Prostaglandins & other Lipid Mediators 91 (2010) 130–138

Contents lists available at ScienceDirect

Prostaglandins and Other Lipid Mediators

Review

Lysophosphatidic acid (LPA) receptors: Signaling properties and disease relevance

Mu-En Lin, Deron R. Herr, Jerold Chun*

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

ARTICLE INFO

Article history:
Received 1 January 2009
Received in revised form 13 February 2009
Accepted 18 February 2009
Available online 4 March 2009

Keywords:
Lysophospholipids
LPA
S1P
GPCRs
Receptors
Autotaxin
LPP
PRG

ABSTRACT

Lysophosphatidic acid (LPA), a water-soluble phospholipid, has gained significant attention in recent years since the discovery that it acts as a potent signaling molecule with wide-ranging effects on many different target tissues. There are currently five identified G protein-coupled receptors for LPA and more are undergoing validation. The complexity of the expression pattern and signaling properties of LPA receptors results in multiple influences on developmental, physiological, and pathological processes. This review provides a summary of LPA receptor signaling and current views on the potential involvement of this pathway in human diseases that include cardiovascular, cancer, neuropathic pain, neuropsychiatric disorders, reproductive disorders, and fibrosis. The involvement of LPA signaling in these processes implicates multiple, potential drug targets including LPA receptor subtypes and LPA metabolizing enzymes. Modulation of LPA signaling may thus provide therapeutic inroads for the treatment of human disease.

Contents

1. Introduction

Lysophosphatidic acid (LPA), once thought to be an inert metabolite in the biosynthesis of membrane phospholipids, is now well-recognized as an important signaling molecule. Acting through G protein-coupled receptors (GPCRs), LPA alters many different cellular responses, such as proliferation, survival, cytoskeletal changes, calcium influx and much more [1,2]. The stimulating action of LPA was recognized by the 1960s for its ability to elicit calcium responses in smooth muscle cells [3]. In the ensuing decades, numerous studies indicated that LPA could serve as a signaling molecule. The primary molecular mechanism was reported in 1996 with the cloning of the first cognate receptor for LPA [4]. The receptor, now called LPA_1, is a GPCR that couples to heterotrimeric G proteins (G_i, G_q, $G_{12/13}$ alpha subunits) and can elicit multiple cellular responses upon LPA stimulation [1,5]. Based on sequence similarity, two other LPA receptors were soon identified: LPA_2 and LPA_3 [6,7]. Recently, two more distantly related GPCRs have been shown to respond specifically to LPA, LPA_4/P2Y9/GPR23

* Corresponding author. Tel.: +1 858 784 8410; fax: +1 858 784 7084.
E-mail address: jchun@scripps.edu (J. Chun).

1098-8823/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.prostaglandins.2009.02.002

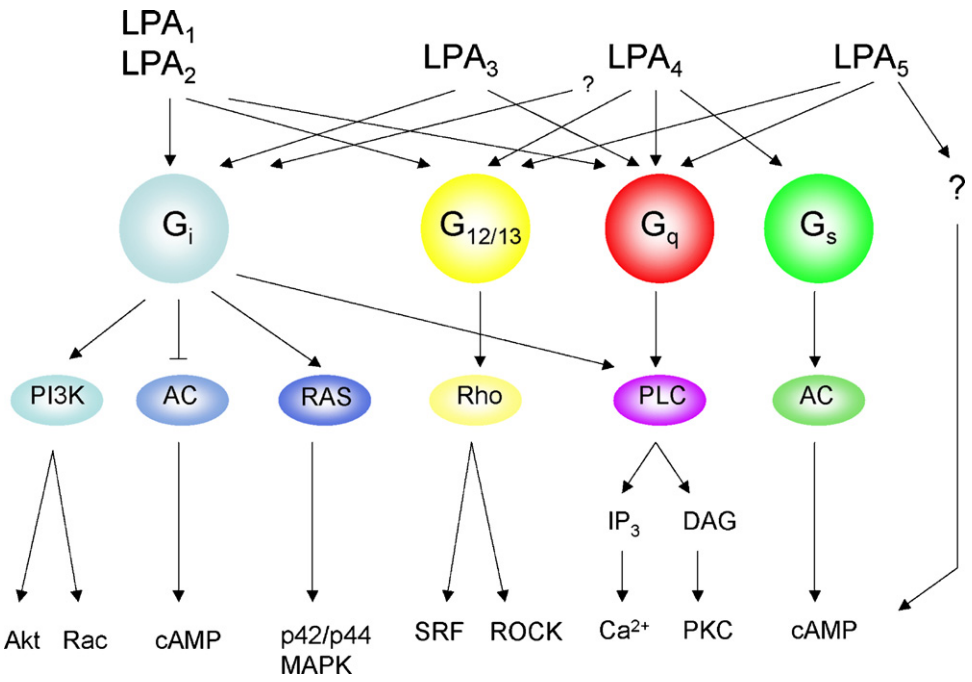

Fig. 1. Summary of the downstream signaling pathways activated by known lysophosphatidic acid (LPA) receptors.

and LPA_5/GPR92 [8,9]. LPA_4 is more closely related to purinergic receptors while sharing only 20–24% amino acid identity with $LPA_{1\text{-}3}$ [8]. LPA_5 was identified using reverse transfection screening and shares about 35% identity with LPA_4 [9,10]. These receptors are encoded by distinct genes that are referred to as *LPAR1-5* (in humans) and *Lpar1-5* (in mouse) [11,12]. Two additional receptors, GPR87 and P2Y5, have been proposed to be new LPA receptors [13,14], however, further validation of these identities is required.

This review will focus on the receptor-mediated signaling characteristics of LPA and its potential involvement in human diseases. We will discuss the effects of LPA in different cell types, their employed receptors, and current disease models influenced by receptor-mediated LPA signaling. GPCRs as a group are a major target for many current medicines suggesting that LPA receptors may represent future drug targets.

2. LPA metabolism and signaling

LPA is present in all mammalian cells and tissues, including blood, where concentrations in plasma range from 0.1 to 1 μM, while serum concentrations can exceed 10 μM. Different detection methods are in current use, including enzymatic assays, TLC-gas chromatography and HPLC/tandem MS. A detailed comparison of the techniques used to measure LPA was recently reviewed [15]. Biologically relevant LPA levels (well above apparent K_d and/or EC50 values for the five known LPA receptors) implicate their importance in physiological function.

There are at least two major pathways of LPA production. The first one involves hydrolysis of phosphatidic acids (PAs) by phospholipase A1 and A2 (PLA_1 and PLA_2). This pathway is thought to be mainly intracellular or on the cell membrane since the substrate PAs are located in cell membranes [16]. The second pathway is via cleavage of lysophospholipids (LPLs), such as lysophosphatidylcholine (LPC) and lysophosphatidylserine (LPS), by lysophospholipase D/autotaxin (LysoPLD/ATX). There are at least two additional pathways that can produce LPA: acylation of glycerol 3-phosphate by glycerophosphate acyltransferase (GPAT) and phosphorylation of monoacylglycerol by monoacylglycerol kinase (MAG-kinase). However, LPA produced by these two pathways appears to serve as precursors for glycerolipid synthesis rather than a source of extracellular signaling molecules [17]. ATX was first identified as a cell motility-stimulating factor that possessed nucleotide phosphodiesterase activity [18], but was subsequently identified as a major enzyme producing LPA [16]. ATX activity is present in blood and strongly correlates with LPA concentration [19]. While homozygous ATX knockout mice die at mid-gestation (see below) heterozygotes have an LPA concentration in the blood that is roughly 50% of that in wild type mice. This suggests that ATX activity accounts for the majority of LPA production in blood [20]. The degradation of LPA involves several different categories of enzymes, including LPA-acyltransferase (LPAAT), lipid phosphate phosphatase (LPP), and lysophospholipase [17]. LPA may be converted back to PA by LPAAT, hydrolyzed by LPP-1, 2, and 3, or converted into glycerol-3-phosphate by lysophospholipases [17,21]. A subclass of the LPP family, lipid phosphatase-related proteins or plasticity related genes (LRPs/PRGs), was also shown to modulate LPA signaling. However, whether the LRPs/PRGs directly hydrolyze LPA remains to be determined [22].

