Lysophospholipid mediators in the vasculature

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Abstract

Acting through cell surface receptors, "extracellular" lysophosphatidic acid (LPA) influences cell growth, differentiation, apoptosis and development in a wide spectrum of settings [1–5]. Within the vasculature, smooth muscle cells [6, 7], endothelial cells [8] and platelets [9, 10] display notable responses to LPA [11, 12], which likely regulate blood vessel development and contribute to vascular pathology. The bioactive effects of LPA are mediated by a family of G-protein coupled receptors with at least six members (termed LPA_{1-6} that are encoded by the *LPAR* genes in humans and *Lpar* in mice) [1–3]. LPA may also serve as a ligand for the receptor for advanced glycation end products (RAGE) [13]. This review summarizes evidence to support a role for LPA signaling in vascular biology based on studies of LPA receptors and enzymes that produce or metabolize the lipid (Figure 1).

LPA receptors

The receptors for LPA are widely distributed on blood and vascular cells. In preclinical animal models, targeting the LPA receptors genetically and pharmacologically suggests that they may contribute to vascular injury and inflammatory responses, as well as endothelial barrier function and vascular stability. Single and multiple deletions of LPA receptors in mice produce differing vascular phenotypes. Deficiency of *Lpar1*, which results in 50% neonatal lethality, gives rise to the development of spontaneous frontal hematomas [14]. This suggests a role for LPA1 in stabilization of vessels, as no defect in hemostasis has been observed in these animals. In experimental arterial injury models, LPA1 regulates the development of intimal hyperplasia, a complex response involving inflammation and smooth muscle cell proliferation and migration. LPA1 may influence the vascular remodeling response via the $G\alpha_{12}/G\alpha_{13}$ pathway that couples to RhoGEF to activate RhoA, given the similarities in development on intimal hyperplasia after injury in the *Lpar1*−/− mice [6] and those lacking the $G\alpha_{12}/G\alpha_{13}$ and Rho pathways [15] in smooth muscle cells. The lack of LPA1 disrupts the endothelial barrier and results in increased vascular permeability in

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response to inflammatory stimuli in the lung [16] and the skin [17]. Conversely, LPA1 antagonists prevent inflammation in response to peritoneal injection of lipopolysaccharide [18]. Whether either a defect in smooth muscle or endothelial cell function accounts for the bleeding observed in the *Lpar1−/−* mice remains unknown. Knockout of both *Lpa1* and *Lpa2* increases the incidence of prefrontal hematomas [19], impairs the response to vascular injury [6], and results in the development of pulmonary hypertension with age [20]; the latter phenotype in not observed in mice with deficiency of either of the receptors alone. Together, these results suggest some redundancy or overlap between the 2 receptor systems. Likewise, LPA1 and LPA3 antagonists reduce arterial remodeling elicited by denudation injury [7] in mice, perhaps due to attenuated signaling through both G_{12}/G_{13} and G_q/G_{11} signaling pathways, which appear to regulate vascular remodeling antagonistically. *Lpar4*-deficient mice display a genetic background-dependent defect in formation of vasculature. On the C57Bl/6 background, the mice develop hemorrhage and edema due to a maturation defect from lack of smooth muscle cell and pericytes recruitment vessels [21]. As described in more detail below, studies in zebrafish also support a role for several of the canonical LPA receptors in blood vessel formation. Additionally, LPA signaling through RAGE may also affect SMC function [13].

LPA synthesis pathways

LPA is present in many biologic fluids, including plasma, ascites, and bronchoalveolar lavage fluid. In the circulation, LPA turns over rapidly [22] and therefore must be maintained by constant production. Certain conditions, such as acute coronary syndromes [23] [24] and chronic liver disease [25] are associated with higher levels of plasma LPA. Whether this is due to increased production or reduced clearance/breakdown or both is currently not known. There are several pathways that can generate LPA. The secreted lysophospholipase D autotaxin (ATX) generates extracellular LPA by hydrolysis of lysophosphatidylcholine (LPC) [26,27][28]. ATX is an is an ecto-nucleotide pyrophosphatase/phospho-diesterase family member (encoded by *ENPP2* in humans and *Enpp2* in mice) that is synthesized as a pre-proenzyme and undergoes sequential signal peptide removal and proprotein convertase cleavage before being secreted from cells. Of five functional isoforms (ATXα, ATXβ, ATXγ, ATXδ, ATXε) generated through alternatively splicing, ATXβ is the most abundant and appears to account for most of the lysophospholipase D activity in plasma. The cellular source(s) of plasma ATX are incompletely understood, however, adipocytes likely secrete a substantial portion [29]. ATX is also stored in platelets and released during their activation [28] [30]. Circulating ATX is rapidly taken up by the scavenger receptors of liver sinusoidal endothelial cells, and then degraded in the liver [31]. Thus, much like hormones, including insulin, ATX is largely removed from the circulation during first passage through the liver. While ATX is normally a major source of plasma LPA levels [22, 32], other minor pathways may contribute to increases in LPA in certain situations, such as in the setting of acute myocardial infarction [23, 24, 33].

