Published in final edited form as:
Biochim Biophys Acta. 2013 January ; 1831(1): 126–132. doi:10.1016/j.bbalip.2012.07.012.

Lipid phosphate phosphatase (LPP3) and vascular development

H.M. Ren[*], **M. Panchatcharam**[*], **P Mueller**[*], **D. Escalante-Alcalde**[†], **A.J. Morris**[*], and **S.S. Smyth**[*,‡]

[*]The Gill Heart Institute, Division of Cardiovascular Medicine, 900 S. Limestone, Lexington, KY, USA, 40536-0200

[†]División de Neurociencias, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, Ciudad Universitaria Mexico, 04510

[‡]Veterans Affairs Medical Center, Lexington, KY, USA

Abstract

Lipid phosphate phosphatases (LPP) are integral membrane proteins with broad substrate specificity that dephosphorylate lipid substrates including phosphatidic acid, lysophosphatidic acid, ceramide 1-phosphate, sphingosine 1-phosphate, and diacylglycerol pyrophosphate. Although the three mammalian enzymes (LPP1-3) demonstrate overlapping catalytic activities and substrate preferences *in vitro,* the phenotypes of mice with targeted inactivation of the *Ppap2* genes encoding the LPP enzymes reveal nonredundant functions. A specific role for LPP3 in vascular development has emerged from studies of mice lacking *Ppap2b*. A meta-analysis of multiple, large genome-wide association studies identified a single nucleotide polymorphism in *PPAP2B* as a novel predictor of coronary artery disease. In this review, we will discuss the evidence that links LPP3 to vascular development and disease and evaluate potential molecular mechanisms.

The LPP family

Lipid phosphate phosphatases are integral membrane proteins with broad substrate specificity that dephosphorylate lipid substrates including phosphatidic acid (PA), lysophosphatidic acid (LPA), ceramide 1-phosphate (C1P), sphingosine 1-phosphate (S1P), and diacylglycerol pyrophosphate (DGPP) [1]. They belong to a broader class of structurally-unrelated phosphatidic acid-phosphatases (PAP) that comprise both membrane and soluble family members [2]. In humans, three genes, *PPAP2A*, *PPAP2C*, and *PPAP2B*, encode the enzymes LPP1, LPP2 and LPP3, respectively [3, 4]. In this review, we refer to the gene names using the *PPAP* nomenclature but the corresponding proteins as LPPs.

The predicted topology of the LPPs suggests that they possess six transmembrane domains, an active site comprised from at least 3 regions of the protein that localizes to the extracellular or luminal surface of the membrane, and a glycosylation site on a hydrophilic loop between the first and second active site domains (Figure 1) [2]. Mammalian LPPs form homo- and hetero-oligomers [5]. The *Drosophila* homolog of mammalian LPP, wunen, forms homodimers via the last C-terminal 35 amino acids, but cannot form heterodimers with wunen2 or mammalian LPP1 or LPP3 [6]. The functional significance of these interactions is not known.

LPPs localize to both the plasma membrane and intracellular membrane organelles, in particular the endoplasmic reticulum and Golgi apparatus [1, 2, 7, 8]. Subcellular localization of these enzymes is both dynamic and cell-specific. LPP1 and LPP3 appear to have distinct subcellular localization [9], between lipid rafts and the apical and basolateral membranes of polarized cells, which could account for their observed differences in

biological functions despite their essentially identical catalytic activities. Evidence that LPPs can act on both extracellular and intracellular substrates has come from studies in which these enzymes are over expressed or inactivated in cell culture systems coupled with measurements of their substrates and products using radiolabeling or mass spectrometry based approaches.

Although the three mammalian LPP enzymes demonstrate overlapping catalytic activities and substrate preferences *in vitro*, the phenotypes of mice with targeted inactivation of the *Ppap2* genes indicates that they have nonredundant functions. The *Ppap2a* gene encoding murine LPP1 has been disrupted using an exon trap insertion strategy. Mice harboring the exon trap inactivated allele appear phenotypically unremarkable [10]. Multiple tissues, including heart, kidney, lung, liver and spleen, isolated from the animals display a reduced ability to dephosphorylate exogenously provided LPA, indicating a role for LPP1 as a widely expressed LPA phosphatase. Decreased dephosphorylation of exogenous LPA by thymocytes from these LPP1 deficient mice indicate that endogenously expressed LPP1 can function as an “ecto” LPA phosphatase, at least in these cells. Mice homozygous for an insertionally inactivated allele of the *Ppap2c* gene encoding murine LPP2 are phenotypically unremarkable [11]. By contrast, inactivation of *Ppap2b* results in early embryonic lethality in part to due to failure of extra-embryonic vascular development [12].

The role of LPP3 in blood vascular development

In mice, LPP3 is first expressed in the anterior visceral endoderm, and the extra-embryonic membranes at E7.5 [12, 13]. As gastrulation proceeds, LPP3 appears around the node and the tip of the allantois at E8.0, and allantois, the developing gut, the pericardio-peritoneal canal and somites at E8.5. LPP3 is absolutely required in these tissues, as chorio-allantoic placenta do not form in its absence. By E9.5, LPP3 is present in umbilical cord and the chorionic region, and later in mid-gestation, in the apical ectodermal ridge, mesenchyme of the limb buds, and nervous system. In adult mice, expression of LPP3 is particularly prominent in lung, cerebellum and heart atrium. The dynamic and tissue-specific expression pattern may reflect the importance of LPP3 in specific tissues during development.

A critical role for LPP3 in vasculogenesis is indicated by the phenotype of mice with inherited deficiency in *Ppap2b*, created by deleting exon 5 that encodes a domain of the protein essential for its catalytic activity [12]. *Ppap2b*-null embryos die between E7.5 to 9.5 as a consequence of an inability to form extra-embryonic vasculature. The *Ppap2b*-null embryos fail to form chorio-allantoic placenta, and their abnormal yolk sac vascular network results in accumulation of blood cells in the yolk sac cavity. The embryos also demonstrate abnormalities in embryonic axis formation, with shortening of the anterior-posterior axis, anterior truncation and frequent duplication of axial structures [13]. We have targeted LPP3 in the vasculature by breeding mice containing a *Ppap2b*-floxed allele with mice expressing Cre recombinase under the control of the *Tie2* promoter (*Tie2-Cre*) to delete exons 3 and 4 of the floxed *Ppap2b* gene in hematopoeitic and endothelial cells [14]. The excised exons encode the second and third transmembrane domains, the first intracellular and the second outer loop, and 12 amino acids of the fourth transmembrane segment. Global Cre-mediated deletion in mice phenocopies complete *Ppap2b* deletion [13]. Mice with *Tie-Cre* mediated deletion, which lack LPP3 in endothelial and some hematopoeitic cells, die embryonically with a milder but similar defect in vasculogenesis as is observed in mice with global lack of *Ppap2b* [12]. Consistent with the observations that LPP3 is essential for normal vascular development, allantois explants from *Ppap2b*-null embryos fail to organize endothelial cells into cords. Finally, LPP3 expression is also upregulated as lymphatic endothelial cells organize into capillary-like structures in collagen matrix *in vitro*. siRNA-targeted knock-down of LPP3 expression enhances capillary formation, suggesting that the protein

negatively regulates the process [15]. At the present time, it is not known if LPP3 catalytic activity is required for normal vessel development although in the absence of other well defined non-catalytic functions for the protein this seems likely. In the following sections, we will discuss potential mechanisms by which LPP3 may affect endothelial cell function. We will focus attention on pathways that may be regulated by LPP3 catalytic activity and ways that LPP3 may influence development in phosphatase independent manners.