The biological activity of LPA is mediated largely through the activation of the five receptors, LPA_1 to LPA_5. All are Type 1, rhodopsin-like GPCRs with seven-transmembrane alpha helices. Distinct associations with heterotrimeric G protein subtypes and different expression patterns allow LPA to produce various effects on different cellular and organ systems. LPA_1 to LPA_3 signaling pathways are extensively reviewed elsewhere and will not be addressed in detail here [1,2,23,24]. Recent studies have provided insights into the signaling characteristics of the newly identified LPA_4 and LPA_5, which will be focused upon next (Fig. 1).

LPA_4 specifically binds to LPA with an apparent K_d value of 45 nM and activates a number of G proteins. Evidence for $G_{q/11}$-coupling was provided in experiments where LPA_4-mediated transient increases in calcium concentration were completely inhibited by YM-254890 [25]. $G_{12/13}$/Rho signaling was demonstrated through LPA_4-mediated cytoskeletal rearrangement (cell rounding) that was completely inhibited by Y-27632 [25,26]. Evidence for G_s-

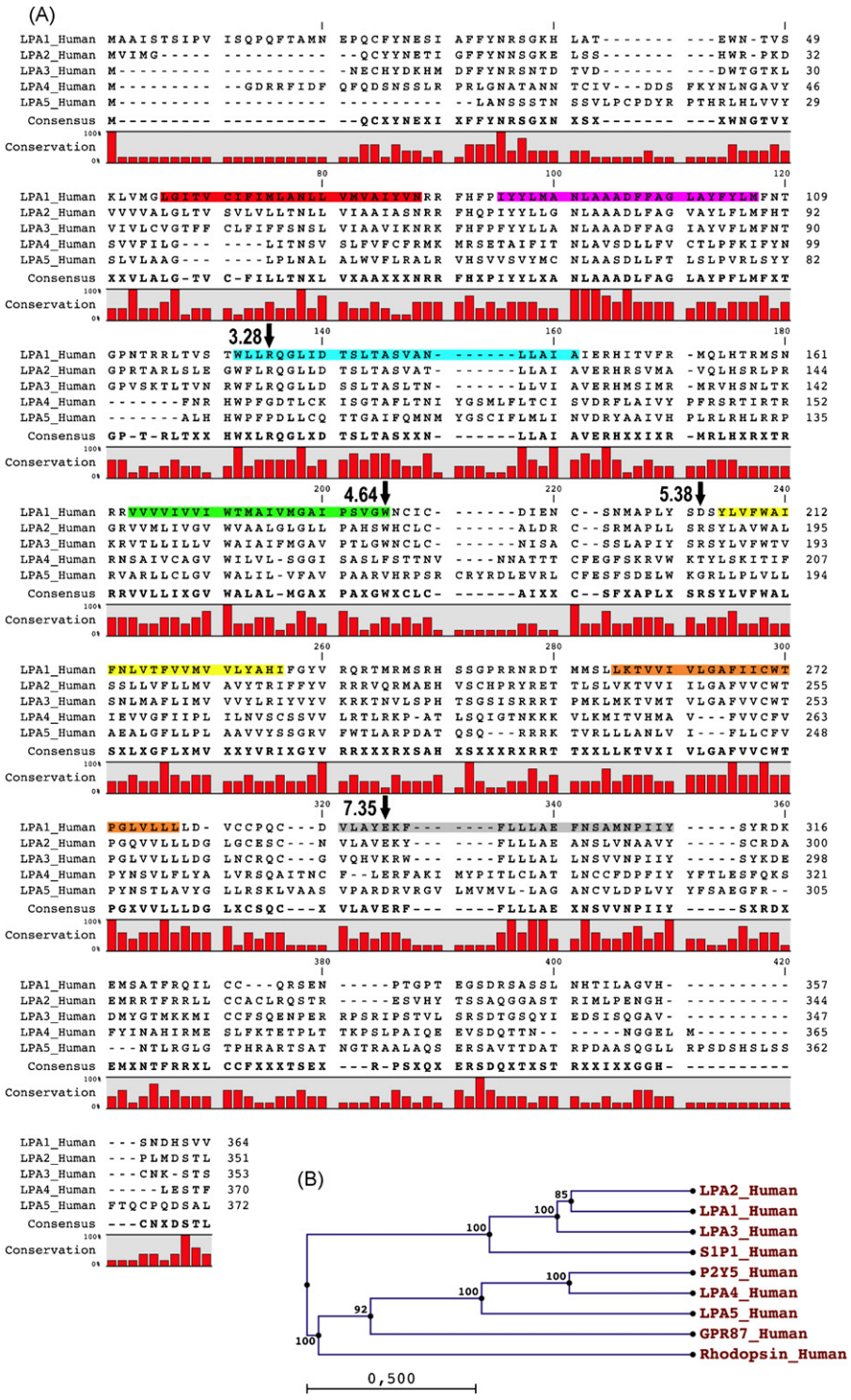

Fig. 2. Protein sequence alignment and phylogenic tree of human lysophosphatidic acid receptors. (A) Multiple alignment of LPA_1 to LPA_5. The seven transmembrane domains of LPA_1 are shaded red, purple, blue, green, yellow, orange, and grey respectively. Critical residues for ligand interactions identified by mutagenesis studies are indicated with black arrows. (B) Phylogenic tree of the five known LPA receptors ($LPA_{1\text{-}5}$), two possible LPA receptors (P2Y5 and GPR87), an S1P receptor ($S1P_1$), and rhodopsin. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

coupling was shown through activation of LPA_4 that resulted in an increase in cAMP concentration using transfected CHO and B103 cells [8,26]. Evidence for G_i-coupling is less clear [8,26]. Recently, LPA_4 was reported to be a negative regulator of fibroblast motility using knock out strategies [27]. LPA_4 is expressed at high levels in the ovary, while moderate expression is seen in the testis, thymus, pancreas, and small intestine [8], and may have broader expression during embryonic development, although the null mutant phenotype is grossly normal [27].

LPA_5 signaling is similar to LPA_4. It couples to G_q to increase intracellular calcium levels, and $G_{12/13}$ to induce neurite retraction [9]. Activation of LPA_5 also induces cAMP accumulation and phosphoinositide hydrolysis. The G proteins responsible for these latter effects remain unclear, however, the phosphoinositide hydrolysis

was insensitive to pertussis toxin treatment, indicating that G_i is not involved [9,10].

3. Receptor mutagenesis

There are currently no crystal structures for any native LPA receptors. Mutagenesis studies combined with computational analysis identified several important residues in LPA_{1-3}, most of them located in transmembrane domains (Fig. 2). R3.28 is important for efficacy and potency for all three receptors, while Q3.29 mutation decreases ligand interaction and activation of LPA_1 and LPA_2 more than LPA_3 [28]. In contrast, W4.64A is important for LPA_3 activation, but not LPA_1 and LPA_2. The R5.38A mutant of LPA_2 and the R5.38N mutant of LPA_3 also show decreased activation by LPA. Mutation K7.36A decreased the potency in LPA_2 but increased E_{max} in LPA_1. Lastly, K7.35A increased LPA_3 EC_{50} to LPA about 10-fold [28]. LPA_4 and LPA_5 share less amino acid identity with LPA_{1-3}, and detailed models of their interaction with LPA are not available. Most of the residues described above are not present in LPA_4 and LPA_5, suggesting that these receptors have different ligand binding characteristics. Further research is needed to identify the critical residues for these receptors, and all will need to be re-evaluated once crystal structure data become available.

