Lysophosphatidic Acid and Cardiovascular Disease: Seeing is believing.

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In this issue of the Journal(1), Bot and colleagues provide further evidence that the bioactive lipid lysophosphatidic acid (LPA) accumulates in human and experimentally induced rodent atheromas and plays a role in the initiation and progression of atherothrombolic cardiovascular disease. These studies, which include direct visualization of LPA in the necrotic core of these lesions using secondary ion mass spectrometry, extend original observations that LPA is a platelet activating agonist(2) present in atheromatous plaques(3). They contribute to a steadily increasing case that LPA, its receptors and enzymes involved in its production and inactivation are important regulators of vascular cell function in health and disease.

LPA is a structurally simple glycerophospholipid although this simplicity is confounded by considerable diversity in the length, saturation and linkage of the radyl hydrocarbon chain substituent. LPA species with an ether linked radyl chain (alkyl glycerol phosphates) are of particular interest because of their more potent agonism at certain of the currently 6 distinct G-protein coupled LPA receptors(4). Some LPA responses may also be mediated by the nuclear peroxisome proliferator receptor-gamma(5) and the immunoglobulin family receptor for advanced glycan endproducts(6). Although LPA is an obligatory intermediate in intracellular phospholipid synthesis the “signaling” pool of LPA is generated extracellularly by the secreted phospholipase D autotaxin(7). LPA signaling can be terminated by enzymatic dephosphorylation catalyzed by members of the integral membrane cell surface lipid phosphate phosphatase (LPP) family(8) (Fig 1). Evidence that the enzymes, receptors and pathways involved in LPA metabolism and signaling are involved in normal cardiovascular development and function and in experimental models of atherosclerosis has been provided by a series of studies from several groups combining genetic gain and loss of function approaches with the application of increasingly sophisticated pharmacological tools. Key observations, which have been reviewed in detail elsewhere(9), include the finding that LPA is a weak activator of platelets from some, but not all, individuals and exerts migration stimulating and proinflammatory actions on several classes of
leukocytes. LPA disrupts the barrier function of cultured vascular endothelial cells and promotes the dedifferentiation, proliferation and migration of vascular smooth muscle cells in vitro. These latter observations appear to be relevant in vivo because mice with genetic inactivation of certain of the aforementioned LPA receptors are protected from neointima formation in arterial injury models while intravascular administration of LPA promotes these responses in mice and rats(10, 11). LPA is present in plasma at concentrations in the range of 0.1-1.0 μM. However, LPA generated locally in atherosclerotic lesions by the actions of autotaxin on lysophosphatidylcholine which accumulates in oxidatively modified low density lipoprotein may be a more important source of this mediator in promotion of atherosclerosis(12). The accompanying paper from Bot and colleagues supports these ideas by showing that perivascular administration of LPA promoted accumulation of mast cells and macrophages in experimentally-induced atherosclerotic lesions in mice, which was associated with intimal accumulation of erythrocytes indicative of intraplaque hemorrhage. Taken together, these observations build a case that localized synthesis and accumulation of LPA in atheromas promotes cardiovascular disease progression through effects on multiple blood and vascular wall cell types.

How might these observations which have largely been made in animal models provide insights into human cardiovascular disease? Family history is well established to provide a strong clinical indicator of cardiovascular disease risk yet until very recently only a limited number of single genes, have been unequivocally implicated in susceptibility to coronary artery disease (CAD) and myocardial infarction (MI). The frequencies of disease associated mutations or variations in these known genes are much too low to account for the estimated contribution of heritable factors to 30-60% of inter-individual variation in CAD risk. Genome Wide Association Studies (GWAS) offer sufficient statistical power and spatial resolution to enable unbiased identification of CAD susceptibility loci. Two recent GWAS identified a strong association of a common polymorphism in the PPAP2B gene with human cardiovascular disease risk independently of other risk factors (13, 14). PPAP2B encodes the LPP3
enzyme which is a cell surface localized lipid phosphate phosphatase that could function to terminate LPA signaling. The relevant polymorphism is located in the final intron of the PPAP2B gene and its functional effect on PPAP2B expression has not been tested experimentally. However, available data indicate that the risk-associated PPAP2B allele predicts lower mRNA expression in blood cells. Inactivation of the PPAP2B gene in vascular smooth muscle cells leads to exaggerated neointima formation in response to arterial injury in vivo and enhanced migration, proliferation and differentiation responses of cultured vascular smooth muscle cells to LPA in vitro(15). These observations support the idea that PPAP2B is normally protective against at least the vascular smooth muscle cell mediated component of experimental atherothrombotic disease. They also raise the possibility that LPP3 expression in other vascular cell types (which include neutrophils and vascular endothelial cells) may play an important role in regulating LPA dependent cardiovascular disease progression.

A potent small molecule autotaxin inhibitor that can dramatically inhibit LPA generation in blood after oral administration has been reported(16) and a selective LPA1 receptor antagonist is currently under development as a treatment for idiopathic pulmonary fibrosis(17). More than 30 years after the original descriptions of the vasoactive and platelet stimulating actions of LPA interest in this simple lipid signaling system as a target for the diagnosis and treatment of human cardiovascular disease continues to grow.
REFERENCES


Figure 1. Lysophosphatidic Acid metabolism and signaling in vascular cells.