LPP3 as a critical regulator of lysophospholipid signaling

The bioactive lysophospholipids LPA and S1P elicit cell responses by binding to and activating distinct G-protein coupled receptors, initially classified as *Edg* (endothelial differentiation gene family) receptors but subsequently rationally re-named as LPA and S1P receptors. LPP3-catalyzed removal of the phosphate group of LPA and S1P renders them inactive at their receptors. Substantial evidence from cell culture experiments indicates that LPP3 can regulate extracellular signaling by lysophospholipids [2, 16, 17]. LPP3 overexpression decreases tumorigenesis and colony forming ability of ovarian cancer cells and the effects of LPP3 on colony-forming activity are substantially reversed by an LPP-resistant LPA analog, O-methylphosphothionate and a series of additional phosphatase resistant LPA analogs which have been developed as synthetic LPA receptor selective ligands [18]. These results imply that the inhibitory effects of LPP3 on tumor growth and survival are mediated at least in part by hydrolysis and inactivation of bioactive LPA. Consistent with these reports, cultures of embryonic fibroblasts derived from LPP3 knockout mice exhibit significantly increased extracellular LPA [12].

LPA in the vasculature

Extracellular, bioactive LPA is generated by the lysophopsholipase D autotaxin, which removes the choline group from lysophosphatidylcholine (LPC) and other lysophopshopholipids (Figure 2) [19]. Plasma LPA levels are <1 μM, but increase with platelet activation, due to phospholipase A1-mediated generation of LPC and association of autotaxin with activated platelet integrins [20]. These mechanisms may account for increases in local concentrations of LPA that could be associated with activation of vascular and blood cells. Given that LPA exerts growth-factor like effects and/or stimulates migration of virtually every cell type studied, enhanced production of LPA could contribute to the pathology of various disorders such as cancer, atherosclerosis and inflammation [21–25].

A link between LPA signaling and vascular development was suggested by the phenotype of mice lacking *Enpp2*, the gene encoding autotaxin. *Enpp2*-null mice die between E9.5 – 10.5 with profound vascular defects in both yolk sac and embryo, and also aberrant neural tube formation [20, 26–28]. Replacing functional autotaxin with a catalytically inactive variant also results in embryonic lethality with the mice displaying apparently similar severe defects in the vascular development, suggesting a requirement for LPA (or other autotaxin-generated products which might be related to the ability of the enzyme to also hydrolyze various nucleotide phosphates) in embryonic vascular formation [29].

The cellular effects of LPA are mediated by at least 8 different G-protein coupled receptors: LPA_1/Edg-2, LPA_2/Edg-4, and LPA_3/Edg-7, LPA_4/GPR23/p2y9, LPA_5/GPR92, and LPA_6/p2y87, LPA_7/p2y5 and LPA_8/p2y10 [30–32]. The $LPA_{1–3}$ receptors, members of the original *Edg* family, share approximately 50% homology in amino acid sequences [33–36], whereas LPA_4 and $LPA_{6–8}$ were initially identified as members of the purinergic receptor family based on sequence homology [30–32, 37, 38]. Each LPA receptor couples to specific G proteins including $G_{12/13}$, G_i, G_q, and G_s, to activate diverse signaling pathways that involve small GTPase Rho, phosphoinositide 3-kinase, phospholipase C, mitogen-activated protein kinase, and adenylyl cyclase [39, 40]. Via these signaling pathways, LPA alters

endothelial cell migration, proliferation and barrier stability. More recently, LPA has been proposed to serve as a ligand for the receptor for advanced glycation endproducts (RAGE) [41].

Insights into the function of LPA in vascular development come from model organisms with targeted deficiencies in specific LPA receptors. None of the LPA receptor knock-out mice phenocopy the absence of autotaxin, suggesting that the LPA receptors may play redundant roles during development and/or indicating the presence of unidentified LPA receptors or that autotaxin has functions that are independent of its ability to generate LPA. *Lpar4*-deficient mice exhibit impaired blood vessel formation, with up to 30% of the *Lpar4*-null embryos failing to survive to birth [42]. Embryos lacking *Lpar4* develop hemorrhage in many organs, including the heart, skin and lung apparent between E10.5 and E18.5. In addition to subcutaneous hemorrhage, blood vessel dilatation and reduced smooth muscle cell recruitment occurs. *Lpar1*-deficient mice exhibit variable frontal cephalic hemorrhages, with higher penetrance of the phenotype in mice lacking both LPA_1 and LPA_2 receptors. In zebrafish, combined targeting of *Lpar1* and *Lpar4*, but not either individual receptor, impairs vascular development [43]. Normally in zebrafish embryo development, segmental arteries sprout from the dorsal aorta and extend to the horizontal myoseptum to form longitudinal anastomotic vessels. Zebrafish embryos in which both LPA_1 and LPA_4 receptors have been targeted for knockdown by morpholino antisense oligonucleotides, extension of the segmental arteries stalls and instead of connecting with the myoseptum, abnormal connections are formed between neighboring segmental arteries. A similar defect occurs when autotaxin is targeted by morpholino antisense oligonucleotides, indicating a critical role of LPA signaling in arterial development.

In cell culture systems, LPA can promote endothelial cell migration and proliferation [44, 45]. LPA stimulated fetal bovine heart endothelial cells and β1GD25 cells migration is sensitive to both C3 toxin and pertussis toxin, suggesting that its effects are through $G_{12/13}$/Rho and G_i/Ras pathways [46]. LPA may also promote angiogenesis by suppressing endothelial cell CD36 surface expression via Ca^{2+}/calmodulin-dependent Ser/Thr kinase PKD-1 [47]. In cultured allantois explants, LPA prevents the disassembly of blood vessels, supporting a role for LPA signaling in the maintenance of existing vasculature [48]. LPA can stimulate endothelial cell invasion in matrigel by inducing matrix metalloproteinase-2 expression and degradation of extracellular matrix [49]. LPA can also stimulate vascular endothelial growth factor (VEGF) expression through hypoxia-inducible factor-1-alpha dependent and independent pathways in cancer cells, suggesting a role for LPA signaling in pathologic angiogenesis [50].

S1P in the vasculature

S1P, another important substrate for LPP3, has been widely implicated in cellular differentiation, proliferation, migration and contributes to angiogenesis [51–53]. S1P is generated intracellularly from sphingosine by sphingosine kinase 1 and 2. Kinase activity is influenced by various stimuli, including VEGF, platelet-derived growth factor, tumor necrosis factor-alpha, transforming growth factor-beta, epidermal growth factor and cytokines [54]. S1P requires transport out of the cell to act on its specific receptors [55]. Plasma contains high nM concentrations of S1P [56]. Multiple cell types likely contribute to circulating S1P, including blood and endothelial cells. Both platelets and RBCs store and release S1P [57, 58]. After release from cells, plasma S1P circulates largely bound to apoliprotein M in HDL particles [59].