4. LPA signaling in human disease

4.1. Cardiovascular disease

Heart failure is one of the leading causes of death in the western world. In myocardial infarction, ischemia and hypoxia are the major causes of damage to cardiac myocytes. LPA appears to play a protective role under ischemic conditions. LPA levels are elevated and have been shown to protect different cell types from hypoxia-induced apoptosis, including cardiac myocytes, mesenchymal stem cells and renal cells [29–31]. The protective effect requires the PI3K/Akt and Erk pathway activation downstream of G_i [30,32]. In response to cardiac damage, the heart often enlarges to compensate for reduced contractile force, in a process known as hypertrophy. Experiments both *in vivo* and *in vitro* showed that LPA_1 and LPA_3 contribute to the hypertrophic response through the activation of G_i and multiple downstream effectors, including Rho, PI3K/Akt, and NF-kB [33,34].

In addition to their survival, myocyte contractility is also regulated by LPA [35]. LPA suppressed the cell shortening induced by isoprenaline through the activation of LPA_1 and/or LPA_3 in a PTX-sensitive manner. It was also shown that LPA increases lipoprotein lipase (LPL) activity in cardiac myocytes, augmenting the utilization and deposition of lipids, and might lead to contractility impairment [36].

Outside of the heart, LPA induces vascular smooth muscle cell (SMC) contraction [37] and elevates arterial blood pressure in rats [38]. LPA was reported to induce intimal hyperplasia, one of the steps leading to atherosclerosis, by the activation of membrane-bound GPCRs. With the use of LPA_1/LPA_2 double knock out mice, Panchatcharam et al. showed that these receptors are responsible for the growth of arterial walls following ligation-induced vascular injury. The *in vitro* proliferation and migration of smooth muscle cells (SMCs) were also attenuated in this mouse, which might be the cause of the protective effect [39]. However, LPA_1 and LPA_2 are not required for LPA induced SMCs de-differentiation, an important step in neointima formation, which suggested the function of other LPA receptors in this model.

LPA not only participates in neointimal formation, but also in a number of other processes involved in arterial plaque formation, such as: endothelium dysfunction, monocyte attraction and adhesion, LDL uptake and pro-inflammatory cytokine release [40–46]. LPA increased the permeability of the endothelium via RhoA activation without altering the calcium concentration [40]. The increase of permeability may facilitate the entry of monocytes and LDL infiltration. Additionally, LPA recruits monocytes via inducing MCP-1 secretion in endothelial cells [42]. Monocytes differentiate into macrophages after invading the endothelium. Uptake of oxidized LDL may also be regulated by LPA through an LPA_3/G_i/class A scavenger receptor (SR-A) [45]. Furthermore, LPA also induces platelet activation. Since LPA is released by activated platelets, this forms a positive feedback loop *in situ*, thus underlying its role in clot formation [41,47].

Taken together, the data summarized here indicate that LPA is involved in many different aspects relevant to cardiovascular disorders. Depending on the expression of different receptors in various cell types, LPA may exert either a protective or destructive effect on the system.

4.2. Cancer

The progression of cancer involves the dysregulation of multiple cellular processes, including cell proliferation, growth, survival, migration, invasion, and promotion of angiogenesis. In both *in vivo* and *in vitro* systems, LPA has been shown to participate in each of these processes (see reviews [23,24,48,49]), underscoring the involvement of LPA and the potential therapeutic benefit of targeting LPA signaling.

LPA was first reported to induce *in vitro* tumor cell invasion in 1993 [50]. Thereafter, studies using many different tumor cell lines and samples from cancer patients showed that LPA was involved in cancer etiology. Pronounced LPA accumulation was identified in the ascites and blood of ovarian cancer patients [51,52]. LPA activates ovarian cancer cells and protects them from apoptosis [53,54]. It also increases the expression of urokinase plasminogen activator (uPA) and matrix metalloproteases (MMPs), which are important mediators of metastasis and invasion [55–57]. Through Rho/ROCK/actomyosin and Ras/MEKK1, LPA accelerates focal adhesion formation and enhances cancer cell migration [58,59]. Similar effects were also seen on other cancers including gastric, colon, prostate, pancreas, liver, and brain (glioma) [60–66]. The LPA effects described above are primarily mediated through LPA_2 and LPA_3, while LPA_4 was suggested to participate in the positive feedback of LPA production [67–71]. Interestingly, LPA_1 was recently reported to be a negative regulator in ovarian cancer [72]. Also, in two other reports, LPA_1 mutations were found in lung and liver tumors in rats [73,74]. This suggests that LPA_1, unlike the other known LPA receptors, may act as a tumor-suppressor gene.

These data suggested that LPA signaling may be important in influencing cancer, and may represent therapeutic targets for cancer treatment. Indeed, at least *in vitro*, inhibition of LPA generating enzymes (iPLA2 and ATX), introduction of LPA degrading enzyme (lipid phosphatase-3), and inhibition of LPA_2 all produced an attenuation of cancer cell activity [67,75–77].

During tumor growth, it is important to increase the supply of oxygen- and nutrient-rich blood through angiogenesis. Vascular endothelial growth factor (VEGF) is one of the factors produced by tumor cells to promote angiogenesis and its inhibition leads to tumor growth suppression [78,79]. Interestingly, LPA was shown to induce VEGF expression in ovarian cancer cells via LPA_2 but not LPA_1 [80], an effect that requires the activation of hypoxia-inducible factor 1 alpha [81]. Additionally, evidence from knockout mouse phenotypes implicates the involvement of LPA in angiogenesis. *Lpar1*$^{-/-}$ and *Lpar1*$^{-/-}$/*Lpar2*$^{-/-}$ mice are born with frontal cranial hematomas (2.5% and 26% respectively) [82,83]; and ATX knockout mice die at embryonic day 9.5 (E9.5) with severe vas-

cular defects [84]. Taken together, these results implicate LPA as a potential regulator of tumor angiogenesis.

LPA signaling clearly affects different aspects of tumor progression, and there are many different pharmacological targets that may be exploited, including specific receptor subtypes and enzymes involved in LPA production/degradation. Since the effect of LPA is generally pro-tumorigenic, yet might also be paradoxically tumor-suppressive (via activation of LPA_1), more studies on LPA's mechanism of action through different receptors and cell types will be needed to optimize a clinically beneficial approach.

4.3. Neuropathic pain

Neuropathic pain, or peripheral neuropathy, is a chronic pain caused by a primary trauma or inflammation in the nervous system. Approximately 7–8% of the populations of developed countries are affected by neuropathic pain, with 5% of these representing severe cases [85,86]. Unfortunately, there is no effective therapeutic drug treatment for neuropathic pain. Treatment generally involves the use of analgesia or narcotic pain relievers, which often have limited efficacy. The cause of neuropathic pain is largely unknown; however, spontaneous signaling from nociceptive c-fibers or cross talk with low threshold A-delta sensory fibers may be contributing factors [87,88].

In mouse models of neuropathy, LPA has been shown to elicit pain when administrated locally to the hind paw. This occurs through the activation of LPA_1 and subsequent release of the pro-nociceptive factor substance P [89,90]. The role of LPA in neuropathic pain was further demonstrated with the use of LPA_1 knockout mice. Intrathecal injection of LPA produced allodynia and hyperalgesia in wild type mice, which is seen commonly in neuropathic pain [91]. This effect is totally blocked by LPA_1 deletion or by inhibition of Rho signaling, thus demonstrating the involvement of LPA_1/Rho/ROCK pathways in the initiation of neuropathic pain [91]. Furthermore, *Lpar1*$^{-/-}$ mice are also resistant to neuropathic pain induced by partial nerve ligation [91].

