblast differentiation and vascular tone. S1P inhibited the differentiation of primary human cytotrophoblasts into syncytiotrophoblasts. This inhibition of differentiation was mediated through $S1P_{1-3}$, G_i, adenylate cyclase and intracellular cAMP. The study suggested that S1P signaling may play a role in pregnancy disorders, such as

pre-eclampsia, that are related to improper differentiation of placental trophoblasts (Johnstone *et al.*, 2005). S1P induced vasoconstriction in human placental arteries, a process mediated by increased Ca^{2+}-sensitization via Rho-associated kinases and modulated by nitric oxide (Hemmings *et al.*, 2006). S1P also induced the isometric tension of myometrial arteries isolated from normal pregnant women at term. $S1P_1$, $S1P_2$ and $S1P_3$ were detected in these arteries. These results suggest that S1P may help regulate vascular tone during pregnancy (Hudson *et al.*, 2007).

Third, the following studies suggest that LP signaling could potentially regulate uterine contractility as well as load-bearing during pregnancy and labor. An early study indicated that LPA had similar effects as $PGF_{2\alpha}$ on rat smooth muscle contraction and intrauterine pressure (Tokumura *et al.*, 1980). Although the effect of LPA signaling in parturition *per se* has not been established *in vivo*, deletion of FP, the GPCR for $PGF_{2\alpha}$, led to parturition failure (Sugimoto *et al.*, 1997). LPA stimulated myosin light chain phosphorylation through RhoA signaling in pregnant myometrial tissue (Moore *et al.*, 2000). LPA also induced stress fiber formation that may be involved in the maintenance of uterine contractions. The $G_{12/13}$-Rho kinase signaling pathway was suggested to mediate this effect (Gogarten *et al.*, 2001). In addition, the $G_{i/o}$ signaling pathway involving the regulation of $[Ca^{2+}]_i$ was responsible for LPA-induced cell proliferation of human myometrial smooth muscle cells (Nilsson *et al.*, 1998). A follow-up study identified the critical role of Ca^{2+}/calmodulin-dependent protein kinase in this effect as well as the detection of LPA_1, LPA_2 and LPA_3 in the human myometrial smooth muscle cells (Nilsson and Svensson, 2003).

LPC may play a role in infection-related preterm labor. Significant higher level of LPC was detected in human uterine endometrial cells upon exposure to extract from common anaerobes in intrauterine infection, accompanied with an elevation of arachidonic acid, a key precursor for PG synthesis in regulating labor. PLA2 activity was involved in the reported lipid metabolism (Mikamo *et al.*, 1998a, b). Since PLA2 and LPC are important components in the LPA metabolism pathway (Fig. 1) (Aoki, 2004), it is reasonable to expect that LPA might also be involved in the infection-related preterm labor.

S1P can induce a contractile effect in rat myometrium presumably through $S1P_2$ (Leiber *et al.*, 2007). S1P may play a role in labor. S1P was identified as one of the components in the amniotic fluid that can modulate the synthesis of PGs, key regulators of labor (Sugimoto *et al.*, 1997), in human amnion-derived cells (Kim *et al.*, 2003). In addition, SphK1, a key enzyme for S1P production, was detected in rat glandular epithelium, vasculature and the myometrium, and was up-regulated by P4. A recent study also suggested that SphK1 involved growth and differentiation of uterine tissues during pregnancy (Jeng *et al.*, 2007).

LP signaling in cancer

A number of articles have reviewed the roles of LP signaling in various cancers (Mills and Moolenaar, 2003; Xu *et al.*, 2003; Brindley, 2004; Milstien and Spiegel, 2006; Sabbadini, 2006; Bandhuvula and Saba, 2007; Morales and Fernandez-Checa, 2007; Murph and Mills, 2007; Oskouian and Saba, 2007; Tokumura *et al.*, 2007; Van Brocklyn, 2007; van Meeteren and Moolenaar, 2007). LPA levels increased in the plasma and ascites of patients with ovarian cancer, cervical cancer or endometrial cancer (Shen *et al.*, 1998; Mills *et al.*, 2002; Tokumura *et al.*, 2007). LPs were suggested as potential biomarkers for these cancers (Umezu-Goto *et al.*, 2004). This section only covers the potential roles of LP signaling in cancers in reproductive organs, such as ovary, cervix, mammary gland and prostate, as well as in related cell lines.