Analogous to LPA signaling, the extracellular effects of S1P are mediated by G-protein coupled receptors. Five S1P receptors have been identified: $S1P_1$/Edg1, $S1P_2$/Edg5, $S1P_3$/

Edg3, $S1P_4$/Edg6, and $S1P_5$/Edg8 [60–62]. $S1P_{1–3}$ are expressed on vascular cells, including endothelial and smooth muscle cells, cardiomyocytes, and cardiac fibroblasts [63]. $S1P_1$ couples exclusively to G_i to activate Ras/ERK and PI 3-kinase/Akt signaling pathways, and Rho family small GTPase Rac, whereas $S1P_2$ couples to $G_{12/13}$ - RhoA to inhibit Rac and Akt activity [64–66]. $S1P_3$ can elicit signaling through multiple G proteins, such as G_i, G_q and, to a lesser extent, $G_{12/13}$ [64, 66–73]. Compared with $S1P_{1-3}$, the functions of $S1P_4$ and $S1P_5$ are less well-characterized.

Deletion of *S1pr1* in mice results in embryonic lethality around E12.5 due to massive hemorrhage as a consequence of failure to recruit vascular smooth muscle cells to developing vessels [74]. Tissue-specific deletion of *S1pr1* in the endothelium produces an identical phenotype, demonstrating an essential role for endothelial S1P1 [75]. In contrast, tumor angiogenesis is enhanced in *S1pr2*-null mice, which demonstrate increased mural cell recruitment and myeloid cell mobilization [67]. *S1pr2*-null mice also develop deafness that may be due to vascular abnormalities within the *stria vascularis* [76]. Lung endothelial cells isolated from *S1pr2*-null mice have enhanced Rac activity, Akt phosphorylation, cell migration, proliferation, and tube formation *in vitro* [77]. *S1pr3*-deficient mice have no obvious vascular defects [73]. However, loss of both $S1P_2$ and $S1P_3$ results in bleeding and edema in the subcutaneous regions and reduced viability at E13.5 [78]. Ultrastructural analysis of microvessels in the combined $S1pr2^{-/-}S1pr3^{-/-}$ mice revealed abnormal endothelial cells with thin cell bodies that may result in fragile vessels prone to rupture.

S1P plays a critical role in maintaining endothelial barrier integrity. $S1P_1$ promotes barrier function by stabilizing tight and adherent junctions. Genetic manipulations that lower S1P levels [79] and pharmacologic antagonism of $S1P_1$ signaling elicits vascular leak in mice [80], whereas acute administration of S1P or $S1P_1$ agonists prevent vascular leak in acute lung injury models [81–83]. Interestingly, prolonged activation of $S1P_1$ signaling has the opposite effect and increases vascular permeability [79, 84].

Based on the results described above, it is evident that both LPA and S1P signaling pathways regulate vascular development and endothelial barrier function. However, given the redundancy and opposing effects within both the LPA and S1P receptor systems, it is not currently possible to determine if the role of LPP3 in vascular development is due to its ability to dephosphorylate LPA and/or S1P or other lipid phosphate mediators. Moreover, LPP3 may contribute to vascular cell function in a manner independent of its lipid phosphate phosphatase activity.

LPP3 and adhesive interactions

The phenotype of axis duplication that occurs in mice globally lacking *Ppap2b* resembles that observed in animals with altered Wnt signaling, suggesting cross-talk between the two pathways [12]. Wnt signaling is regulated by β-catenin and its interactions with p120-catenin and VE-cadherins. Tyrosine phosphorylation of β-catenin reduces its affinity for cadherins and redistributes the protein to the cytosol, where it can either be targeted for ubiquitin-mediated degradation or it can translocate to the nucleus and, via interactions with T cell factor (TCF)/ lymphoid enhancer-binding factor (LEF), alter the transcription of Wnt target genes including fibronectin, cyclin D, and LEF-1 [85, 86]. β-catenin-mediated TCF/LEF-transcription is upregulated in $Ppap2b^{-/-}$ embryonic stem cells, as is expression of the Wnt target gene *brachyury* [87], implicating LPP3 as a negative regulator of the Wnt pathway. In HEK cells, catalytically inactive LPP3 inhibits β-catenin-mediated TCF/LEF transcription and also suppresses axis duplication, although not as effectively as active LPP3, indicating that phosphatase activity may not be required for LPP3's effects on β-catenin [12]. However, in subconfluent endothelial cells, overexpression of LPP3 increases

TCF/LEF activity and fibronectin expression, in association with a reduction in β-catenin phosphorylation. siRNA-mediated knock-down of LPP3 reduces levels of VE cadherin, p120 catenin and fibronectin and impairs branch point formation in collagen matrix. No effect of LPP3 on TCF/LEF transription was observed in confluent endothelial cells. [88].

LPP3 may also affect vessel development and function through integrin interactions. Both human and rodent LPP3 recognize $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrins [89]. Human LPP3 contains an arginine-glycine-aspartate (RGD) cell adhesion sequence in its third extramembrane loop, which may mediate the interactions [90, 91]. In mouse and rat, the corresponding sequence is RGE [92]. Antibody inhibition of LPP3 blocks vascular endothelial cell growth factor (VEGF) and basic fibroblast growth factor (bFGF)-induced capillary morphogenesis in vitro [93]. These growth factors stimulate new vessel growth, in part via integrin-mediated adhesion to the extracellular matrix. Antibodies to LPP3 also inhibit endothelial cell aggregation mediated by $\alpha_v\beta_3$ and $\alpha_5\beta_1$ [92]. Recognition of LPP3 by integrins does not require LPP3 catalytic activity.

LPP3 in human vascular disease

The most compelling evidence of a role for LPP3 in human disease comes from a meta-analysis of multiple, large genome-wide association studies [94]. The analysis identified heritable single nucleotide sequence variants that predict the development coronary artery disease (CAD) and used data from over 86,000 individuals. *PPAP2B* emerged as 1 of 13 new loci that associate with CAD. A single nucleotide polymorphism in the *PPAP2B* gene is associated with a 1.17-odds ratio for CAD ($P= 3.81 \times 10^{-19}$). The polymorphism lacked association with traditional risk factors such as hypertension, cholesterol, diabetes, obesity or smoking. Interestingly, CAD risk is associated with the minor allele of the polymorphism, termed rs17114036, which is located in the final intron of the gene. Intronic variants can be associated with alterations in gene expression through effects on transcription, RNA processing or stability [95–98]. Thus, it is possible that the polymorphism or a linked allele influences LPP3 expression levels. In support of this, we have interrogated publically available data sets for *PPAP2B* gene expression and observed lower mRNA levels in leukocytes from individuals with a polymorphism that is in linkage disequilibrium with rs17114036. Taken together, these findings suggest that LPP3 may play a role as a predictor in genetic screening for early prevention and treatment for CAD. At present, essentially no information is available about how LPP3 may contribute to the pathogenesis of CAD, however, it is possible that LPP3 expression in vascular smooth muscle and endothelial cells is necessary for normal adult vessel function analogous to its requirement in vascular development.

