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The autotaxin-LPA axis emerges as a novel regulator of lymphocyte homing and inflammation

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Abstract

Lyophosphatidic acid (LPA) is a pleiotropic lipid molecule with potent effects on cell growth and motility. Major progress has been made in recent years in deciphering the mechanisms of LPA generation and how it acts on target cells. Most research to-date has been conducted in other disciplines, but emerging data indicate that LPA has an important role to play in immunity. A key discovery was that autotaxin (ATX), an enzyme previously implicated in cancer cell motility, generates extracellular LPA from the precursor lysophosphatidylcholine (LPC). Steady-state ATX is expressed by only a few tissues including high-endothelial venules in lymph nodes, but inflammatory signals can up-regulate ATX expression in different tissues. Here we review current thinking about the ATX/LPA axis in lymphocyte homing, as well as in models of allergic airway inflammation and asthma. New insights into the role of LPA in regulating immune responses should be forthcoming in the near future.

Nomenclature and LPA generation

Lysophosphatidic acid is a member of the glycerophospholipid family, specifically a monoacylglycerophosphate (GP1005, according to Lipid Maps classification, <http://www.lipidmaps.org>). LPA has a three carbon glycerol backbone with one acyl side chain that can vary in length and saturation (Figure 1). The prefix “lyso” indicates that only one fatty acid is attached to the phospholipid backbone, and distinguishes LPA from phosphatidic acid. The acyl group is usually located on the sn-1 carbon (i.e. 1-acyl-2-hydroxy-sn-glycero-3-phosphate). In serum, most LPA species are polyunsaturated (e.g. 18:2 and 20:4) or monounsaturated (e.g. 18:1) (1). Emerging data indicate that the acyl moiety affects the function of LPA, but this is a virtually unexplored area in the immune system. One exception is the observation that immature mouse bone marrow-derived dendritic cells (BM-DC) preferentially migrate *in vitro* to unsaturated (18:1 and 20:4) but not saturated (16:0 and 18:0) LPA (2), possibly reflecting affinity for the cell surface receptor LPA3 (see below).

LPA can be generated by multiple mechanisms, and a current challenge in the field is to relate different potential sources of LPA to biological activities *in vivo*. Extracellular LPA is thought to derive from at least two pathways. First LPA can be produced by the action of phospholipases on membrane microvesicles shed by activated platelets and erythrocytes (1, 3, 4). These pathways involve the direct hydrolysis of a fatty acid moiety from membrane-

derived phosphatidic acid. Second, LPA can be generated from lysophosphatidylcholine (LPC) by removal of the choline moiety by the enzyme lysophospholipase D (lyso-PLD). LPC is an intermediate in multiple lipid metabolic pathways and circulates in the blood stream at much higher concentration than LPA (5). These two pathways are not mutually exclusive, since certain phospholipases can produce LPC and other lysophospholipids from activated platelets that are then cleaved by lyso-PLD to produce LPA (4).

In 2002, the dominant lyso-PLD in serum was found to be an enzyme known as autotaxin (ATX) (6, 7). ATX had been discovered ten years earlier by Liotta and colleagues, who were studying autocrine factors that promoted cancer cell motility (8). Cloning of the autotaxin cDNA revealed domains similar to the ectonucleotide phosphodiesterase and pyrophosphatase (ENPP) family, and ATX was designated ENPP2 (9). However, the preferred substrates for ATX are not nucleotides but actually lysophospholipids including LPC (4), and it is becoming clear that many functions previously ascribed to ATX can be explained by its ability to generate LPA. This is especially true in the field of cancer biology, where the ATX/LPA axis is involved in the growth and metastasis of many different tumors and pathway antagonists are under active development (10).

LPA is unstable in plasma with a half-life of <5 minutes and technically challenging to measure (11, 12). Experiments using lipid phosphate phosphatase 1 (LPP1) hypomorphic mice revealed that this enzyme is a major determinant of LPA instability *in vivo* (11). Interestingly, there appear to be tissue-specific differences in LPP expression and activity suggesting that extracellular LPA may be more stable in some tissues than others (11). Relatively little is known about the stability of LPA in secondary lymphoid organs, although LPP expression is relatively high in the spleen.