Ovarian cancer is the most extensively studied cancer with respect to LP signaling in carcinogenesis. Early studies demonstrated LPA, whose levels elevated in the plasma and ascites of ovarian cancer patients, promoted ovarian cancer cell proliferation. LPA, S1P and LPC were suggested as potential biomarkers for ovarian cancers and LPA-like lipids were proposed as being responsible for intraperitoneal malignancies (Xu *et al.*, 1995a, b, 1998; Westermann *et al.*, 1998; Sutphen *et al.*, 2004). However, another study indicated that serum LPA could not differentiate benign from malignant ovarian tumors (Pozlep *et al.*, 2007). LPA acyltransferase beta, which converts LPA to PA, was suggested as a specific prognostic marker (Niesporek *et al.*, 2005; Springett *et al.*, 2005). The increased production of LPA might be related to the down-regulation of LPP1, which degrades LPA, in ovarian cancer cells (Tanyi *et al.*, 2003).

LPA signaling may exert its role in ovarian cancers through regulating other factors: glycodelin, an angiogenic protein with a potential immunosuppressive role in carcinogenesis (Ramachandran *et al.*, 2002); TRIP6 (thyroid receptor interacting protein 6), a focal adhesion molecule involved in cell migration (Xu *et al.*, 2004); telomerase, a ribonucleprotein expressed in 95% of ovarian cancers and involved in tumor progress (Bermudez *et al.*, 2007); granulin-epithelin precursor, a growth and survival factor for ovarian cancer (Kamrava *et al.*, 2005); internalization of Fas from the cell membrane to the cytosol, a process that would protect ovarian cancer cells from FasL-bearing immune cells (Meng *et al.*, 2005); IL-6 and IL-8, angiogenic cytokines (Chou *et al.*, 2005); COX-2, which potentiates aggressive cellular behavior (Symowicz *et al.*, 2005); growth-regulated oncogene alpha (GROalpha), a chemokine with increased levels detected in the plasma and ascites of ovarian cancer patients (Lee *et al.*, 2006b) and urokinase plasminogen activator (uPA), a critical component present at high concentration in ovarian ascites and ovarian cancers which bears an inverse correlation with cancer prognosis (Pustilnik *et al.*, 1999; Estrella *et al.*, 2007; Gil *et al.*, 2008).

LPA receptors seem to play different roles in the ovarian cancers. LPA_2 and LPA_3 but not LPA_1 were up-regulated in ovarian cancer tissues (Nakamoto *et al.*, 2005; Wang *et al.*, 2007a). LPA_2 was a key receptor in mediating LPA-induced production of GROalpha (Lee *et al.*, 2006b). LPA-induced uPA secretion in ovarian cancer cells was dominantly mediated through LPA_2 with contribution from LPA_3 (Pustilnik *et al.*, 1999; Estrella *et al.*, 2007). LPA_3 was a key receptor for mediating the chemotactic activity of LPA (Sengupta *et al.*, 2003). However, LPA_1 seemed to be the key receptor in mediating ascitic LPA effects on other cells (Yamada *et al.*, 2004; Sako *et al.*, 2006).