Recently, Inoue et al. published a series of papers providing evidence that autotaxin induces neuropathic pain through the conversion of LPC to LPA [92–94]. This is supported by the observation that heterozygous autotaxin knockout mice ($ATX^{+/-}$) are characterized by a 50% decrease in ATX activity and a 50% recovery from the neuropathic pain induced by partial sciatic nerve ligation (PSNL) [92]. All the data above implicate LPA signaling in the initiation of, and altering neuronal responses in, neuropathic pain.

In addition, another aspect of neuropathic pain, demyelination, is influenced by LPA signaling. The two axon-myelinating cell types, Schwann cells of the periphery and oligodendrocytes of the CNS, are responsive to LPA. It has been shown that LPA increases Schwann cell survival during serum withdrawal through LPA_1/G_i/PI3K pathway [95]. LPA also causes Schwann cells to form wreath-like structures, cell–cell adhesions, and focal adhesion reassembly [96]. In addition, LPA_1 mRNA expression levels are increased after sciatic nerve transection [96]. Similarly, oligodendrocytes also responded to LPA exposure. Phospholipase C (PLC) activity, intracellular calcium levels, protein kinase C (PKC) activity, and mitogen-activated protein kinase (MAPK) activity were all activated through LPA signaling in oligodendrocytes [97,98]. Recently, it was shown that LPA participates in oligodendrocyte maturation, since exogenous LPA administration leads to an increased oligodendrocyte protrusion network, an important step in maturation. Also, LPA stimulates myelin basic protein (MBP) mRNA expression and the numbers of MBP positive oligodendrocytes [98]. This LPA effect requires ATX downregulation, while ATX also regulates focal adhesion formation in oligodendrocytes [98,99]. Combined with the previous observations that *Lpar1*$^{-/-}$ mice are resistant to injury induced demyelination, and that LPA induces *ex vivo* DRG neuron demyelination [91,100], it has become clear that LPA signaling influences the histopathological events associated with demyelinating lesions. Further investigation is needed to characterize the relationship between LPA, myelination, and neuropathic pain.

4.4. Neuropsychiatric disorders

Many studies have suggested that there is a significant contribution of genetic/biological factors in psychiatric disorders. Developmental defects are thought to be involved in different conditions, such as schizophrenia and bipolar disorders [101,102]. LPA might contribute to the progression of these diseases in view of its potential to alter the physiology of neurons, glial cells, and their progenitors. Effects of LPA on these cell types include survival, proliferation, rounding, process retraction, growth cone collapse, migration and differentiation [2,103]. The measurement of LPA concentration also reveals a biologically significant amount of LPA in rat brain [104]. Moreover, in *ex vivo* cultures of mouse embryonic brain, LPA exposure induced cortical folding, thickening of the cortical wall, increased terminal mitosis/early differentiation in neural progenitor cells (NPCs), and increased survival for the proliferating cells of the ventricular zone (VZ) [105]. Neuronal plasticity comes from the rearrangement of synaptic connections, requiring such processes as neurite retraction and outgrowth, which are regulated by LPA signaling [106,107]. Cytoskeletal rearrangement is also a critical step in long-term memory formation: both processes involve the activation of the Rho-ROCK pathway, which is a major endpoint of receptor-mediated LPA signaling. This signaling pathway may account for reported LPA-related increases in long-term spatial memory [108].

LPA receptor knockout mice provide essential information on the potential role of LPA in CNS function. *Lpar1*$^{-/-}$ mice are characterized by craniofacial dysmorphism, which is also seen in some cases of schizophrenia [83]. Additionally, a variant of this mouse line called the "Malaga variant" showed some additional phenotypes compared to the original null mutant for LPA_1 [83]. Specifically, neurogenesis, maturation, and proliferation of NPCs were decreased, implicating the interaction of a single receptor, LPA_1, with as yet unknown genetic modifiers that can influence cortical development [109,110]. Another LPA_1 knockout strain, independently produced by Harrison et al., showed a schizophrenia-like phenotype [111]. The LPA_1 knockout causes deficits in prepulse inhibition (PPI), a phenotype observed in schizophrenia [112]. Additionally, the 5-HT (serotonin) neurotransmitter system, which is the target of many antipsychotic and antidepressant drugs, is significantly affected through lowered 5-HT turnover in the brains of knockout mice [111]. In other studies, LPA-induced calcium responses were altered in B lymphoblast cell lines originating from bipolar disorder patients [113]. This elevated calcium concentration has been reported to be associated with bipolar 1 disorders [114]. LPA was also shown to interfere with the signaling of an atypical antipsychotic agent, Risperidone, on glial cells [115].

Taken together, evidence is emerging that supports a contribution by LPA signaling to psychiatric disorders. Understanding the complexity of this relationship will require more detailed investigation. The use of receptor subtype-specific agonists/antagonists combined with genetic and behavioral studies on wild type and receptor null-mice will provide more insights into the role of LPA signaling in neuropsychiatric disorders.

4.5. Reproductive disorders

LPA receptors are differentially expressed in both testis and ovary, along with other reproductive tissues [116]. In mouse tissues, $LPA_{1\text{-}3}$ are highly expressed in testis, while LPA_1, LPA_2, and LPA_4 are

present in the ovary [116]. In humans, LPA_{1-4} are also expressed in the ovary, and interestingly, LPA_4 expression is higher in the ovary than in any other tissue examined [8,116]. Also, the LPA generating enzymes, PLA1, PLA2, and autotaxin are seen in the testis, while other experiments showed increased autotaxin activity in ovaries of women who received hormonal stimulation [116]. These observations suggest that LPA plays a significant role in the function of the male and female reproductive systems.

The use of LPA_3 knockout mice provided key data demonstrating involvement of LPA signaling in reproductive processes. Timing and spacing of embryo implantation into the uterine wall are affected by the loss of LPA_3, leading to delayed implantation and complete loss of normal spacing of embryos in *Lpar3*$^{-/-}$ dams [117]. The timing defect was caused by the disruption of prostaglandin signaling, since the exogenous administration of prostaglandins rescued the delayed implantation phenotype in LPA_3 knockout mice [118]. In contrast, embryo spacing was not mediated through prostaglandins, but appeared to be the result of uterine contraction induced by LPA_3 activation [119]. Recently, similar LPA/prostaglandin signaling was shown to be important in embryonic development and maintenance of pregnancy in sheep and pig, further confirming the role of LPA signaling in reproduction [120,121]. Other studies have also revealed a role for receptor-mediated LPA signaling in male reproduction. $LPA_{1/2/3}$ triple knockout mice showed reduced sperm production and lowered mating activity, followed by age-related azoospermia (no sperm detected in semen) [122]. This phenotype was associated with increased apoptosis of germ cells in the testis, suggesting that LPA promotes cell survival in the male reproductive system.

Taken together, LPA showed significant involvement in both the male and female reproductive systems. This area requires further investigation and may result in novel therapeutics for assisted reproductive technologies and/or birth control in the future.

4.6. Fibrosis

Fibrosis, the formation of excess fibrous connective tissues, was found to be strongly influenced by receptor-mediated LPA in different organs. LPA effects were examined in an animal model of renal fibrosis: unilateral ureteral obstruction (UUO). UUO resulted in increased LPA_1 expression while LPA_3 expression was decreased. The levels of LPA in conditioned media from kidney explants also significantly increased [123]. LPA has been shown to induce connective tissue growth factor (CTGF) expression in renal fibroblast cell lines [124]. Not surprisingly, *Lpar1*$^{-/-}$ mice showed attenuated renal fibrosis in this model; an observation that was further confirmed using Ki16425 and ROCK-inhibitors [124]. Similar effects were also seen in pulmonary fibrosis, however, through a slightly different mechanism. LPA was identified as a fibroblast chemoattractant in post-injury bronchoalveolar lavage (BAL). In a model using bleomycin to induce fibrosis in lung, *Lpar1*$^{-/-}$ mice showed decreased fibroblasts and collagen deposition [125]. Also, the vascular leakage induced by bleomycin is also attenuated in these mice, demonstrating LPA involvement in pulmonary fibrosis. Furthermore, LPA was shown to induce stellate cell and hepatocyte proliferation, which are the main contributors to extracellular matrix (ECM) accumulation in liver [126,127], and the plasma levels of LPA and ATX also rise in hepatitis C induced liver fibrosis [19].