Studies of organisms that lack or express catalytically-inactive ATX have shed light on its role, and by inference, the role of LPA signaling, in vascular biology. ATX expression is required for normal vascular development in mice. *Enpp2*-deficient mice [34] [35] die

between embryonic days 9.5–10.5 with blood vessel formation defects in the yolk sac and embryo. In the absence of ATX, initial blood vessel formation appears normal, but vessels fail to mature, suggesting that ATX is critical for extension and stabilization of blood vessels but perhaps not for the initial endothelial cell differentiation and migration. The phenotype of *Enpp2−/−* mice resembles that observed in $G\alpha_{13}$ knockout embryos, which would be consistent with ATX-generated LPA signaling through $G\alpha_{13}$-coupled receptors. To date, no single or multiple LPA receptor knock-out mice have fully recapitulated the phenotype observed in embryos lacking ATX or $G\alpha_{13}$. However, mice expressing a functionally inactive ATX (T210A) also die embryonically [36], indicating that the catalytic activity of ATX, and likely LPA synthesis, is essential for vascular development. Enpp2-heteroxygous mice are viable and express half of normal levels of ATX and LPA. However, they are hyper-responsive to hypoxia-induced vasoconstriction and remodeling, and prone to develop pulmonary hypertension [20]. Knockdown of ATX in zebrafish embryos by morpholino antisense oligonucleotides also causes aberrant vascular connections [20] with normal initial sprouting from the dorsal aorta. A similar defect occurs in fish embryos lacking functional LPA_1 and LPA_4. Together these results suggest that the ATX/LPA signaling nexus, likely acting through multiple receptors coupled to $G\alpha_{13}$, is required for normal blood vessel maturation.

ATX, originally identified as a motility factor in serum, can modulate angiogenesis directly and indirectly [19]. In angiogenesis models, ATX stimulates cultured endothelial cells to form tubules in vitro and new blood vessel formation within Matrigel™ plugs in vivo. ATX promotes the motility in human coronary artery smooth muscle cells, a function that may also support vessel maturation and remodeling [37]. Finally, ATX may promote blood vessel maturation by recruiting pericytes [38] and/or smooth muscle cells to developing blood vessels. While most of the ATX effects may be attributed to the production of LPA, ATX may have LPA-independent effects. ATX binds integrins and heparan sulfates on the cell surface through its somatomedin-B-like (SMB) domain and may promote non-LPA receptor mediated signaling. Finally, ATX has been reported to hydrolyze sphingosylphosphorylcholine (SPC) to sphingosine-1-phosphate (S1P) [39], another potent bioactive lipid mediator implicated in vascular signaling.

LPPs regulate LPA signaling

Degradation of LPA by removal of the phosphate group eliminates signaling through LPA receptors. Lipid phosphate phosphatases (LPPs) constitute a family of three enzymes that dephosphorylate a broad range of lipid phosphates, including LPA. LPPs are encoded by the *PPAP2* genes: LPP1 by the *PPAP2A* gene, LPP2 by the *PPAP2C* gene, and LPP3 by *PPAP2B* [40]. LPPs share a common structure with a core of six predicted transmembrane helices linked by extra membrane loops. The enzymes are oriented with their N- and C-termini in the cytoplasm and their active sites on the extracellular or luminal surface of the membrane (Figure 2). Subcellular localization of these enzymes is both dynamic and cell-specific. Although the three LPP enzymes demonstrate similar catalytic activities and substrate preferences *in vitro*, the phenotypes of mice with targeted inactivation of the *Ppap2* genes establishes that their functions are non-redundant. Primary cells isolated from mice harboring an exon trap inactivated allele of *Ppap2a* gene display a reduced ability to

dephosphorylate exogenously provided LPA, indicating a role for LPP1 as a cell surface "ecto" LPA phosphatase [41]. Mice homozygous for an insertionally inactivated allele of the *Ppap2c* gene, encoding murine LPP2, are phenotypically indistinguishable [42]. By contrast, inactivation of *Ppap2b* results in embryonic lethality in part to due to failure of extra-embryonic vasculature [43]. Media from cultured embryonic fibroblasts isolated from *Ppap2b*-null mice contains higher levels of LPA suggesting that the other LPPs cannot compensate for the regulation of extracellular accumulation of LPA. Recent evidence from the LPP3 homologs in *Drosophila*, Wunen and Wunen2, demonstrated that LPPs generate and regulate phospholipid gradients *in vivo,* and that the establishment of a phospholipid gradient may drive migration of germ cells. The maximum range of influence of Wunen-expressing cells on germ cells is approximately 33μm [44].