Conclusion

LPP3 is essential for vascular development by regulating cell proliferation, cell migration, invasion and morphology. Recent exciting findings suggest that an allelic variant of PPAP2b is associated with elevated risk of CAD and PPAP2b expression is also increased in atherosclerotic plaques. However, current understanding of LPP3 function in the vasculature is largely limited to a large body of evidence implicating its bioactive substrates, S1P and LPA in vascular development and function. Further studies to develop LPP isoform-specific inhibitors or tissue specific knockout models could facilitate the understanding and the development of effective pharmacologic approaches to treat CAD and other cardiovascular diseases.

Acknowledgments

The authors thank Matt Hazard for assistant with graphics. This work was supported in part by the National Center for Research Resources and the National Center for Advancing Translational Sciences (UL1RR033173), the Heart Lung and Blood Institute (R01HL078663), the National Center for Research Resources (P20RR021954), and the National Institute of General Medical Sciences (P20GM103527) and by CONACYT and PAPIIT grants to D.E.-A. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. This material is also based on work supported in part by resources at the Lexington VA Medical Center. HMR was supported in part by a Beginning Grant in Aid from the American Heart Association; MP by a Scientist Development Award from the American Heart Association, and PM by T32HL072743 from the Heart Lung and Blood Institute.

References

1. Sciorra VA, Morris AJ. Roles for lipid phosphate phosphatases in regulation of cellular signaling. Biochim Biophys Acta. 2002; 1582:45–51. [PubMed: 12069809]
2. Sigal YJ, McDermott MI, Morris AJ. Integral membrane lipid phosphatases/phosphotransferases: common structure and diverse functions. The Biochemical journal. 2005; 387:281–293. [PubMed: 15801912]
3. Kai M, Wada I, Imai S, Sakane F, Kanoh H. Cloning and characterization of two human isozymes of Mg2+-independent phosphatidic acid phosphatase. J Biol Chem. 1997; 272:24572–24578. [PubMed: 9305923]
4. Roberts R, Sciorra VA, Morris AJ. Human type 2 phosphatidic acid phosphohydrolases. Substrate specificity of the type 2a, 2b, and 2c enzymes and cell surface activity of the 2a isoform. J Biol Chem. 1998; 273:22059–22067. [PubMed: 9705349]
5. Long JS, Pyne NJ, Pyne S. Lipid phosphate phosphatases form homo- and hetero-oligomers: catalytic competency, subcellular distribution and function. The Biochemical journal. 2008; 411:371–377. [PubMed: 18215144]
6. Burnett C, Makridou P, Hewlett L, Howard K. Lipid phosphate phosphatases dimerise, but this interaction is not required for in vivo activity. BMC Biochem. 2004; 5:2. [PubMed: 14725715]
7. Brindley DN, English D, Pilquil C, Buri K, Ling ZC. Lipid phosphate phosphatases regulate signal transduction through glycerolipids and sphingolipids. Bba-Mol Cell Biol L. 2002; 1582:33–44.
8. Ishikawa T, Kai M, Wada I, Kanoh H. Cell surface activities of the human type 2b phosphatidic acid phosphatase. J Biochem. 2000; 127:645–651. [PubMed: 10739957]
9. Kai M, Sakane F, Jia YJ, Imai S, Yasuda S, Kanoh H. Lipid phosphate phosphatases 1 and 3 are localized in distinct lipid rafts. J Biochem. 2006; 140:677–686. [PubMed: 17005594]
10. Tomsig JL, Snyder AH, Berdyshev EV, Skobeleva A, Mataya C, Natarajan V, Brindley DN, Lynch KR. Lipid phosphate phosphohydrolase type 1 (LPP1) degrades extracellular lysophosphatidic acid in vivo. The Biochemical journal. 2009; 419:611–618. [PubMed: 19215222]
11. Morris, AJ.; Smyth, SS.; Salous, A.; Renault, AD. Lysophospholipid Receptors: Signaling and Biochemistry. John Wiley; 2012. Lipid phosphate phosphatases: Recent progress and assay methods.
12. Escalante-Alcalde D, Hernandez L, Le Stunff H, Maeda R, Lee HS, Gang C Jr, Sciorra VA, Daar I, Spiegel S, Morris AJ, Stewart CL. The lipid phosphatase LPP3 regulates extra-embryonic vasculogenesis and axis patterning. Development. 2003; 130:4623–4637. [PubMed: 12925589]
13. Escalante-Alcalde D, Morales SL, Stewart CL. Generation of a reporter-null allele of Ppap2b/Lpp3 and its expression during embryogenesis. Int J Dev Biol. 2009; 53:139–147. [PubMed: 19123136]
14. Panchatcharam M, Miriyala S, Wheeler J, Salous AK, Dong A, Sunkara M, Morris AJ, Escalante-Alcalde D, Smyth SS. Mice with Endothelial-Targeted Inactivation of Ppap2b (Lipid Phosphate Phosphatase 3) Display Enhanced Vascular Inflammation. Circulation. 2011; 124
15. Senda K, Koizumi K, Prangsaengtong O, Minami T, Suzuki S, Takasaki I, Tabuchi Y, Sakurai H, Doki Y, Misaki T, Saiki I. Inducible capillary formation in lymphatic endothelial cells by blocking lipid phosphate phosphatase-3 activity. Lymphatic research and biology. 2009; 7:69–74. [PubMed: 19473074]
16. Pyne S, Long JS, Ktistakis NT, Pyne NJ. Lipid phosphate phosphatases and lipid phosphate signalling. Biochemical Society transactions. 2005; 33:1370–1374. [PubMed: 16246121]

17. Brindley DN, Pilquil C. Lipid phosphate phosphatases and signaling. Journal of lipid research. 2009; 50(Suppl):S225–230. [PubMed: 19066402]

18. Tanyi JL, Morris AJ, Wolf JK, Fang X, Hasegawa Y, Lapushin R, Auersperg N, Sigal YJ, Newman RA, Felix EA, Atkinson EN, Mills GB. 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 research. 2003; 63:1073–1082. [PubMed: 12615725]

19. Umezu-Goto M, Kishi Y, Taira A, Hama K, Dohmae N, Takio K, Yamori T, Mills GB, Inoue K, Aoki J, Arai H. Autotaxin has lysophospholipase D activity leading to tumor cell growth and motility by lysophosphatidic acid production. J Cell Biol. 2002; 158:227–233. [PubMed: 12119361]

20. Pamuklar Z, Federico L, Liu S, Umezu-Goto M, Dong A, Panchatcharam M, Fulkerson Z, Berdyshev E, Natarajan V, Fang X, van Meeteren LA, Moolenaar WH, Mills GB, Morris AJ, Smyth SS. Autotaxin/lysopholipase D and lysophosphatidic acid regulate murine hemostasis and thrombosis. J Biol Chem. 2009; 284:7385–7394. [PubMed: 19139100]

21. Mills GB, Moolenaar WH. The emerging role of lysophosphatidic acid in cancer. Nat Rev Cancer. 2003; 3:582–591. [PubMed: 12894246]

22. Baker DL, Morrison P, Miller B, Riely CA, Tolley B, Westermann AM, Bonfrer JM, Bais E, Moolenaar WH, Tigyi G. Plasma lysophosphatidic acid concentration and ovarian cancer. JAMA : the journal of the American Medical Association. 2002; 287:3081–3082. [PubMed: 12069669]