LPA can be measured by colorimetric assays or mass spectrometry (MS), which has the advantage of detecting specific acyl side chains. A typical approach involves lipid extraction followed by high-pressure liquid chromatography (HPLC) and tandem MS in negative ion mode, monitoring for the glycerol phosphoryl moiety ($m/z=152.9$) and parent compound acyl groups. In order to estimate LPA concentrations, a closely related LPA species not normally present should be spiked into the original sample, extracted and processed identically, and used to generate a standard curve. However, the efficiency of extraction of different LPA species varies based on the sample and method used, and at present the true bioactive concentrations of LPA in plasma or biological fluids is not clear. Plasma concentrations are probably in the 100 nM range and are higher in women than men (5, 13, 14). In mice, similar variability in plasma LPA concentrations has been reported reflecting poorly-understood effects of age, gender and strain (11).

The function of circulating extracellular LPA is not known. Since the K_D of cell surface LPA receptors is in the nM range, one possibility is that LPA receptors on circulating leukocytes or endothelial cells are continually engaged. Tonic engagement would lead to receptor desensitization, and is difficult to reconcile with the pro-inflammatory / barrier disruptive effects of LPA on endothelial cell subsets when studied *in vitro* (15). LPA likely circulates in microparticles or bound to albumin and other proteins, and it seems likely that this restricts its interaction with target receptors.

LPA binds to different cell surface receptors and intracellular targets

The discovery that LPA interacted with specific cell surface receptors was a major advance. A detailed discussion of LPA receptors is beyond the scope of this Brief Review, but this topic has been recently summarized (16). There are at least six G-protein coupled receptors (GPCR) that bind LPA and vary in their tissue distribution. LPA1 (Edg2), LPA2 (Edg4) and

LPA3 (Edg7) belong to the Edg family, whereas LPA4-6 are more closely related to cell surface purinergic receptors (16, 17). Other Edg receptor family members bind sphingosine-1 phosphate (S1P), including S1P1 (Edg2). Signal transduction via LPA receptors leads to activation of mitogen-activated protein kinases, phosphoinositide-3 kinases (PI3K), and Rho kinases, which affect cell activation, survival and migration. This is a rapidly evolving field where new candidate receptors are being actively pursued, but the lack of antibodies directed against extracellular domains that detect surface expression or antagonize LPA binding is a major hindrance. The availability of LPA receptor deficient mice is starting to provide insights into the function of this molecule *in vivo* (18), although more research is needed in models of innate and adaptive immunity.

LPA can also bind to non-GPCR targets that are both extracellular (e.g. receptor for advanced glycosylation end products, RAGE) and intracellular (e.g. the nuclear receptor PPAR- γ and the cation channel TRPV1) (19–21). Whereas most canonical LPA GPCR's demonstrate preferential binding to longer chain length unsaturated species, PPAR γ is only activated by unsaturated LPA species and is critically important for the effects of LPA on vascular remodeling (20). Very little is known about the role of these non-canonical LPA receptors in immune cells.

LPA receptors are expressed by T cells

LPA enhances the motility of human and mouse T cells *in vitro*, although generally not in a directed manner (22–24). LPA also induces actin remodeling, uropod formation, and T cell polarization on ICAM-1 and CCL21 coated chambers (24, 25). The T cell LPA receptors involved in these responses is not known. LPA enhances the invasion of T lymphoma cells into tissue substrates, which in the case of Jurkat T cells depended on LPA2 (22, 23). LPA5 (GPR92) mRNA is abundant in the small intestine, especially in CD8+ intra-epithelial lymphocytes (26, 27), but the function of this receptor is currently unknown. More research using gene-targeted mice and LPA receptor antagonists should help clarify the role of LPA in T cell migration in the near future.