4.7. Other diseases

In addition to the major disease areas described above, associations between LPA and other disorders have been reported. A single nucleotide polymorphism (SNP) analysis on 368 individuals with osteoarthritis revealed a linkage between LPA_1 and this disease

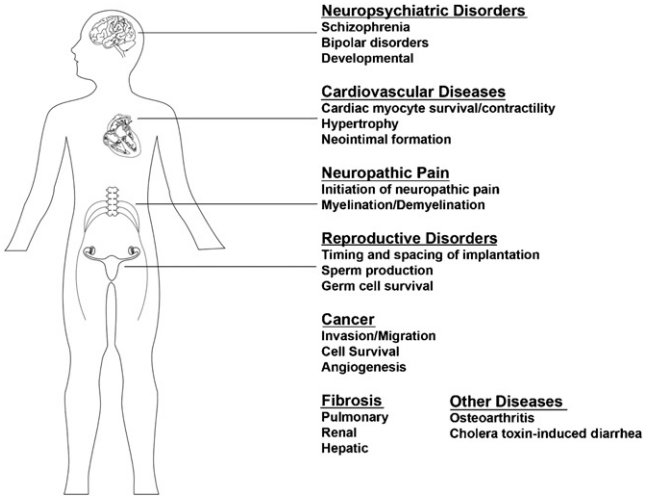

Fig. 3. Schematic summary of human diseases that are known or suspected to involve dysregulation of LPA signaling.

[128]. This SNP (rs3739708) located in the promoter region of LPA_1, affects AP-1-mediated transcriptional activity and may increase the expression of LPA_1 [128]. Being the major receptor of LPA in the synovium, the increase of LPA_1 expression might contribute to disease progression, since LPA stimulation *in vitro* induces synovial cells to release inflammatory cytokines and MMPs [128].

Lastly, cholera toxin-induced secretory diarrhea seems to be inhibited by LPA. LPA_2 is expressed by intestinal epithelial cells and interacts with cystic fibrosis transmembrane conductance regulator (CFTR), leading to inhibition of CFTR-induced iodide efflux [129]. CFTR-dependent intestinal fluid secretion in mice was attenuated by LPA administration, suggesting a therapeutic potential of LPA in certain forms of diarrhea [129].

5. Concluding remarks

LPA signaling has received increasing attention for its involvement in various disease processes as well as normal physiological functions. Here we have tried to provide a brief summary of the mechanisms of LPA signaling and recent findings regarding its potential involvement in different human disease settings (Fig. 3). LPA signaling participates in organismal development and maintains normal physiological functions through the orchestrated regulation of LPA production, degradation, receptor expression, and activity. Not surprisingly, LPA plays both positive and negative roles in disease processes. Key to both mechanistic and potential therapeutic approaches is the identification of specific LPA receptors and their involved functions. Further research will provide a foundation towards the development of clinically beneficial therapies based upon receptor-mediated LPA signaling.

Acknowledgements

We would like to thank Howard Tsai for graphical assistance. This work is supported by National Institutes of Health (NIH) grants MH051699, NS048478, and HD050685 awarded to J.C.

References

[1] Fukushima N, Ishii I, Contos JJ, Weiner JA, Chun J. Lysophospholipid receptors. Annu Rev Pharmacol Toxicol 2001;41:507–34.
[2] Ishii I, Fukushima N, Ye X, Chun J. Lysophospholipid receptors: signaling and biology. Annu Rev Biochem 2004;73:321–54.
[3] Vogt W. Pharamacologically active acidic phospholipids and glycolipids. Biochem Pharmacol 1963;12:415–20.