23. Cui MZ. Lysophosphatidic acid effects on atherosclerosis and thrombosis. Clinical lipidology. 2011; 6:413–426. [PubMed: 22162980]

24. Gustin C, Van Steenbrugge M, Raes M. LPA modulates monocyte migration directly and via LPA-stimulated endothelial cells. American journal of physiology Cell physiology. 2008; 295:C905–914. [PubMed: 18632732]

25. Gomaraschi M, Sinagra G, Serdoz LV, Pitzorno C, Fonda M, Cattin L, Calabresi L, Franceschini G. The plasma concentration of Lpa-I:A-II particles as a predictor of the inflammatory response in patients with ST-elevation myocardial infarction. Atherosclerosis. 2009; 202:304–311. [PubMed: 18486943]

26. Koike S, Keino-Masu K, Ohto T, Sugiyama F, Takahashi S, Masu M. Autotaxin/Lysophospholipase D-mediated Lysophosphatidic Acid Signaling Is Required to Form Distinctive Large Lysosomes in the Visceral Endoderm Cells of the Mouse Yolk Sac. Journal of Biological Chemistry. 2009; 284:33561–33570. [PubMed: 19808661]

27. Fotopoulou S, Oikonomou N, Grigorieva E, Nikitopoulou I, Paparountas T, Thanassopoulou A, Zhao Z, Xu Y, Kontoyiannis DL, Remboutsika E, Aidinis V. ATX expression and LPA signalling are vital for the development of the nervous system. Dev Biol. 2010; 339:451–464. [PubMed: 20079728]

28. van Meeteren LA, Ruurs P, Stortelers C, Bouwman P, van Rooijen MA, Pradere JP, Pettit TR, Wakelam MJO, Saulnier-Blache JS, Mummery CL, Moolenaar WH, Jonkers J. Autotaxin, a secreted lysophospholipase D, is essential for blood vessel formation during development. Mol Cell Biol. 2006; 26:5015–5022. [PubMed: 16782887]

29. Ferry G, Giganti A, Coge F, Bertaux F, Thiam K, Boutin JA. Functional invalidation of the autotaxin gene by a single amino acid mutation in mouse is lethal. FEBS letters. 2007; 581:3572–3578. [PubMed: 17628547]

30. Parrill AL. Lysophospholipid interactions with protein targets. Biochim Biophys Acta. 2008; 1781:540–546. [PubMed: 18501204]

31. Pasternack SM, von Kugelgen I, Al Aboud K, Lee YA, Ruschendorf F, Voss K, Hillmer AM, Molderings GJ, Franz T, Ramirez A, Nurnberg P, Nothen MM, Betz RC. G protein-coupled receptor P2Y5 and its ligand LPA are involved in maintenance of human hair growth. Nature genetics. 2008; 40:329–334. [PubMed: 18297070]

32. 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; 363:861–866. [PubMed: 17905198]

33. 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; 135:1071–1083. [PubMed: 8922387]
34. An S, Bleu T, Hallmark OG, Goetzl EJ. Characterization of a novel subtype of human G protein-coupled receptor for lysophosphatidic acid. J Biol Chem. 1998; 273:7906–7910. [PubMed: 9525886]
35. Bandoh K, Aoki J, Hosono H, Kobayashi S, Kobayashi T, Murakami-Murofushi K, Tsujimoto M, Arai H, Inoue K. Molecular cloning and characterization of a novel human G-protein-coupled receptor, EDG7, for lysophosphatidic acid. J Biol Chem. 1999; 274:27776–27785. [PubMed: 10488122]
36. Im DS, Heise CE, Harding MA, George SR, O'Dowd BF, Theodorescu D, Lynch KR. Molecular cloning and characterization of a lysophosphatidic acid receptor, Edg-7, expressed in prostate. Mol Pharmacol. 2000; 57:753–759. [PubMed: 10727522]
37. 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; 278:25600–25606. [PubMed: 12724320]
38. Murakami M, Shiraishi A, Tabata K, Fujita N. Identification of the orphan GPCR, P2Y(10) receptor as the sphingosine-1-phosphate and lysophosphatidic acid receptor. Biochem Biophys Res Commun. 2008; 371:707–712. [PubMed: 18466763]
39. Radeff-Huang J, Seasholtz TM, Matteo RG, Brown JH. G protein mediated signaling pathways in lysophospholipid induced cell proliferation and survival. Journal of cellular biochemistry. 2004; 92:949–966. [PubMed: 15258918]
40. Brindley DN, Pilquil C, Sariahmetoglu M, Reue K. Phosphatidate degradation: phosphatidate phosphatases (lipins) and lipid phosphate phosphatases. Biochim Biophys Acta. 2009; 1791:956–961. [PubMed: 19250975]
41. Rai, V.; Touré, F.; Chitayat, S.; Pei, R.; Lu, Y.; Li, Q.; Rosario, R.; Zhu, Z.; Qu, W.; Song, F.; Ramasamy, R.; Chazin, WJ.; Schmidt, AM. Arteriosclerosis, Thrombosis, and Vascular Biology. Chicago, IL: 2011. Lysophosphatidic Acid Mediates Vascular Signaling via an Immunoglobulin Superfamily Receptor; p. 68
42. Sumida H, Noguchi K, Kihara Y, Abe M, Yanagida K, Hamano F, Sato S, Tamaki K, Morishita Y, Kano MR, Iwata C, Miyazono K, Sakimura K, Shimizu T, Ishii S. LPA4 regulates blood and lymphatic vessel formation during mouse embryogenesis. Blood. 2010; 116:5060–5070. [PubMed: 20713964]
43. Yukiura H, Hama K, Nakanaga K, Tanaka M, Asaoka Y, Okudaira S, Arima N, Inoue A, Hashimoto T, Arai H, Kawahara A, Nishina H, Aoki J. Autotaxin regulates vascular development via multiple lysophosphatidic acid (LPA) receptors in zebrafish. J Biol Chem. 2011; 286:43972–43983. [PubMed: 21971049]
44. English D, Kovala AT, Welch Z, Harvey KA, Siddiqui RA, Brindley DN, Garcia JG. Induction of endothelial cell chemotaxis by sphingosine 1-phosphate and stabilization of endothelial monolayer barrier function by lysophosphatidic acid, potential mediators of hematopoietic angiogenesis. Journal of hematotherapy & stem cell research. 1999; 8:627–634. [PubMed: 10645770]
45. Lee H, Goetzl EJ, An S. Lysophosphatidic acid and sphingosine 1-phosphate stimulate endothelial cell wound healing. American journal of physiology Cell physiology. 2000; 278:C612–618. [PubMed: 10712250]
46. Panetti TS, Mosher DF. Lysophospholipid-induced cell migration. Annals of the New York Academy of Sciences. 2000; 905:326–329. [PubMed: 10818476]
47. Ren B, Hale J, Srikanthan S, Silverstein RL. Lysophosphatidic acid suppresses endothelial cell CD36 expression and promotes angiogenesis via a PKD-1-dependent signaling pathway. Blood. 2011; 117:6036–6045. [PubMed: 21441463]
48. Tanaka M, Okudaira S, Kishi Y, Ohkawa R, Iseki S, Ota M, Noji S, Yatomi Y, Aoki J, Arai H. Autotaxin stabilizes blood vessels and is required for embryonic vasculature by producing lysophosphatidic acid. J Biol Chem. 2006; 281:25822–25830. [PubMed: 16829511]