Autotaxin is expressed by HEV: role in T cell homing

In 2008, two reports revealed that ATX is constitutively expressed and released from lymphoid organ high endothelial venule (HEV) endothelial cells (EC's) (24, 28). These and other studies challenged the notion that ATX was a trans-membrane protein, and suggested that secreted ATX could act at a distance from its site of production. One working model suggests that ATX is secreted into the lumen of the HEV where it binds to receptors on nearby cells, hydrolyzes the abundant LPC found in the plasma, and generates a locally restricted high concentration of LPA. Kanda et al. showed that ATX can bind to chemokine-activated human lymphocytes in a β 1-integrin dependent manner, but binding to mouse lymphocytes interestingly appeared to be integrin-independent (24). Subsequently, Zhang et al. found that polarized T cells possess Mn²⁺-activatable receptors for ATX that are localized at the leading edge (25). Since activated platelets can produce and bind ATX (4, 29), and also participate in lymphocyte trafficking at HEV (30, 31), an additional possibility is that platelets contribute to ATX-dependent LPA production in lymphoid organs.

The recent crystal structure of ATX provided insights into how this molecule may function *in vivo* (32, 33). In addition to phosphodiesterase domains, ATX contains N-terminal cysteine-rich somatomedin-B-like (SMB) domains and a C-terminal nuclease domain. Integrin binding by ATX appears to involve the SMB domains in an RGD-independent manner (32). A splice variant of ATX termed ATX α was recently shown to bind heparan sulfate proteoglycans (34). One unusual feature was the existence of a hydrophobic pocket

and nearby channel that was large enough to accommodate a phospholipid with only a single acyl side chain. In addition to helping explain the preference of ATX for lysolipid substrates, these structural features indicate that ATX can act as a lipid carrier, and suggested a model in which integrin or substrate binding induces a conformational change, allowing ATX to release bound LPA to target receptors on nearby cells. A corollary of this model is that tethering of ATX will restrict newly generated bioactive LPA to an extremely precise location *in vivo*, such as HEV.

It is currently unknown if ATX-generated LPA acts on T cells, HEV EC, or both, and different models have been proposed. One model suggests that locally generated LPA provides a chemokinetic “boost” that facilitates T cell exit from the circulation and entry into lymph nodes along chemotactic gradients established by canonical lymph node associated cytokines. The receptors involved in LPA-dependent T cell emigration from HEV are not known. A second model suggests that the ATX/LPA axis regulates T cell homing indirectly by acting on HEV EC. These data are supported by the observations that: (i) HEV EC express LPA1 and LPA4, (ii) LPA induces changes in the EC cytoskeleton, and (iii) a potent small molecule inhibitor of ATX (HA130) did not affect lymphocyte accumulation at HEVs but did attenuate their extravasation (25, 28, 35). Furthermore, using novel imaging approaches Bai et al. demonstrated that after lymphocytes infiltrate the EC layer, migration across the HEV basal lamina required LPA (35). These data suggest that by inducing EC motility and shape change, LPA allows lymphocytes to detach from the HEV basal lamina and migrate into the lymph node parenchyma.

Manipulating the ATX/LPA axis with pathway antagonists

If the model proposed above is correct, then antagonists of the ATX/LPA axis should inhibit steady-state lymphocyte trafficking, whereas agonists should have the opposite effects. Experimental evidence supporting the ability of ATX/LPA antagonists to inhibit lymphocyte homing into lymphoid organs is starting to emerge, but we currently have no evidence that this affects generation of antigen-specific immunity. For example, incubating T cells with an inactive form of ATX (T120A), which probably acts as a dominant negative manner, attenuated cell homing to lymph nodes following adoptive transfer, as demonstrated by reduction of T cells in vicinity of HEVs 15 minutes later (24). Another small molecule inhibitor of ATX (HA130) specifically attenuated lymphocyte extravasation (discussed above) (25). However, an anti-ATX monoclonal antibody administered intraperitoneally that depleted plasma ATX did not inhibit lymphocyte trafficking to lymph nodes or the spleen, suggesting that ATX in the circulation is not as important as locally produced ATX at the HEV (28). BrP-LPA is a dual inhibitor of ATX and LPA receptors, and local administration of this compound diminished the trafficking of adoptively transferred lymphocytes into lymph nodes 30 minutes later (35). Ki16425 is an LPA receptor antagonist with selectivity for LPA1 and LPA3. When injected into the footpad of mice, Ki16425 did not significantly reduce T cell migration *in vitro* or lymphocyte trafficking to lymph nodes (35). These data are consistent with the possibility that T lymphocyte LPA2 is important for lymph node entry, but also support a role for LPA acting on endothelial cells in an LPA1/3-independent manner. Newer and more stable antagonists of ATX and LPA receptors are actively being developed, with the hope that these will demonstrate efficacy in cancer therapeutics (10). These compounds will also be useful tools to study the ATX/LPA axis in the initiation and regulation of adaptive immunity. However, clinical trials of ATX antagonists in cancer patients will need to be carefully monitored for untoward effects on the immune system, including immunosuppression. Is it possible to boost antigen-specific immunity by activating the ATX/LPA axis? Currently, there is little experimental evidence to support this possibility, but future studies investigating whether enhancing ATX activity or LPA production could boost generation of adaptive immunity seem worthwhile.