[4] Hecht JH, Weiner JA, Post SR, Chun J. Ventricular zone gene-1 (vzg-1) encodes a lysophosphatidic acid receptor expressed in neurogenic regions of the developing cerebral cortex. J Cell Biol 1996;135:1071–83.
[5] Fukushima N, Kimura Y, Chun J. A single receptor encoded by vzg-1/lpA1/edg-2 couples to G proteins and mediates multiple cellular responses to lysophosphatidic acid. Proc Natl Acad Sci U S A 1998;95:6151–6.
[6] An S, Dickens MA, Bleu T, Hallmark OG, Goetzl EJ. Molecular cloning of the human Edg2 protein and its identification as a functional cellular receptor for lysophosphatidic acid. Biochem Biophys Res Commun 1997;231:619–22.
[7] Bandoh K, Aoki J, Hosono H, et al. Molecular cloning and characterization of a novel human G-protein-coupled receptor, EDG7, for lysophosphatidic acid. J Biol Chem 1999;274:27776–85.
[8] Noguchi K, Ishii S, Shimizu T. Identification of p2y9/GPR23 as a novel G protein-coupled receptor for lysophosphatidic acid, structurally distant from the Edg family. J Biol Chem 2003;278:25600–6.
[9] Lee CW, Rivera R, Gardell S, Dubin AE, Chun J. GPR92 as a new G12/13- and Gq-coupled lysophosphatidic acid receptor that increases cAMP, LPA5. J Biol Chem 2006;281:23589–97.
[10] Kotarsky K, Boketoft A, Bristulf J, et al. Lysophosphatidic acid binds to and activates GPR92, a G protein-coupled receptor highly expressed in gastrointestinal lymphocytes. J Pharmacol Exp Ther 2006;318:619–28.
[11] HUGO-Human Genome Organization [http://www.hugo-international.org/].
[12] MGI-Mouse Genome Informatics [http://www.informatics.jax.org/].
[13] Tabata K, Baba K, Shiraishi A, Ito M, Fujita N. The orphan GPCR GPR87 was deorphanized and shown to be a lysophosphatidic acid receptor. Biochem Biophys Res Commun 2007;363:861–6.
[14] Pasternack SM, von Kugelgen I, Aboud KA, et al. G protein-coupled receptor P2Y5 and its ligand LPA are involved in maintenance of human hair growth. Nat Genet 2008;40:329–34.
[15] Smyth SS, Cheng HY, Miriyala S, Panchatcharam M, Morris AJ. Roles of lysophosphatidic acid in cardiovascular physiology and disease. Biochim Biophys Acta 2008;1781:563–70.
[16] Aoki J, Inoue A, Okudaira S. Two pathways for lysophosphatidic acid production. Biochim Biophys Acta 2008;1781:513–8.
[17] Pages C, Simon MF, Valet P, Saulnier-Blache JS. Lysophosphatidic acid synthesis and release. Prostaglandins Other Lipid Mediat 2001;64:1–10.
[18] Murata J, Lee HY, Clair T, et al. cDNA cloning of the human tumor motility-stimulating protein, autotaxin, reveals a homology with phosphodiesterases. J Biol Chem 1994;269:30479–84.
[19] Watanabe N, Ikeda H, Nakamura K, et al. Both plasma lysophosphatidic acid and serum autotaxin levels are increased in chronic hepatitis C. J Clin Gastroenterol 2007;41:616–23.
[20] Tanaka M, Okudaira S, Kishi Y, et al. Autotaxin stabilizes blood vessels and is required for embryonic vasculature by producing lysophosphatidic acid. J Biol Chem 2006;281:25822–30.
[21] Brauer AU, Savaskan NE, Kuhn H, Prehn S, Ninnemann O, Nitsch R. A new phospholipid phosphatase, PRG-1, is involved in axon growth and regenerative sprouting. Nat Neurosci 2003;6:572–8.
[22] Brauer AU, Nitsch R. Plasticity-related genes (PRGs/LRPs): a brain-specific class of lysophospholipid-modifying proteins. Biochim Biophys Acta 2008;1781:595–600.
[23] Anliker B, Chun J. Cell surface receptors in lysophospholipid signaling. Semin Cell Dev Biol 2004;15:457–65.
[24] Anliker B, Chun J. Lysophospholipid G protein-coupled receptors. J Biol Chem 2004;279:20555–8.
[25] Yanagida K, Ishii S, Hamano F, Noguchi K, Shimizu T. LPA4/p2y9/GPR23 mediates rho-dependent morphological changes in a rat neuronal cell line. J Biol Chem 2007;282:5814–24.
[26] Lee CW, Rivera R, Dubin AE, Chun J. LPA(4)/GPR23 is a lysophosphatidic acid (LPA) receptor utilizing G(s)-, G(q)/G(i)-mediated calcium signaling and G(12/13)-mediated Rho activation. J Biol Chem 2007;282:4310–7.
[27] Lee Z, Cheng CT, Zhang H, et al. Role of LPA4/p2y9/GPR23 in negative regulation of cell motility. Mol Biol Cell 2008;19:5435–45.
[28] Valentine WJ, Fells JI, Perygin DH, et al. Subtype-specific residues involved in ligand activation of the endothelial differentiation gene family lysophosphatidic acid receptors. J Biol Chem 2008;283:12175–87.
[29] Karliner JS, Honbo N, Summers K, Gray MO, Goetzl EJ. The lysophospholipids sphingosine-1-phosphate and lysophosphatidic acid enhance survival during hypoxia in neonatal rat cardiac myocytes. J Mol Cell Cardiol 2001;33:1713–7.
[30] Chen J, Baydoun AR, Xu R, et al. Lysophosphatidic acid protects mesenchymal stem cells against hypoxia and serum deprivation-induced apoptosis. Stem Cells 2008;26:135–45.
[31] Okusa MD, Ye H, Huang L, Sigismund L, Macdonald T, Lynch KR. Selective blockade of lysophosphatidic acid LPA3 receptors reduces murine renal ischemia-reperfusion injury. Am J Physiol Renal Physiol 2003;285:F565–574.
[32] Seewald S, Sachinidis A, Dusing R, et al. Lysophosphatidic acid and intracellular signalling in vascular smooth muscle cells. Atherosclerosis 1997;130:121–31.
[33] Hilal-Dandan R, Means CK, Gustafsson AB, et al. Lysophosphatidic acid induces hypertrophy of neonatal cardiac myocytes via activation of Gi and Rho. J Mol Cell Cardiol 2004;36:481–93.
[34] Chen J, Chen Y, Zhu W, et al. Specific LPA receptor subtype mediation of LPA-induced hypertrophy of cardiac myocytes and involvement of Akt and NFkappaB signal pathways. J Cell Biochem 2008;103:1718–31.
[35] Cremers B, Flesch M, Kostenis E, et al. Modulation of myocardial contractility by lysophosphatidic acid (LPA). J Mol Cell Cardiol 2003;35:71–80.
[36] Pulinilkunnil T, An D, Ghosh S, et al. Lysophosphatidic acid-mediated augmentation of cardiomyocyte lipoprotein lipase involves actin cytoskeleton reorganization. Am J Physiol Heart Circ Physiol 2005;288:H2802–2810.
[37] Ainslie K, Shi ZD, Garanich JS, Tarbell JM. Rat aortic smooth muscle cells contract in response to serum and its components in a calcium independent manner. Ann Biomed Eng 2004;32:1667–75.
[38] Tokumura A, Fukuzawa K, Tsukatani H. Effects of synthetic and natural lysophosphatidic acids on the arterial blood pressure of different animal species. Lipids 1978;13:572–4.
[39] Panchatcharam M, Miriyala S, Yang F, et al. Lysophosphatidic acid receptors 1 and 2 play roles in regulation of vascular injury responses but not blood pressure. Circ Res 2008;103:662–70.
[40] van Nieuw Amerongen GP, Vermeer MA, van Hinsbergh VW. Role of RhoA and Rho kinase in lysophosphatidic acid-induced endothelial barrier dysfunction. Arterioscler Thromb Vasc Biol 2000;20:E127–133.
[41] Siess W, Zangl KJ, Essler M, et al. Lysophosphatidic acid mediates the rapid activation of platelets and endothelial cells by mildly oxidized low density lipoprotein and accumulates in human atherosclerotic lesions. Proc Natl Acad Sci U S A 1999;96:6931–6.
[42] Lin CI, Chen CN, Chen JH, Lee H. Lysophospholipids increase IL-8 and MCP-1 expressions in human umbilical cord vein endothelial cells through an IL-1-dependent mechanism. J Cell Biochem 2006;99:1216–32.
[43] Palmetshofer A, Robson SC, Nehls V. Lysophosphatidic acid activates nuclear factor kappa B and induces proinflammatory gene expression in endothelial cells. Thromb Haemost 1999;82:1532–7.
[44] Rizza C, Leitinger N, Yue J, et al. Lysophosphatidic acid as a regulator of endothelial/leukocyte interaction. Lab Invest 1999;79:1227–35.
[45] Chang CL, Hsu HY, Lin HY, Chiang W, Lee H. Lysophosphatidic acid-induced oxidized low-density lipoprotein uptake is class A scavenger receptor-dependent in macrophages. Prostaglandins Other Lipid Mediat 2008;87:20–5.
[46] Chang CL, Lin ME, Hsu HY, et al. Lysophosphatidic acid-induced interleukin-1 beta expression is mediated through Gi/Rho and the generation of reactive oxygen species in macrophages. J Biomed Sci 2008;15:357–63.
[47] Eichholtz T, Jalink K, Fahrenfort I, Moolenaar WH. The bioactive phospholipid lysophosphatidic acid is released from activated platelets. Biochem J 1993;291(Pt 3):677–80.
[48] Rivera R, Chun J. Biological effects of lysophospholipids. Rev Physiol Biochem Pharmacol 2008;160:25–46.
[49] Gardell SE, Dubin AE, Chun J. Emerging medicinal roles for lysophospholipid signaling. Trends Mol Med 2006;12:65–75.
[50] Imamura F, Horai T, Mukai M, Shinkai K, Sawada M, Akedo H. Induction of in vitro tumor cell invasion of cellular monolayers by lysophosphatidic acid or phospholipase D. Biochem Biophys Res Commun 1993;193:497–503.
[51] Xu Y, Shen Z, Wiper DW, et al. Lysophosphatidic acid as a potential biomarker for ovarian and other gynecologic cancers. JAMA 1998;280:719–23.
[52] Yoon HR, Kim H, Cho SH. Quantitative analysis of acyl-lysophosphatidic acid in plasma using negative ionization tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 2003;788:85–92.
[53] Xu Y, Fang XJ, Casey G, Mills GB. Lysophospholipids activate ovarian and breast cancer cells. Biochem J 1995;309(Pt 3):933–40.
[54] Meng Y, Kang S, So J, Reierstad S, Fishman DA. Translocation of Fas by LPA prevents ovarian cancer cells from anti-Fas-induced apoptosis. Gynecol Oncol 2005;96:462–9.
[55] Pustilnik TB, Estrella V, Wiener JR, et al. Lysophosphatidic acid induces urokinase secretion by ovarian cancer cells. Clin Cancer Res 1999;5:3704–10.
[56] Fishman DA, Liu Y, Ellerbroek SM, Stack MS. Lysophosphatidic acid promotes matrix metalloproteinase (MMP) activation and MMP-dependent invasion in ovarian cancer cells. Cancer Res 2001;61:3194–9.
[57] Do TV, Symowicz JC, Berman DM, et al. Lysophosphatidic acid down-regulates stress fibers and up-regulates pro-matrix metalloproteinase-2 activation in ovarian cancer cells. Mol Cancer Res 2007;5:121–31.
[58] Sawada K, Morishige K, Tahara M, et al. Lysophosphatidic acid induces focal adhesion assembly through Rho/Rho-associated kinase pathway in human ovarian cancer cells. Gynecol Oncol 2002;87:252–9.
[59] Bian D, Su S, Mahanivong C, et al. Lysophosphatidic acid stimulates ovarian cancer cell migration via a Ras-MEK kinase 1 pathway. Cancer Res 2004;64:4209–17.
[60] Kim MH, Park JS, Chang HJ, et al. Lysophosphatidic acid promotes cell invasion by up-regulating the urokinase-type plasminogen activator receptor in human gastric cancer cells. J Cell Biochem 2008;104:1102–12.
[61] Rusovici R, Ghaleb A, Shim H, Yang VW, Yun CC. Lysophosphatidic acid prevents apoptosis of Caco-2 colon cancer cells via activation of mitogen-activated protein kinase and phosphorylation of Bad. Biochim Biophys Acta 2007;1770:1194–203.
[62] Chang CL, Liao JJ, Huang WP, Lee H. Lysophosphatidic acid inhibits serum deprivation-induced autophagy in human prostate cancer PC-3 cells. Autophagy 2007;3:268–70.
[63] Kishi Y, Okudaira S, Tanaka M, et al. Autotaxin is overexpressed in glioblastoma multiforme and contributes to cell motility of glioblastoma by converting lysophosphatidylcholine to lysophosphatidic acid. J Biol Chem 2006;281:17492–500.
[64] Yamada T, Sato K, Komachi M, et al. Lysophosphatidic acid (LPA) in malignant ascites stimulates motility of human pancreatic cancer cells through LPA1. J Biol Chem 2004;279:6595–605.