Lack of LPP3 in endothelial cells results in embryonic lethality with extra-embryonic vascular defects similar to those observed in germline *Ppap2b*-null mice [17]. In adult mice, inducible deletion of *Ppap2b* in endothelial cells increases vascular leak, especially in settings of inflammation. Thus, LPP3 may function to attenuate the ATX/LPA-mediated permeability described above. LPP3 has also been implicated as a negative regulator of Wnt pathway potentially through interactions with β-catenin that may not require the LPP's phosphatase activity [43]. In human dermal microvascular endothelial cells, siRNA mediated knockdown of LPP3 results in reduced VE cadherin, p120 catenin and fibronectin levels as well as displayed reduced branch point formation in a collagen matrix – a finding which implicates LPP3 in the β-catenin/LEF-1 signaling pathway regulating endothelial cell migration as well as cell-to-cell adhesion. LPP3 also contains an RGD cell adhesion sequence in its third extracellular loop which has been postulated to regulate its interactions with α5β1 and αvβ3 integrins [45] [46].

Mice that lack LPPs in smooth muscle cells display exaggerated development of neointimal formation associated with heightened inflammatory cell accumulation [47]. Isolated *Ppap2b* −/− smooth muscle cells display reduced LPA metabolism and heightened cell proliferation, ERK activity, Rho activation, and cell migration in response to serum and LPA. These exaggerated responses are attenuated by lentiviral expression of human or mouse LPP3, but not a catalytically inactive LPP3 mutant. Taken together these results indicate that LPP3 normally functions to attenuate SMC proliferation and vascular inflammation, possibly due to its ability to degrade LPA (and/or S1P) and thereby limit signaling effects.

Role of the ATX/LPA/LPP3 signaling nexus in atherosclerosis

Levels of vessel-associated LPA increase during progression of atherosclerosis [48, 49] and are substantially higher in advanced lesions [50]. Cholesterol feeding influences levels and distribution of plasma LPA [51]. Additionally, feeding mice a chow diet supplemented with unsaturated LPA mimics the inflammatory effects of Western diets [52]. LPA that is generated during atherosclerosis may have pro-atherosclerotic, pro-inflammatory, and pro-thrombotic effects [53]. Genome wide association studies of patients with coronary artery disease revealed single nucleotide polymorphisms in *PPAP2B*, that are associated with disease risk [54] [55]. The identified risk SNPs predict lower LPP3 expression in human vascular endothelial cells, and the effect is exacerbated by exposing the cells to oxidized

PAPC [56]. The risk allele also attenuates the upregulation of PPAP2B by oxLDL in macrophages, at least in part by reducing enhancer activity and decreasing binding of C/EBP beta. Together, these findings suggest that variation in the PPAP2B gene regulates gene – environment interactions by influencing the response to lipid risk factors.

In summary, the evidence reviewed above implicates LPA signaling in a range of important events during blood cell development and in the response to inflammation and environmental injury. Observations in experimental models support a role for LPA in regulating vascular biology and pathology. These concepts need to be tested using strategies in preclinical animal models and in translational studies in humans.

Acknowledgments

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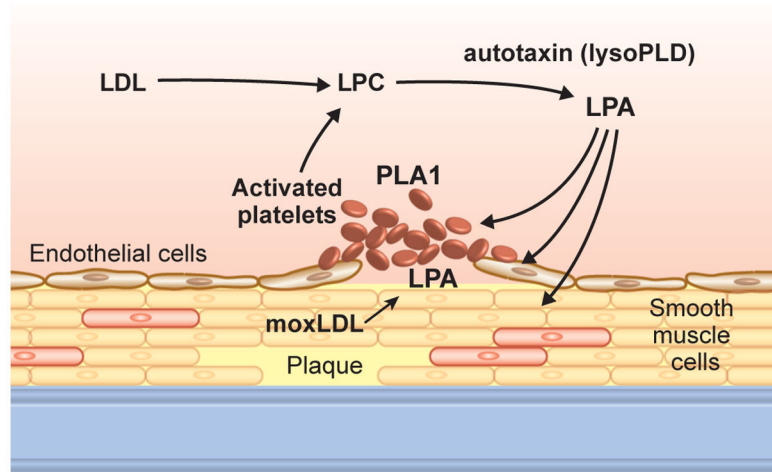
Figure 1.
Autotaxin (ATX) and LPA actions in blood and vascular cells.