Regardless of mechanisms involved, the possibility that LPA promotes steady-state T recirculation through lymph nodes and secondary lymphoid organs is an exciting new direction, and complements the now well-recognized role for the related sphingolipid S1P in lymphocyte egress (36). Future studies in which LPA receptor expression can be regulated in a cell-type specific manner will be needed to determine the relative importance of LPA induced T cell motility, endothelial shape change, or both in regulating T cell homing. It will be interesting in future studies to determine if receptor desensitization influences the effects of LPA on T cell migration, similar to the effects of GRK2 on S1PR1 (37). Several other unanswered questions remain that should be readily addressable in the coming years. For example, what are the concentrations of LPA in afferent or efferent lymphatics? Does the ATX/LPA axis regulate T cell homing in a subset specific manner? What receptors are involved in this process? Do ATX/LPA regulate recirculation or LN entry of other immune cells besides T cells? Future research into these questions should enhance our understanding of how ATX and LPA regulate adaptive immunity *in vivo*.

LPA effects on dendritic cells and other cell types

In addition to lymphocytes, other immune cells express LPA receptors and are influenced by LPA including NK cells, mast cells, eosinophils, and B cells (summarized in Table 1) (38–52). LPA induces chemotaxis of immature mouse BM-DC dendritic cells (DC), which involves pertussis-toxin sensitive receptors. Interestingly, this effect is lost in DC's matured in the presence of lipopolysaccharide (LPS) (2, 53). LPS does not induce major changes in LPA receptor mRNA or protein expression in cell lysates (2, 53, 54), suggesting that G-protein coupling or LPA receptor surface expression are inhibited during DC maturation. Immature DC derived from LPA3 gene-targeted mice do not migrate to LPA *in vitro*, demonstrating a critical requirement for this receptor in LPA directed migration (2). In addition to inducing immature DC motility, LPA can influence DC function. LPA inhibited the production of IL-12 and TNF- α from LPS-stimulated DC in a pertussis toxin-insensitive manner (53). We recently reported that LPA inhibited LPS-dependent DC activation at least in part in an LPA2-dependent manner, and furthermore that LPA2-deficient DC were hyperactive after adoptive transfer *in vivo* (55). Consequently, the effects of LPA on DC are complex, and influenced by LPA species (discussed above), DC activation status, and receptors engaged. By inducing the mobility of both naive T cells and immature DC, LPA would seem to be well-suited to promote DC:T interactions in lymphoid organs and the initiation of adaptive immune responses.

ATX is also upregulated during inflammation: lessons from asthma models

In addition to lymph node HEV, ATX is constitutively expressed in a few other tissues in adult mice and humans including adipocytes and the lung (24, 28, 56–58). Interestingly, ATX was recently identified in mice in a screen for genes affecting lung development (59). Constitutive expression of ATX in the lung may help explain the fact that LPA is a normal component of epithelial lining fluids (60). The function of LPA in the lung at steady-state is not known, but it may play a role in maintaining homeostasis by promoting epithelial barrier integrity (61). Interestingly, both wild-type and lyso-PLD mutant ATX induce airway epithelial migration, suggesting that some of the effects of ATX in the airway are independent of LPA generation (62).