[65] Genda T, Sakamoto M, Ichida T, et al. Cell motility mediated by rho and Rho-associated protein kinase plays a critical role in intrahepatic metastasis of human hepatocellular carcinoma. Hepatology 1999;30:1027–36.
[66] Goetzl EJ, Dolezalova H, Kong Y, Zeng L. Dual mechanisms for lysophospholipid induction of proliferation of human breast carcinoma cells. Cancer Res 1999;59:4732–7.
[67] Wang GL, Wen ZQ, Xu WP, Wang ZY, Du XL, Wang F. Inhibition of lysophosphatidic acid receptor-2 expression by RNA interference decreases lysophosphatidic acid-induced urokinase plasminogen activator activation, cell invasion, and migration in ovarian cancer SKOV-3 cells. Croat Med J 2008;49:175–81.
[68] Yu S, Murph MM, Lu Y, et al. Lysophosphatidic acid receptors determine tumorigenicity and aggressiveness of ovarian cancer cells. J Natl Cancer Inst 2008;100:1630–42.
[69] Hope JM, Wang FQ, Whyte JS, et al. LPA receptor 2 mediates LPA-induced endometrial cancer invasion. Gynecol Oncol 2008.
[70] Ptaszynska MM, Pendrak ML, Bandle RW, Stracke ML, Roberts DD. Positive feedback between vascular endothelial growth factor-A and autotaxin in ovarian cancer cells. Mol Cancer Res 2008;6:352–63.
[71] Estrella VC, Eder AM, Liu S, et al. Lysophosphatidic acid induction of urokinase plasminogen activator secretion requires activation of the p38MAPK pathway. Int J Oncol 2007;31:441–9.
[72] Murph MM, Nguyen GH, Radhakrishna H, Mills GB. Sharpening the edges of understanding the structure/function of the LPA1 receptor: expression in cancer and mechanisms of regulation. Biochim Biophys Acta 2008;1781:547–57.
[73] Obo Y, Yamada T, Furukawa M, et al. Frequent mutations of lysophosphatidic acid receptor-1 gene in rat liver tumors. Mutat Res 2008.
[74] Yamada T, Obo Y, Furukawa M, et al. Mutations of lysophosphatidic acid receptor-1 gene during progression of lung tumors in rats. Biochem Biophys Res Commun 2008.
[75] Song Y, Wilkins P, Hu W, et al. Inhibition of calcium-independent phospholipase A2 suppresses proliferation and tumorigenicity of ovarian carcinoma cells. Biochem J 2007;406:427–36.
[76] Tanyi JL, Morris AJ, Wolf JK, et al. The human lipid phosphate phosphatase-3 decreases the growth, survival, and tumorigenesis of ovarian cancer cells: validation of the lysophosphatidic acid signaling cascade as a target for therapy in ovarian cancer. Cancer Res 2003;63:1073–82.
[77] Saunders LP, Ouellette A, Bandle R, et al. Identification of small-molecule inhibitors of autotaxin that inhibit melanoma cell migration and invasion. Mol Cancer Ther 2008;7:3352–62.
[78] Dvorak HF, Sioussat TM, Brown LF, et al. Distribution of vascular permeability factor (vascular endothelial growth factor) in tumors: concentration in tumor blood vessels. J Exp Med 1991;174:1275–8.
[79] Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature 1993;362:841–4.
[80] Hu YL, Tee MK, Goetzl EJ, et al. Lysophosphatidic acid induction of vascular endothelial growth factor expression in human ovarian cancer cells. J Natl Cancer Inst 2001;93:762–8.
[81] Lee J, Park SY, Lee EK, et al. Activation of hypoxia-inducible factor-1alpha is necessary for lysophosphatidic acid-induced vascular endothelial growth factor expression. Clin Cancer Res 2006;12:6351–8.
[82] Contos JJ, Ishii I, Fukushima N, et al. Characterization of lpa(2) (Edg4) and lpa(1)/lpa(2) (Edg2/Edg4) lysophosphatidic acid receptor knockout mice: signaling deficits without obvious phenotypic abnormality attributable to lpa(2). Mol Cell Biol 2002;22:6921–9.
[83] Contos JJ, Fukushima N, Weiner JA, Kaushal D, Chun J. Requirement for the lpA1 lysophosphatidic acid receptor gene in normal suckling behavior. Proc Natl Acad Sci U S A 2000;97:13384–9.
[84] van Meeteren LA, Ruurs P, Stortelers C, et al. Autotaxin, a secreted lysophospholipase D, is essential for blood vessel formation during development. Mol Cell Biol 2006;26:5015–22.
[85] Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain 2008;136:380–7.
[86] Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain 2006;7:281–9.
[87] Wu G, Ringkamp M, Hartke TV, et al. Early onset of spontaneous activity in uninjured C-fiber nociceptors after injury to neighboring nerve fibers. J Neurosci 2001;21:RC140.
[88] Amir R, Devor M. Functional cross-excitation between afferent A- and C-neurons in dorsal root ganglia. Neuroscience 2000;95:189–95.
[89] Renback K, Inoue M, Yoshida A, Nyberg F, Ueda H. Vzg-1/lysophosphatidic acid-receptor involved in peripheral pain transmission. Brain Res Mol Brain Res 2000;75:350–4.
[90] Renback K, Inoue M, Ueda H. Lysophosphatidic acid-induced, pertussis toxin-sensitive nociception through a substance P release from peripheral nerve endings in mice. Neurosci Lett 1999;270:59–61.
[91] Inoue M, Rashid MH, Fujita R, Contos JJ, Chun J, Ueda H. Initiation of neuropathic pain requires lysophosphatidic acid receptor signaling. Nat Med 2004;10:712–8.
[92] Inoue M, Ma L, Aoki J, Chun J, Ueda H. Autotaxin, a synthetic enzyme of lysophosphatidic acid (LPA), mediates the induction of nerve-injured neuropathic pain. Mol Pain 2008;4:6.
[93] Inoue M, Ma L, Aoki J, Ueda H. Simultaneous stimulation of spinal NK1 and NMDA receptors produces LPC which undergoes ATX-mediated conversion to LPA, an initiator of neuropathic pain. J Neurochem 2008.
[94] Inoue M, Xie W, Matsushita Y, Chun J, Aoki J, Ueda H. Lysophosphatidylcholine induces neuropathic pain through an action of autotaxin to generate lysophosphatidic acid. Neuroscience 2008;152:296–8.
[95] Weiner JA, Chun J. Schwann cell survival mediated by the signaling phospholipid lysophosphatidic acid. Proc Natl Acad Sci U S A 1999;96:5233–8.
[96] Weiner JA, Fukushima N, Contos JJ, Scherer SS, Chun J. Regulation of Schwann cell morphology and adhesion by receptor-mediated lysophosphatidic acid signaling. J Neurosci 2001;21:7069–78.