LDL = low density liprotein; LPC = lysophosphatidylcholine; moxLDL = minimally oxidized LDL; PLA = phospholipase A.
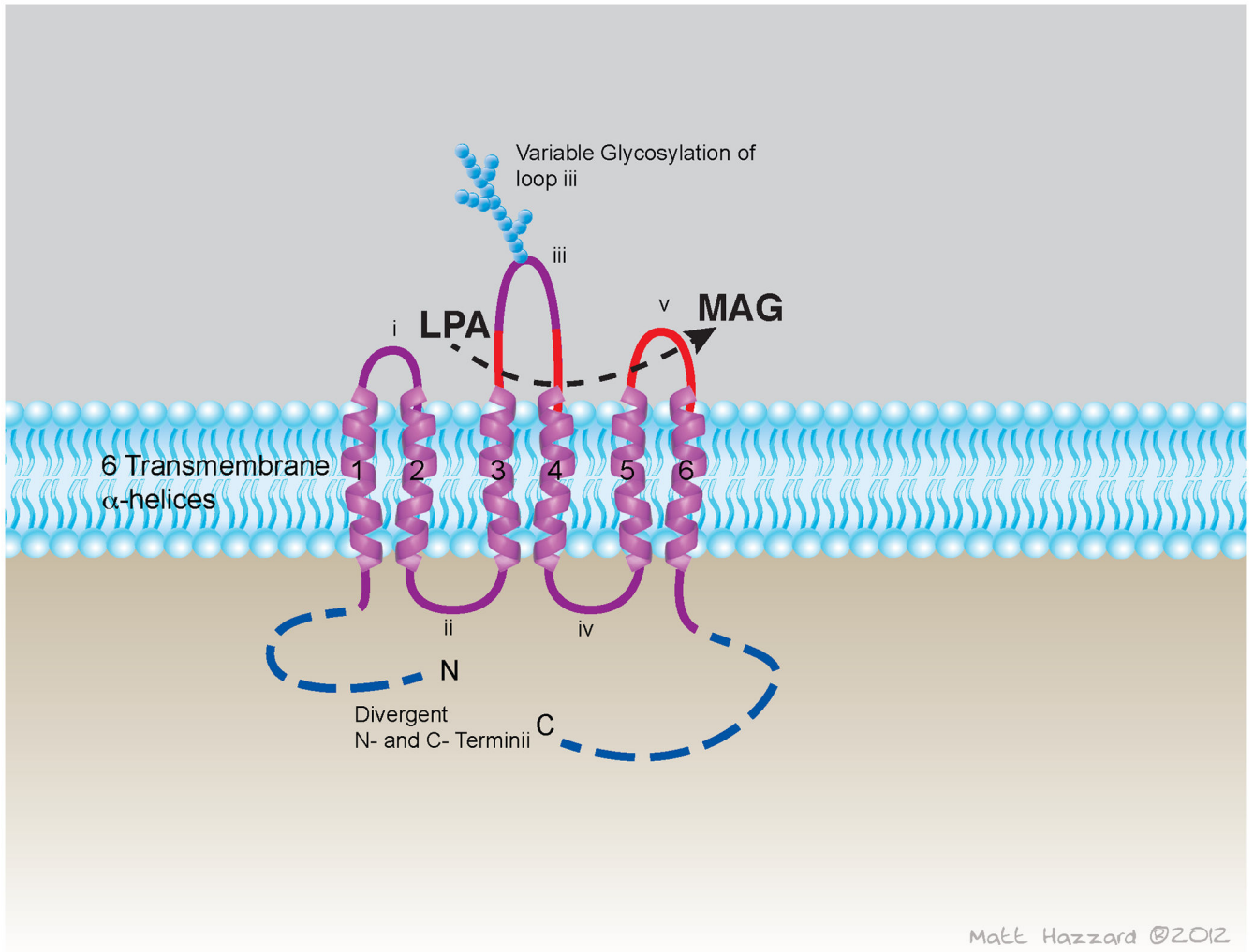
Figure 2.
Proposed topology of lipid phosphate phosphatase (LPP) transmembrane enzymes. LPA = lysophosphatidic acid; MAG = monoacyl glycerol.