ATX expression and activity increase in different disease states, which suggests that the ATX/LPA axis may play a broader role in inflammation in general. For example, ATX is inducibly expressed on endothelial cells in the inflamed pancreas (28), and in lung epithelial cells following bleomycin exposure (63). Excitingly, inhibition or genetic deletion of ATX significantly attenuated lung fibrosis, supporting a crucial role for LPA in these models (63,

64). ATX expression is upregulated in synovial cells in patients with rheumatoid arthritis, and recent studies have firmly implicated ATX-derived LPA in the pathogenesis of inflammatory arthritis (65–68). The signals that regulate both steady-state and inducible ATX expression require further study. In monocytic THP1 cells, Li et al. reported that ATX mRNA and protein were induced by the toll-like receptor (TLR) 4 ligand lipopolysaccharide (69), but constitutive ATX expression in HEV was independent of the TLR adaptor Myd88 (28).

Growing evidence points to an important role for the ATX/LPA axis in mouse models of allergic airway inflammation and humans with asthma. Using HPLC-MS/MS, we found that LPA is constitutively detectable in bronchoalveolar lavage (BAL) fluids at baseline, but significantly increased 18 hours following segmental allergen challenge of allergic human subjects (from 483 ± 77 to 1506 ± 358 nM) (60). Assuming a ~100-fold dilution during BAL (70), we estimated that epithelial lining fluid LPA levels in the lung are in micromolar range. Interestingly, the accumulation of LPA species after allergen challenge was not uniform but enriched in poly-unsaturated species including 20:4 and 22:6 LPA (60). More recently, Park and Christman confirmed these findings and also showed that 22:5 LPA was also enriched in BAL fluids after allergen challenge (71). The function of polyunsaturated LPA in the lung is not entirely clear. Although LPA can promote eosinophil chemotaxis *in vitro* (72), we found that LPA levels did not correlate with eosinophil influx 18 hrs after challenge (60) arguing that LPA was not a dominant eosinophilic chemoattractant in this model. It remains to be seen whether LPA promotes the recruitment of leukocyte subsets or immature dendritic cells to the lung. Using a novel ATX antagonist in a triple allergen challenge mouse model of asthma, Park et al. showed that LPA generation in the allergic lung was dependent on ATX activity, and suggested based on immunohistochemical analysis and cell culture experiments that lung epithelial cells and IL-4 stimulated macrophages were potential sources of ATX (71). Furthermore, some of the inflammatory effects of triple allergen challenge were attenuated in LPA2-deficient mice (71).

Separate from its potential effects on cell migration, LPA has other functions and cellular targets relevant to the pathophysiology of asthma. For example, LPA can: (i) induce the differentiation and activation of mast cells (40, 43, 44) (see Table 1), (ii) promote airway epithelial chemokine/cytokine production (73, 74), and (iii) augment airway smooth muscle cell growth and contractility (75–77). The ability of LPA to induce airway epithelial TSLP production is noteworthy (74), given the crucial role for this cytokine in initiation of Th2-dependent immunity. Although these studies suggest that LPA may be a novel pro-inflammatory molecule and contribute to initiation of allergic airway inflammation, other results paint a more nuanced picture. For example, we used mouse models of asthma involving both systemic immunization (intraperitoneal Ova + alum) and mucosal sensitization (inhaled Ova + low-dose LPS), and found that LPA2-deficient mice developed surprisingly more inflammation and AHR compared to their wild-type counterparts (55). Using reciprocal bone marrow chimeras, this mapped in part to an inhibitory effect of LPA2 on hematopoietic cells, and we concluded that LPA has a previously unsuspected inhibitory role on dendritic cell activation (55). These data are in keeping with other potentially inhibitory effects of LPA including: (i) suppression of DC cytokine production discussed above (53), (ii) protection from endotoxin-induced inflammation and neutrophilia (61, 78), (iii) induction of the decoy receptor IL-13R α 2 on epithelial cells (79), and (iv) stimulation of α v β 6 integrin-mediated activation of TGF β (80). Taken together, these data point to both pro-inflammatory and potentially anti-inflammatory effects of LPA in asthma, depending on the timing and context of its production. Under conditions of acute inflammation such as following allergen challenge in allergic human subjects or mouse models of repetitive allergen exposure, LPA may act alone or in concert with other mediators to promote the recruitment or activation of inflammatory cell subsets. More chronically, LPA may play a

regulatory role and it is tempting to speculate that over time repeated cycles of LPA generation might contribute to airway remodeling in chronic asthma.