[97] Yu N, Lariosa-Willingham KD, Lin FF, Webb M, Rao TS. Characterization of lysophosphatidic acid and sphingosine-1-phosphate-mediated signal transduction in rat cortical oligodendrocytes. Glia 2004;45:17–27.
[98] Nogaroli L, Yuelling LM, Dennis J, Gorse K, Payne SG, Fuss B. Lysophosphatidic acid can support the formation of membranous structures and an increase in MBP mRNA levels in differentiating oligodendrocytes. Neurochem Res 2008.
[99] Dennis J, White MA, Forrest AD, et al. Phosphodiesterase-Ialpha/autotaxin's MORFO domain regulates oligodendroglial process network formation and focal adhesion organization. Mol Cell Neurosci 2008;37:412–24.
[100] Fujita R, Kiguchi N, Ueda H. LPA-mediated demyelination in ex vivo culture of dorsal root. Neurochem Int 2007;50:351–5.
[101] Lencz T, Cornblatt B, Bilder RM. Neurodevelopmental models of schizophrenia: pathophysiologic synthesis and directions for intervention research. Psychopharmacol Bull 2001;35:95–125.
[102] Blumberg HP, Kaufman J, Martin A, Charney DS, Krystal JH, Peterson BS. Significance of adolescent neurodevelopment for the neural circuitry of bipolar disorder. Ann N Y Acad Sci 2004;1021:376–83.
[103] de Sampaio ESTC, Choi JW, Gardell SE, et al. Lysophosphatidic acid receptor-dependent secondary effects via astrocytes promote neuronal differentiation. J Biol Chem 2008;283:7470–9.
[104] Das AK, Hajra AK. Quantification, characterization and fatty acid composition of lysophosphatidic acid in different rat tissues. Lipids 1989;24:329–33.
[105] Kingsbury MA, Rehen SK, Contos JJ, Higgins CM, Chun J. Non-proliferative effects of lysophosphatidic acid enhance cortical growth and folding. Nat Neurosci 2003;6:1292–9.
[106] Fukushima N, Weiner JA, Kaushal D, et al. Lysophosphatidic acid influences the morphology and motility of young, postmitotic cortical neurons. Mol Cell Neurosci 2002;20:271–82.
[107] Fukushima N, Morita Y. Actomyosin-dependent microtubule rearrangement in lysophosphatidic acid-induced neurite remodeling of young cortical neurons. Brain Res 2006;1094:65–75.
[108] Dash PK, Orsi SA, Moody M, Moore AN. A role for hippocampal Rho-ROCK pathway in long-term spatial memory. Biochem Biophys Res Commun 2004;322:893–8.
[109] Estivill-Torrus G, Llebrez-Zayas P, Matas-Rico E, et al. Absence of LPA1 signaling results in defective cortical development. Cereb Cortex 2008;18:938–50.
[110] Matas-Rico E, Garcia-Diaz B, Llebrez-Zayas P, et al. Deletion of lysophosphatidic acid receptor LPA1 reduces neurogenesis in the mouse dentate gyrus. Mol Cell Neurosci 2008;39:342–55.
[111] Harrison SM, Reavill C, Brown G, et al. LPA1 receptor-deficient mice have phenotypic changes observed in psychiatric disease. Mol Cell Neurosci 2003;24:1170–9.
[112] Braff DL, Geyer MA. Sensorimotor gating and schizophrenia. Human and animal model studies. Arch Gen Psychiatry 1990;47:181–8.
[113] Perova T, Wasserman MJ, Li PP, Warsh JJ. Hyperactive intracellular calcium dynamics in B lymphoblasts from patients with bipolar I disorder. Int J Neuropsychopharmacol 2008;11:185–96.
[114] Emamghoreishi M, Schlichter L, Li PP, et al. High intracellular calcium concentrations in transformed lymphoblasts from subjects with bipolar I disorder. Am J Psychiatry 1997;154:976–82.
[115] Quincozes-Santos A, Abib RT, Leite MC, et al. Effect of the atypical neuroleptic risperidone on morphology and S100B secretion in C6 astroglial lineage cells. Mol Cell Biochem 2008;314:59–63.
[116] Ye X. Lysophospholipid signaling in the function and pathology of the reproductive system. Hum Reprod Update 2008;14:519–36.
[117] Ye X, Hama K, Contos JJ, et al. LPA3-mediated lysophosphatidic acid signalling in embryo implantation and spacing. Nature 2005;435:104–8.
[118] Hama K, Aoki J, Inoue A, et al. Embryo spacing and implantation timing are differentially regulated by LPA3-mediated lysophosphatidic acid signaling in mice. Biol Reprod 2007;77:954–9.
[119] Hama K, Aoki J, Fukaya M, et al. Lysophosphatidic acid and autotaxin stimulate cell motility of neoplastic and non-neoplastic cells through LPA1. J Biol Chem 2004;279:17634–9.
[120] Liszewska E, Reinaud P, Billon-Denis E, Dubois O, Robin P, Charpigny G. Lysophosphatidic acid signaling during embryo development in sheep: involvement in prostaglandin synthesis. Endocrinology 2008.
[121] Ziecik AJ, Waclawik A, Bogacki M. Conceptus signals for establishment and maintenance of pregnancy in pigs - lipid signaling system. Exp Clin Endocrinol Diabetes 2008;116:443–9.
[122] Ye X, Skinner MK, Kennedy G, Chun J. Age-dependent loss of sperm production in mice via impaired lysophosphatidic acid signaling. Biol Reprod 2008;79:328–36.
[123] Pradere JP, Gonzalez J, Klein J, et al. Lysophosphatidic acid and renal fibrosis. Biochim Biophys Acta 2008;1781:582–7.

[124] Heusinger-Ribeiro J, Eberlein M, Wahab NA, Goppelt-Struebe M. Expression of connective tissue growth factor in human renal fibroblasts: regulatory roles of RhoA and cAMP. J Am Soc Nephrol 2001;12:1853–61.
[125] Tager AM, LaCamera P, Shea BS, et al. The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. Nat Med 2008;14:45–54.
[126] Ikeda H, Yatomi Y, Yanase M, et al. Effects of lysophosphatidic acid on proliferation of stellate cells and hepatocytes in culture. Biochem Biophys Res Commun 1998;248:436–40.
[127] Wu J, Zern MA. Hepatic stellate cells: a target for the treatment of liver fibrosis. J Gastroenterol 2000;35:665–72.
[128] Mototani H, Iida A, Nakajima M, et al. A functional SNP in EDG2 increases susceptibility to knee osteoarthritis in Japanese. Hum Mol Genet 2008;17:1790–7.
[129] Li C, Dandridge KS, Di A, et al. Lysophosphatidic acid inhibits cholera toxin-induced secretory diarrhea through CFTR-dependent protein interactions. J Exp Med 2005;202:975–86.