49. Wu WT, Chen CN, Lin CI, Chen JH, Lee H. Lysophospholipids enhance matrix metalloproteinase-2 expression in human endothelial cells. Endocrinology. 2005; 146:3387–3400. [PubMed: 15878967]
50. Song Y, Wu J, Oyesanya RA, Lee Z, Mukherjee A, Fang X. Sp-1 and c-Myc mediate lysophosphatidic acid-induced expression of vascular endothelial growth factor in ovarian cancer cells via a hypoxia-inducible factor-1-independent mechanism. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009; 15:492–501. [PubMed: 19147754]
51. Ahn EH, Schroeder JJ. Induction of apoptosis by sphingosine, sphinganine, and C(2)-ceramide in human colon cancer cells, but not by C(2)-dihydroceramide. Anticancer research. 2010; 30:2881–2884. [PubMed: 20683027]
52. Moriue T, Igarashi J, Yoneda K, Nakai K, Kosaka H, Kubota Y. Sphingosine 1-phosphate attenuates H2O2-induced apoptosis in endothelial cells. Biochem Biophys Res Commun. 2008; 368:852–857. [PubMed: 18267109]
53. Huang YL, Lin HS, Chen SU, Lee H. Tyrosine Sulphation of Sphingosine 1-Phosphate 1 (S1P(1)) is Required for S1P-mediated Cell Migration in Primary Cultures of Human Umbilical Vein Endothelial Cells. J Biochem. 2009; 146:815–820. [PubMed: 19692429]
54. Lebman DA, Spiegel S. Cross-talk at the crossroads of sphingosine-1-phosphate, growth factors, and cytokine signaling. Journal of lipid research. 2008; 49:1388–1394. [PubMed: 18387885]
55. Strub GM, Maceyka M, Hait NC, Milstien S, Spiegel S. Extracellular and intracellular actions of sphingosine-1-phosphate. Advances in experimental medicine and biology. 2010; 688:141–155. [PubMed: 20919652]
56. Hla T, Venkataraman K, Michaud J. The vascular S1P gradient-cellular sources and biological significance. Biochim Biophys Acta. 2008; 1781:477–482. [PubMed: 18674637]
57. Selim S, Sunkara M, Salous AK, Leung SW, Berdyshev EV, Bailey A, Campbell CL, Charnigo R, Morris AJ, Smyth SS. Plasma levels of sphingosine 1-phosphate are strongly correlated with haematocrit, but variably restored by red blood cell transfusions. Clin Sci (Lond). 2011; 121:565–572. [PubMed: 21749329]
58. Ulrych T, Bohm A, Polzin A, Daum G, Nusing RM, Geisslinger G, Hohlfeld T, Schror K, Rauch BH. Release of sphingosine-1-phosphate from human platelets is dependent on thromboxane formation. Journal of thrombosis and haemostasis : JTH. 2011; 9:790–798. [PubMed: 21251196]
59. Christoffersen C, Obinata H, Kumaraswamy SB, Galvani S, Ahnstrom J, Sevvana M, Egerer-Sieber C, Muller YA, Hla T, Nielsen LB, Dahlback B. Endothelium-protective sphingosine-1-phosphate provided by HDL-associated apolipoprotein M. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108:9613–9618. [PubMed: 21606363]
60. Spiegel S, Milstien S. Functions of a new family of sphingosine-1-phosphate receptors. Biochim Biophys Acta. 2000; 1484:107–116. [PubMed: 10760461]
61. An S, Goetzl EJ, Lee H. Signaling mechanisms and molecular characteristics of G protein-coupled receptors for lysophosphatidic acid and sphingosine 1-phosphate. Journal of cellular biochemistry Supplement. 1998; 30–31:147–157. [PubMed: 19594448]
62. Moolenaar WH. Bioactive lysophospholipids and their G protein-coupled receptors. Experimental cell research. 1999; 253:230–238. [PubMed: 10579925]
63. Michel MC, Mulders AC, Jongsma M, Alewijnse AE, Peters SL. Vascular effects of sphingolipids. Acta Paediatr Suppl. 2007; 96:44–48. [PubMed: 17391441]
64. Okamoto H, Takuwa N, Gonda K, Okazaki H, Chang K, Yatomi Y, Shigematsu H, Takuwa Y. EDG1 is a functional sphingosine-1-phosphate receptor that is linked via a Gi/o to multiple signaling pathways, including phospholipase C activation, Ca2+ mobilization, Ras-mitogen-activated protein kinase activation, and adenylate cyclase inhibition. J Biol Chem. 1998; 273:27104–27110. [PubMed: 9765227]
65. Paik JH, Chae S, Lee MJ, Thangada S, Hla T. Sphingosine 1-phosphate-induced endothelial cell migration requires the expression of EDG-1 and EDG-3 receptors and Rho-dependent activation of alpha vbeta3- and beta1-containing integrins. J Biol Chem. 2001; 276:11830–11837. [PubMed: 11150298]

66. Sugimoto N, Takuwa N, Okamoto H, Sakurada S, Takuwa Y. Inhibitory and stimulatory regulation of Rac and cell motility by the G12/13-Rho and Gi pathways integrated downstream of a single G protein-coupled sphingosine-1-phosphate receptor isoform. Mol Cell Biol. 2003; 23:1534–1545. [PubMed: 12588974]

67. Du W, Takuwa N, Yoshioka K, Okamoto Y, Gonda K, Sugihara K, Fukamizu A, Asano M, Takuwa Y. S1P(2), the G protein-coupled receptor for sphingosine-1-phosphate, negatively regulates tumor angiogenesis and tumor growth in vivo in mice. Cancer research. 2010; 70:772–781. [PubMed: 20068174]

68. Zondag GC, Postma FR, Etten IV, Verlaan I, Moolenaar WH. Sphingosine 1-phosphate signalling through the G-protein-coupled receptor Edg-1. The Biochemical journal. 1998; 330(Pt 2):605–609. [PubMed: 9480864]

69. Windh RT, Lee MJ, Hla T, An S, Barr AJ, Manning DR. Differential coupling of the sphingosine 1-phosphate receptors Edg-1, Edg-3, and H218/Edg-5 to the G(i), G(q), and G(12) families of heterotrimeric G proteins. J Biol Chem. 1999; 274:27351–27358. [PubMed: 10488065]

70. Takuwa Y, Du W, Qi X, Okamoto Y, Takuwa N, Yoshioka K. Roles of sphingosine-1-phosphate signaling in angiogenesis. World journal of biological chemistry. 2010; 1:298–306. [PubMed: 21537463]

71. Sato K, Kon J, Tomura H, Osada M, Murata N, Kuwabara A, Watanabe T, Ohta H, Ui M, Okajima F. Activation of phospholipase C-Ca2+ system by sphingosine 1-phosphate in CHO cells transfected with Edg-3, a putative lipid receptor. FEBS letters. 1999; 443:25–30. [PubMed: 9928946]