Conclusions

New research will likely be soon forthcoming that will define with greater precision the role of the ATX/LPA axis in immune and inflammatory diseases. It seems apparent that ATX and LPA have previously underappreciated roles in steady-state lymphocyte homing, but we need to understand how effects on T cell migration translate into regulation of adaptive immunity. Newer generation and more stable ATX antagonists will likely prove useful tools in this regard in the near future. In addition to their clinical efficacy in cancer, these agents may have untoward effects on the immune system (e.g. immunosuppression), which will need to be carefully monitored. It will be interesting to determine if gain-of-function approaches that enhance ATX/LPA activity can be used to boost generation of immunity. More research is needed into the mechanisms and consequences of ATX upregulation in inflammatory diseases. It will be important to decipher whether the dominant action of LPA in these models is in the regulation of cell motility/migration, activation, or survival. Since both LPA and LPC are involved in numerous metabolic pathways, it is tempting to speculate that these novel lysolipid compounds are at the intersection of metabolism and immunity.

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Figure 1.

Two main sources of LPA generation are from phosphatidic acid (left) via the action of phospholipases, or by hydrolysis of the choline moiety of lysophosphatidylcholine (Lyso-PC), by autotaxin (also known as Lyso-PLD). Newly generated LPA can act on cell surface GPCR's or intracellular receptors as indicated. Free LPA is rapidly degraded by lipid phosphate phosphatases into monoacyl glycerol.

Table 1

Cell Type	LPA receptors implicated	Summary of findings	LPA species (concentration)	References
Natural Killer	LPA1,2,3	Chemotaxis; mobilization of Ca ²⁺ in activated cells; enhanced IFN- γ secretion; LPAR detected by flow cytometry	18:1 (1–10 μ M)	(38)
	LPA2	Inhibited release of perforin and cytotoxic activity; enhances cAMP levels and activates PKA	14:0 (0.02–20 μ M)	(39)
Mast cells	LPA1,2,3,4 (mRNA)	Growth factor (human); induces proliferation and differentiation	18:1 (5 μ M)	(40)
	NA	Activates mast cells; causes tryptase release and vascular leakage in a mast-cell dependent manner in mice	LPA gel	(41)
	LPA1,3	Histamine release, inhibited by DGPP	18:1 (10 μ g/ml)	(42)
	LPA2	Production of MIP-1 β , IL-8, MCP-1 in an IL-4 dependent manner	18:1 and 18:2 (1–50 μ M)	(43)
Neutrophils	LPA5 (mRNA)	MIP-1 β release (human)	18:1 (1–5 μ M)	(44)
	NA	Infiltration of neutrophils in BALF of guinea pigs in Rho/ROCK dependent manner	18:1 (1–10 μ g/ml)	(45)
	LPA1, 2 (mRNA and protein)	Chemotaxis, greater in for neutrophils from pneumonia patients	LPA (0.1–1 μ M)	(46)
Macrophage/Monocyte	NA	Degranulation, PA production	18:1 (10–40 μ M)	(47)
	NA	Survival factor for murine macrophages via PI3K	18:1 (7.7 μ M)	(48)
	NA	Upregulated IL-1 β in mouse and human macrophages	NA	(49)
	NA	Monocyte migration to MCP-1 via iPLA2 at the leading edge	NA	(50)
B cells	LPA2 (mRNA)	B lymphoblast growth factor; MAPK activation; immunoglobulin production	18:1 (0.1–1 μ M)	(51)
Lymphatic endothelium	LPA2	Proliferation and lymphangiogenesis via IL-8	18:1 (0.5–10 μ M)	(52)

Notes: NA = not available; BALF = bronchoalveolar lavage fluids; PA = phosphatidic acid