Several LPA downstream signaling pathways have been identified in ovarian cancer cells. The up-regulation of uPA by LPA was mainly mediated through the G_i-Ras-PKCα-CARMA3-NF-kappaB signaling pathway in ovarian cancer cells. CARMA3 (CARD and MAGUK domain-containing protein 3) is a scaffolding protein required for GPCR-induced NF-kappaB activation (Li *et al.*, 2005; Grabiner *et al.*, 2007; Mahanivong *et al.*, 2008). Both G_i-Ras-MEKK1 (MAPK kinase kinase 1) and $G_{12/13}$-RhoA-ROCK (Rho-associated kinase) signaling pathways contributed to LPA-stimulated ovarian cancer cell migration by facilitating focal adhesion kinase redistribution and autophosphorylation, respectively (Sawada *et al.*, 2002; Bian *et al.*, 2004, 2006). LPA signaling in ovarian cancer cells could be attenuated by RGS, a regulator of G protein signaling proteins that deactivates G proteins (Hurst *et al.*, 2008). LPA-induced IL-6 expression was via a G_i/PI3K-Akt/NF-kappaB pathway (Chou

et al., 2005), while transcription factors NF-kappaB and AP-1, which were induced by LPA, might synergistically stimulate IL-8 expression (Fang *et al.*, 2004).

S1P was also identified in the ascites of ovarian cancer patients and as a mitogenic and cell survival factor for ovarian cancer cells (Hong *et al.*, 1999). At low concentrations S1P had an invasive effect similar to LPA, but S1P inhibited the invasiveness at high concentrations. The dual effects on ovarian cancer invasion were probably through the regulation of LP receptors (Smicun *et al.*, 2006, 2007). S1P induced $[Ca^{2+}]_i$ and chemotactic migration of ovarian cancer cells. $S1P_{1/2/3}$-G_i-ERK/p38 MAPK/Akt mediated these effects (Park *et al.*, 2007). S1P and SPC had an effect similar to LPA on induction of IL-8 expression (Schwartz *et al.*, 2001).

The cervical cancer cell line HeLa has been used to study the roles of LPs in cervical cancer. LPA induced HeLa cell migration and survival. $S1P_1$, $S1P_2$ and $S1P_3$ were detectable in HeLa cells, but only over-expressed $S1P_2$ and $S1P_3$ seemed to mediate S1P-induced $[Ca^{2+}]_i$ and cell survival (Rapizzi *et al.*, 2007), whereas $S1P_1$ seemed to mediate HeLa cell proliferation (Xu *et al.*, 2006). A class II PI3K-activated signaling pathway was identified as mediating cell migration (Maffucci *et al.*, 2005), while the $G_{i/o}$-PI3K-Akt signaling cascade was responsible for survival (Fang *et al.*, 2000). Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is able to induce apoptosis in many cancer cells. Both S1P and LPA inhibited TRAIL-induced apoptosis in HeLa cells. This anti-apoptotic effect of LPs involved the activation of the PI3K-Akt signaling pathway (Kang *et al.*, 2004).

LP signaling may also play a role in breast cancer progression. Human mammary gland expressed LPA_1, LPA_2 and a lower level of LPA_3. The up-regulation of LPA_2, but not that of LPA_1 and LPA_3, in the mammary gland carcinoma tissue and post-menopausal women suggest that LPA_2 may be related to breast cancer, especially post-menopausal breast cancer (Kitayama *et al.*, 2004). Studies from breast cancer cell lines indicated that both LPA_1 and LPA_2 could mediate LPA-induced chemotaxis in breast carcinoma cells, but LPA_1 was more efficacious than LPA_2 (Chen *et al.*, 2007). LPA_1 was also considered to be the culprit for LPA-promoted breast cancer cell migration (Stadler *et al.*, 2006) and metastasis in bone (Boucharaba *et al.*, 2004, 2006). LP signaling might be involved in breast cancer cell proliferation (Imagawa *et al.*, 1995; Xu *et al.*, 1995a). LPA induced stress fiber and focal adhesion formation in breast cancer cells (Dorfleutner *et al.*, 2007). EGF receptor, whose overexpression is a prognostic indicator of a poor outcome in multiple tumor types, was identified to be in the signaling network for LPA-induced breast cancer progression (Boerner *et al.*, 2005). The effects of LPA on breast cancer cells could be potentiated by insulin through the induction of geranylgeranylated RhoA, and consequently the augmentation of LPA-induced cyclin E expression and degradation of $p27^{Kip1}$ (cyclin-dependent kinase inhibitor) and cell cycle progression (Chappell *et al.*, 2000, 2001). LPA and S1P could promote the migration of metastatic human breast cancer cells (Sliva *et al.*, 2000). S1P could induce $[Ca^{2+}]_i$ and chemokinetic migration in human breast cancer cells, a process that might be mediated through $S1P_2$ and $S1P_3$, but not $S1P_1$ (Dolezalova *et al.*, 2003).