72. Okamoto H, Takuwa N, Yokomizo T, Sugimoto N, Sakurada S, Shigematsu H, Takuwa Y. Inhibitory regulation of Rac activation, membrane ruffling, and cell migration by the G protein-coupled sphingosine-1-phosphate receptor EDG5 but not EDG1 or EDG3. Mol Cell Biol. 2000; 20:9247–9261. [PubMed: 11094076]

73. Ishii I, Friedman B, Ye X, Kawamura S, McGiffert C, Contos JJ, Kingsbury MA, Zhang G, Brown JH, Chun J. Selective loss of sphingosine 1-phosphate signaling with no obvious phenotypic abnormality in mice lacking its G protein-coupled receptor, LP(B3)/EDG-3. J Biol Chem. 2001; 276:33697–33704. [PubMed: 11443127]

74. Liu Y, Wada R, Yamashita T, Mi Y, Deng CX, Hobson JP, Rosenfeldt HM, Nava VE, Chae SS, Lee MJ, Liu CH, Hla T, Spiegel S, Proia RL. Edg-1, the G protein-coupled receptor for sphingosine-1-phosphate, is essential for vascular maturation. The Journal of clinical investigation. 2000; 106:951–961. [PubMed: 11032855]

75. Allende ML, Yamashita T, Proia RL. G-protein-coupled receptor S1P1 acts within endothelial cells to regulate vascular maturation. Blood. 2003; 102:3665–3667. [PubMed: 12869509]

76. Kono M, Belyantseva IA, Skoura A, Frolenkov GI, Starost MF, Dreier JL, Lidington D, Bolz SS, Friedman TB, Hla T, Proia RL. Deafness and stria vascularis defects in S1P2 receptor-null mice. J Biol Chem. 2007; 282:10690–10696. [PubMed: 17284444]

77. Inoki I, Takuwa N, Sugimoto N, Yoshioka K, Takata S, Kaneko S, Takuwa Y. Negative regulation of endothelial morphogenesis and angiogenesis by S1P2 receptor. Biochem Biophys Res Commun. 2006; 346:293–300. [PubMed: 16756949]

78. Kono M, Mi Y, Liu Y, Sasaki T, Allende ML, Wu YP, Yamashita T, Proia RL. The sphingosine-1-phosphate receptors S1P1, S1P2, and S1P3 function coordinately during embryonic angiogenesis. J Biol Chem. 2004; 279:29367–29373. [PubMed: 15138255]

79. Camerer E, Regard JB, Cornelissen I, Srinivasan Y, Duong DN, Palmer D, Pham TH, Wong JS, Pappu R, Coughlin SR. Sphingosine-1-phosphate in the plasma compartment regulates basal and inflammation-induced vascular leak in mice. The Journal of clinical investigation. 2009; 119:1871–1879. [PubMed: 19603543]

80. Sanchez T, Estrada-Hernandez T, Paik JH, Wu MT, Venkataraman K, Brinkmann V, Claffey K, Hla T. Phosphorylation and action of the immunomodulator FTY720 inhibits vascular endothelial cell growth factor-induced vascular permeability. J Biol Chem. 2003; 278:47281–47290. [PubMed: 12954648]

81. Peng X, Hassoun PM, Sammani S, McVerry BJ, Burne MJ, Rabb H, Pearse D, Tuder RM, Garcia JG. Protective effects of sphingosine 1-phosphate in murine endotoxin-induced inflammatory lung

injury. American journal of respiratory and critical care medicine. 2004; 169:1245–1251. [PubMed: 15020292]

82. McVerry BJ, Peng X, Hassoun PM, Sammani S, Simon BA, Garcia JG. Sphingosine 1-phosphate reduces vascular leak in murine and canine models of acute lung injury. American journal of respiratory and critical care medicine. 2004; 170:987–993. [PubMed: 15282202]
83. Sanna MG, Wang SK, Gonzalez-Cabrera PJ, Don A, Marsolais D, Matheu MP, Wei SH, Parker I, Jo E, Cheng WC, Cahalan MD, Wong CH, Rosen H. Enhancement of capillary leakage and restoration of lymphocyte egress by a chiral S1P1 antagonist in vivo. Nature chemical biology. 2006; 2:434–441.
84. Shea BS, Brooks SF, Fontaine BA, Chun J, Luster AD, Tager AM. Prolonged exposure to sphingosine 1-phosphate receptor-1 agonists exacerbates vascular leak, fibrosis, and mortality after lung injury. American journal of respiratory cell and molecular biology. 2010; 43:662–673. [PubMed: 20081052]
85. Bazzoni G, Dejana E. Endothelial cell-to-cell junctions: molecular organization and role in vascular homeostasis. Physiological reviews. 2004; 84:869–901. [PubMed: 15269339]
86. Grosheva I, Shtutman M, Elbaum M, Bershadsky AD. p120 catenin affects cell motility via modulation of activity of Rho-family GTPases: a link between cell-cell contact formation and regulation of cell locomotion. Journal of cell science. 2001; 114:695–707. [PubMed: 11171375]
87. Arnold SJ, Stappert J, Bauer A, Kispert A, Herrmann BG, Kemler R. Brachyury is a target gene of the Wnt/beta-catenin signaling pathway. Mechanisms of development. 2000; 91:249–258. [PubMed: 10704849]
88. Humtsoe JO, Liu M, Malik AB, Wary KK. Lipid phosphate phosphatase 3 stabilization of beta-catenin induces endothelial cell migration and formation of branching point structures. Mol Cell Biol. 2010; 30:1593–1606. [PubMed: 20123964]
89. Humtsoe JO, Bowling RA Jr, Feng S, Wary KK. Murine lipid phosphate phosphohydrolase-3 acts as a cell-associated integrin ligand. Biochem Biophys Res Commun. 2005; 335:906–919. [PubMed: 16099422]
90. Kai M, Wada I, Imai S, Sakane F, Kanoh H. Identification and cDNA cloning of 35-kDa phosphatidic acid phosphatase (type 2) bound to plasma membranes. Polymerase chain reaction amplification of mouse H2O2-inducible hic53 clone yielded the cDNA encoding phosphatidic acid phosphatase. J Biol Chem. 1996; 271:18931–18938. [PubMed: 8702556]
91. Jia YJ, Kai M, Wada I, Sakane F, Kanoh H. Differential localization of lipid phosphate phosphatases 1 and 3 to cell surface subdomains in polarized MDCK cells. FEBS letters. 2003; 552:240–246. [PubMed: 14527693]
92. Humtsoe JO, Feng S, Thakker GD, Yang J, Hong J, Wary KK. Regulation of cell-cell interactions by phosphatidic acid phosphatase 2b/VCIP. The EMBO journal. 2003; 22:1539–1554. [PubMed: 12660161]
93. Wary KK, Humtsoe JO. Anti-lipid phosphate phosphohydrolase-3 (LPP3) antibody inhibits bFGF- and VEGF-induced capillary morphogenesis of endothelial cells. Cell communication and signaling : CCS. 2005; 3:9. [PubMed: 16076388]
94. Schunkert H, Konig IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, Preuss M, Stewart AF, Barbalic M, Gieger C, Absher D, Aherrahrou Z, Allayee H, Altshuler D, Anand SS, Andersen K, Anderson JL, Ardissino D, Ball SG, Balmforth AJ, Barnes TA, Becker DM, Becker LC, Berger K, Bis JC, Boekholdt SM, Boerwinkle E, Braund PS, Brown MJ, Burnett MS, Buysschaert I, Carlquist JF, Chen L, Cichon S, Codd V, Davies RW, Dedoussis G, Dehghan A, Demissie S, Devaney JM, Diemert P, Do R, Doering A, Eifert S, Mokhtari NE, Ellis SG, Elosua R, Engert JC, Epstein SE, de Faire U, Fischer M, Folsom AR, Freyer J, Gigante B, Girelli D, Gretarsdottir S, Gudnason V, Gulcher JR, Halperin E, Hammond N, Hazen SL, Hofman A, Horne BD, Illig T, Iribarren C, Jones GT, Jukema JW, Kaiser MA, Kaplan LM, Kastelein JJ, Khaw KT, Knowles JW, Kolovou G, Kong A, Laaksonen R, Lambrechts D, Leander K, Lettre G, Li M, Lieb W, Loley C, Lotery AJ, Mannucci PM, Maouche S, Martinelli N, McKeown PP, Meisinger C, Meitinger T, Melander O, Merlini PA, Mooser V, Morgan T, Muhleisen TW, Muhlestein JB, Munzel T, Musunuru K, Nahrstaedt J, Nelson CP, Nothen MM, Olivieri O, Patel RS, Patterson CC, Peters A, Peyvandi F, Qu L, Quyyumi AA, Rader DJ, Rallidis LS, Rice C, Rosendaal FR, Rubin D, Salomaa V, Sampietro ML, Sandhu MS, Schadt E, Schafer A, Schillert A, Schreiber S, Schrezenmeir J,

