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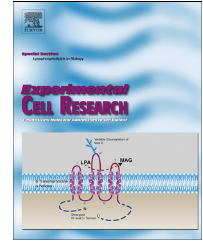

Review Article

Lysophospholipid mediators in the vasculature

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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 (Fig. 1).

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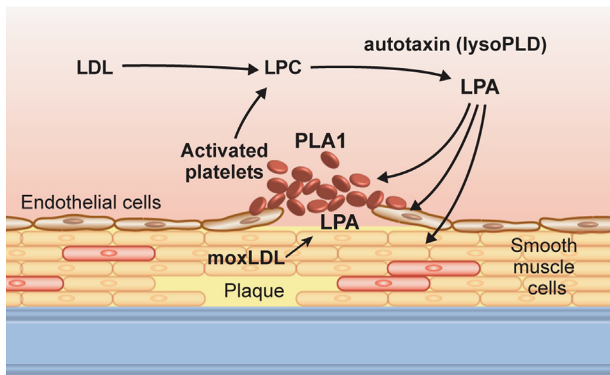

Fig. 1 – Autotaxin (ATX) and LPA actions in blood and vascular cells. LDL=low density liprotein; LPC=lysophosphatidylcholine; moxLDL=minimally oxidized LDL; PLA=phospholipase A.

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 suggest 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 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 is 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 $G\alpha_{12}/G\alpha_{13}$ and G_q/G_{11} signaling pathways, which appear to regulate vascular remodeling antagonistically. *Lpar*4-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 pericyte recruitment to 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) [26–28]. ATX 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, and 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 maturate, 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

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