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Lipoproteins regulation of lysophosphatidic acid metabolism and signaling:

Commentary on "Autotaxin-lysophosphatidic acid axis acts downstream of ApoB lipoproteins in endothelial cells" by Gibbs-Bar, Yaniv and colleagues

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In addition to their role in transporting cholesterol and triglycerides, plasma lipoprotein particles have been long known to promote signaling responses in many blood and vascular cell types. Some of these effects have been attributed to minor but potent bioactive lipid constituents. For example oxidized phosphatidylcholines are inflammatory mediators that likely contribute to the development and progression of atherosclerosis that is driven by subendothelial accumulation of low density lipoproteins[1]. Similarly, some of the athero-and vaso- protective effects of high density lipoproteins may be accounted for by the bioactive lipid sphingosine 1 phosphate (S1P) that is carried on this class of lipoprotein particles in association with apolipoprotein M[2]. A growing body of evidence implicates another bioactive lipid, lysophosphatidic acid (LPA) as a regulator of vascular development and pathologies. LPA is present in plasma bound to both lipoproteins and serum albumin. LPA specific G-protein coupled receptors expressed on vascular endothelial and smooth muscle cells regulate vascular permeability, inflammation, intimal hyperplasia (in the setting of vascular injury) and atherosclerosis[3]. Although LPA is a ubiquitous intermediate in intracellular phospholipid synthesis, extracellular "signaling" LPA is primarily generated by a secreted lysophospholipase D called autotaxin (ATX)[4]. In this issue of the Journal, Yaniv and colleagues identify a new facet of the interplay of lipoproteins with LPA metabolism and signaling. The optical clarity, availability of transgenic lines harboring reporters for lineage tracing and ease of gene targeting using morpholinos have made zebrafish a particularly powerful model system for studying vascular development. In this model, circulating apoB containing lipoproteins are essential for proper development of blood vessels and the lymphatic system. To investigate the mechanisms linking lipoprotein metabolism and developmental angiogenesis, Yaniv and colleagues conducted gene expression profiling in vascular endothelial cells isolated from normal, hypo- and hyper-lipidemic zebrafish embryos. These phenotypes were generated using mutants in the stalagtite (Stl) gene encoding microsomal triglyceride transfer protein that were previously shown to lack apoB containing lipoproteins and to display excessive sprouting angiogenesis[5] and an apoCII morpholino-induced loss of function model in which apoB containing lipoproteins are elevated due to decreased lipoprotein lipase activity[6]. In addition to interesting effects on genes involved in energy metabolism, cell survival and angiogenesis these workers identified a powerful effect on expression of the zebrafish ATX gene which was upregulated in the apoB containing lipoprotein deficient stl mutant and suppressed by hyperlipidemia. Studies using specific small molecule ATX inhibitors, LPA receptor

antagonists, adding back LPA to zebrafish embryos and gene knockdown approaches support the concept that ATX and two specific LPA receptor subtypes constitute an LDL-regulated cell autonomous/autocrine pathway that controls endothelial cell growth and migration during developmental angiogenesis. These zebrafish observations appear translatable to humans, at least in studies using cell culture models, where similar effects of LDL (and consistent with reports from others[7]) manipulations of ATX and LPA signaling recapitulate the pro-angiogenic effects of LPA observed in the zebrafish studies. The zebrafish observations reported here complement and extend previously published work from Aoki and colleagues identifying roles for LPA receptors and ATX as regulators of vascular endothelial cell migration during zebrafish development[8]. ATX can associate with the surface of cells through interactions with integrin class adhesion receptors and may directly deliver its LPA product to LPA receptors[4]. Taken together, these observations support a model in which endothelial cell-generated ATX and spatially distinct localization of cell surface associated ATX could generate a gradient of LPA signaling to control the rate and direction of endothelial cell migration during angiogenesis. These findings have potentially broader implications for our understanding of the contribution of LPA signaling to vascular pathologies in multiple settings. LPA can be dephosphorylated and inactivated by cell surface integral membrane enzymes termed lipid phosphate phosphatases (LPPs). One of these genes (the PLPP3 gene encoding the enzyme LPP3) is expressed in vascular endothelial cells and, like ATX, also has a role in spatial organization of LPA receptor signaling[9]. PLPP3 has a powerful association with heritable coronary artery disease risk[10]. The risk- associated locus appears to attenuate normally strong upregulation of PLPP3 in blood and vascular cells during atherosclerosis and in other settings of vascular inflammation[11]. Deficiency of both ATX (encoded by the ENPP2 gene) and PLPP3 is embryonically lethal in mice due to defects in development of the vascular system. However, mice with inducible post natal inactivation of PLPP3 in vascular endothelial cells exhibit increased vascular permeability and dysregulated angiogenesis[12]. While more details of the cell types involved are needed and other mechanisms are plausible, one could speculate that heritable LPP3 hypomorphism and consequently heightened LPA signaling in vascular endothelial cells might contribute to increased plaque angiogenesis during the development of atherosclerosis. The mechanisms linking LDL to regulation of ATX gene expression were not explored in the present study but would certainly be worth pursuing. Regulation of ATX expression processing and secretion in rodents and humans is complicated but, because adipose tissue appears to be a major systemic site of ATX expression, most studies have reported increased ATX expression during obesity-associated adipose tissue expansion[13]. However the extent to which this might contribute to elevated circulating ATX and LPA levels in obese hyperlipidemic humans remains to be determined. Plasma LPA is associated with both intestinal and liver derived low density lipoproteins and with serum albumin. While recent studies suggest that lipoprotein chaperones alter the signaling properties of the related bioactive lipid S1P, very little is known about the biological activities of LDL-associated LPA. Because LPA is a potent suppressor of ATX expression in mammalian cells and animal models[14] it is possible that LDL-associated LPA is responsible for the sensing mechanism that underlies the reciprocal relationship between LDL levels and ATX expression in the developing zebrafish embryo. Further exploration of the relationships

between LDL levels, ATX expression and LPA signaling will undoubtedly reveal new facets of the links between obesity, hyperlipidemia and vascular pathologies.

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