Schwartz SM, Siscovick DS, Sivananthan M, Sivapalaratnam S, Smith A, Smith TB, Snoep JD, Soranzo N, Spertus JA, Stark K, Stirrups K, Stoll M, Tang WH, Tennstedt S, Thorgeirsson G, Thorleifsson G, Tomaszewski M, Uitterlinden AG, van Rij AM, Voight BF, Wareham NJ, Wells GA, Wichmann HE, Wild PS, Willenborg C, Witteman JC, Wright BJ, Ye S, Zeller T, Ziegler A, Cambien F, Goodall AH, Cupples LA, Quertermous T, Marz W, Hengstenberg C, Blankenberg S, Ouwehand WH, Hall AS, Deloukas P, Thompson JR, Stefansson K, Roberts R, Thorsteinsdottir U, O'Donnell CJ, McPherson R, Erdmann J, Samani NJ. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. Nature genetics. 2011; 43:333–338. [PubMed: 21378990]

95. Olivier M. From SNPs to function: the effect of sequence variation on gene expression. Focus on "a survey of genetic and epigenetic variation affecting human gene expression". Physiological genomics. 2004; 16:182–183. [PubMed: 14726602]
96. Greenwood TA, Kelsoe JR. Promoter and intronic variants affect the transcriptional regulation of the human dopamine transporter gene. Genomics. 2003; 82:511–520. [PubMed: 14559208]
97. Zhang Y, Bertolino A, Fazio L, Blasi G, Rampino A, Romano R, Lee ML, Xiao T, Papp A, Wang D, Sadee W. Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104:20552–20557. [PubMed: 18077373]
98. Wang GS, Cooper TA. Splicing in disease: disruption of the splicing code and the decoding machinery. Nature reviews Genetics. 2007; 8:749–761.

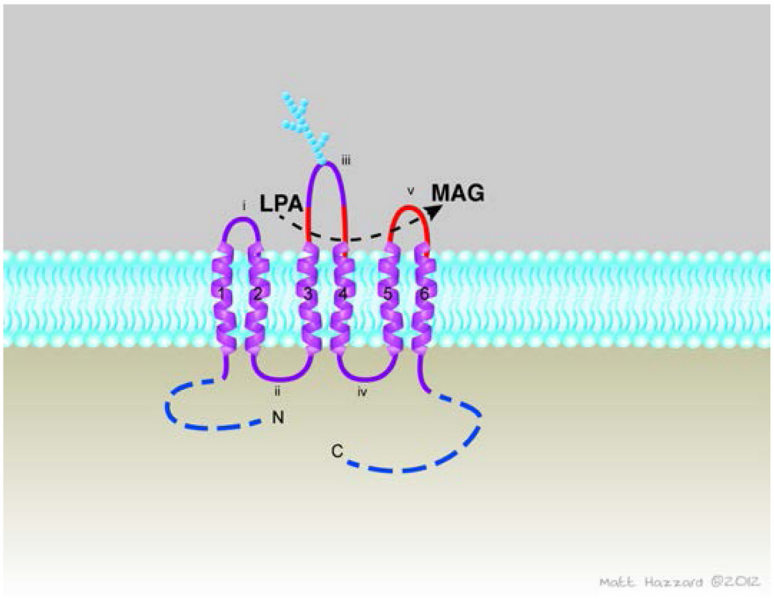

Figure 1. Predicted topology of lipid phosphate phosphatases

The LPP members are predicted to have six transmembrane spanning regions and an active site composed of regions on the extracellular or abluminal surface of the membrane.

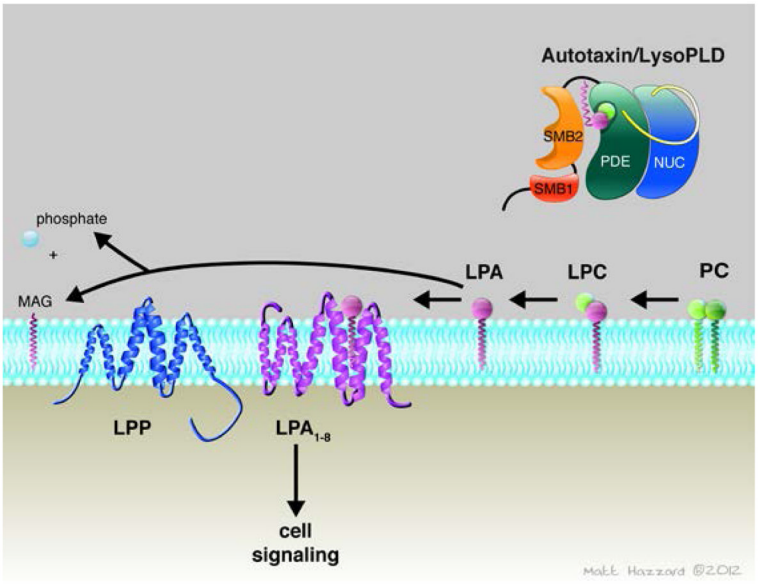

Figure 2. Proposed role of lipid phosphate phosphatases in regulating lysophospholipid signaling

Bioactive lysophosphatidic acid (LPA) production is the result of autoxatin mediated hydrolysis of lysophopshatidyl choline (LPC) generated at least in part from phosphatidyl choline (PC). Extracellular LPA can act via its G-protein coupled receptors to elicit intracellular signaling and/or be degraded by surface LPPs to receptor inactive monoacyl glycerol.