LPA_1, LPA_2 and LPA_3 were detected in the prostate. They had significantly higher expression levels in malignant compared with the benign prostate tissues (Im *et al.*, 2000b; Guo *et al.*, 2006). LPA signaling plays multiple roles in prostate cancer: facilitating early prostate cancer development by inhibiting autophagy (Chang *et al.*, 2007); inducing prostate cancer cell proliferation, survival, morphological changes, migration and invasion. LPA_1 seemed to be the key receptor in mediating LPA-induced prostate cancer cell proliferation and migration (Daaka, 2002; Guo *et al.*, 2006; Hao *et al.*, 2007). Tyrosine kinase EGF and matrix metalloproteinases were involved in the LPA-induced ERK mitogenic signaling pathway (Kue *et al.*, 2002). The LPA receptor-Akt-NF-kappaB signaling axis may mediate LPA-induced prostate cell survival (Raj *et al.*, 2004). LPA may also play its roles via the involvement of other factors: phosphorylation of proline-rich tyrosine kinase 2, a potential marker in prostate epithelium for the malignancy of prostate cancer (Picascia *et al.*, 2002); IL-6, which appeared to mediate LPA-induced prostate cancer cell growth and the cross-talk between stromal and epithelial prostate cells (Sivashanmugam *et al.*, 2004); CYR61, an extracellular matrix signaling protein implicated as a secreted autocrine and/or paracrine mediator for LPA in prostate stromal and epithelial hyperplasia (Sakamoto *et al.*, 2004). LPA stimulated prostate cancer cell invasion through alterations of RhoA and NF-kappaB activity (Hwang *et al.*, 2006). RhoA also played a role in LPA-induced morphological changes of prostate cancer cells (Chen *et al.*, 2005). LPA-induced Rho activation was dependent on PDZrhoGEF, a rho guanine nucleotide exchange factors (Wang *et al.*, 2004). S1P signaling, on the other hand, mainly serves as an anti-apoptotic factor in prostate cancer. Sphk1 balances the ratio of ceramide/S1P. Overexpression of SphK1, which increases the production of S1P and decreases ceramide/S1P ratio, impaired the efficacy of chemotherapy; whereas inhibition of SphK1 was related to a smaller tumor volume as well as reduced occurrence and number of metastases (Pchejetski *et al.*, 2005). Up-regulation of $S1P_1$, $S1P_3$ and SphK1 also accounted for prostate cancer cell escape from anti-cancer drug-induced apoptosis (Akao *et al.*, 2006).

Closing remarks

The abundant presence of signaling LPs in the serum and other biological fluids provides them the opportunity to reach almost every tissue. The potential functions of LP signaling in each tissue are likely determined by many local factors, such as LP metabolism, expression and regulation of LP receptors, and other factors in the LP signaling pathways. The progress on understanding LP signaling in reproduction has been exciting, yet more comprehensive studies on the factors influencing tissue-specific functions as well as receptor-specific functions are needed. The mechanisms of LP signaling in the physiological and pathological reproductive tissues await further exploration to ensure the clarification of LP signaling as a therapeutic target and for the development of modulating agents (Mills and Moolenaar, 2003; Chun and Rosen, 2006; Milstien and Spiegel, 2006; Herr and Chun, 2007).

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