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Lipoprotein lipase: New Roles for an “Old” Enzyme

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Abstract

Purpose of review: Lipoprotein lipase (LpL) is well known for its lipolytic action in blood lipoprotein triglyceride catabolism. This article summarizes the recent mechanistic and molecular studies on elucidating the “unconventional” roles of LpL in mediating biological events related to immune cell response and lipid transport in the pathogenesis of cardiovascular disease (CVD) and tissue degenerative disorders.

Recent findings: Several approaches to inactivate the inhibitors that block LpL enzymatic activity have re-established the importance of systemic LpL activity in reducing CVD risk. On the other hand, increasing evidence suggests that focal arterial expression of LpL relates to aortic macrophage levels and inflammatory processes. In the hematopoietic origin, LpL also plays a role in modulating hematopoietic stem cell proliferation and circulating blood cell levels and phenotypes. Finally, building upon the strong genetic evidence on the association with assorted brain disorders, a new era in exploring the mechanistic insights into the functions and activity of LpL in brain that impacts central nerve systems has begun.

Summary: A better understanding of the molecular action of LpL will help to devise novel strategies for intervention of a number of diseases, including blood cell or metabolic disorders, as well to inhibit pathways related to CVD and tissue degenerative processes.

Keywords

inflammation; lipoprotein lipase; macrophages; n-3 fatty acids

INTRODUCTION

Lipoprotein lipase (LpL) is a member of the lipase superfamily. LpL enzymatic activity was first discovered in 1943 when Paul Hahn observed that intravenous injection of heparin abolished postprandial hyperlipidemia [1]. Subsequent studies established that LpL is a lipolytic enzyme activated by apoCII, and participates in the efficient delivery of fatty acids

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CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest

to tissues. LpL is involved in the metabolism of all classes of lipoproteins, including the clearance of chylomicron remnants, formation of intermediate-density lipoproteins (IDL) and low-density lipoproteins (LDL) from very-low-density lipoproteins (VLDL), and regulation of plasma high-density lipoprotein (HDL) concentrations [2].

LpL is synthesized in parenchymal cells as a monomer, it then moves to the luminal surface of endothelial cells where it is anchored by ionic interactions with heparan sulfate proteoglycans (HSPG) as a dimer. In the microvasculature system, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) anchors and mediates the translocation of LpL from parenchymal cells to endothelial cell surfaces. Dissociation of the LpL dimer into monomers leads to the loss of catalytic function. LpL is predominantly expressed and active in adipose tissue and cardiac and skeletal muscle. Lower expression levels are found in other tissues include macrophages, brain, lung, spleen and pancreatic β -cells. LpL levels and lipolytic activity are regulated at transcriptional and posttranscriptional levels in a tissue-specific manner that has been shown to have major metabolic consequences on macronutrient fuel partitioning, energy homeostasis, insulin action, and lipoprotein metabolism. In contrast to its catalytic action, emerging evidence has demonstrated that LpL associates with lipoproteins or cells and binds to cell surface proteoglycans by acting as a “bridging” molecule. Tissue-specific control of LpL in maintaining its varying biological actions has been studied and discussed extensively in a number of excellent reviews [2-4]. In this review, we will focus on summarizing the recent advances in understanding the lipolytic properties of the LpL system in regulating cardiovascular disease (CVD). We will then discuss the newly discovered roles of tissue LpL in influencing cellular response and cell biology in the pathways related to inflammation and tissue regenerative processes.

Updates on LpL lipolytic activity in CVD intervention

Evidence from current genetic variant studies strongly suggests that elevated levels of plasma lipoprotein triglycerides link to increased risks for atherosclerotic CVD [5]■. Reducing so-called “bad” cholesterol or LDL-cholesterol has been the drug development theme for preventing atherosclerotic CVD. However, even with the substantial reductions in LDL cholesterol levels, cardiovascular risks remain in the subpopulation of high-risk patients [6]. The new systems that enhance LpL activity are attractive approaches in treating both hypertriglyceridemia and atherosclerotic CVD.

Several factors are shown to be important in influencing LpL lipolytic activity. Among them, angiopoietin-like protein (Angptl) 3, 4 and 8, a family of secreted proteins, have emerged as key regulators of plasma lipid metabolism by serving as potent inhibitors of LpL and are associated with hypertriglyceridemia. Studies reported by Dewey et al.[7]■■ have revealed that patients with loss-of-function variants in Angptl3 by exome sequencing have improved plasma lipoprotein profiles, including the decreased levels of plasma triglycerides and cholesterol, which are associated with a strong potential in reducing risk of CVD. When using different strategies to inactivate Angptl3, the authors demonstrated that targeting Angptl3 by antisense oligonucleotides resulted in a significant reduction of triglyceride and cholesterol levels in normal human volunteers and mice. Additionally, they have observed

that the inactivation of Angptl3 reduced hepatic triglyceride content and attenuated the progression of atherosclerosis in mice [7].

These findings are complemented with the results from preclinical and phase I clinical trials demonstrating that inactivating liver-specific Angptl3 with the use of antisense oligonucleotides led to lower levels of triglyceride-rich lipoproteins in humans [8]. In mice, knocking out Angptl3 activated LpL activity and led to the reduced plasma triglyceride levels and increased hepatic lipoprotein clearance. The potential underlying mechanisms of systemic LpL anti-atherogenic actions include: (a) acceleration of the hepatic removal of remnant lipoproteins by increasing lipolysis thus subsequently reducing plasma triglycerides and cholesterol, and (b) elevating plasma HDL levels [4].

Beside its action in regulating triglyceride metabolism and fatty acid delivery, LpL also plays a role in influencing glucose metabolism and insulin signaling pathway. Genetic variant studies have indicated that increased LpL activity are associated with the reduced risk of coronary heart disease and diabetes in humans [9, 10]. A series of comparative animal model studies have reported the consistent findings demonstrating how tissue-specific LpL regulates insulin sensitivity. Nonetheless, increased LpL activity has been shown to be associated with increased insulin sensitization in patients with inactivated Angptl3 mutations and in Angptl3 knockout mice as reported by Dewey et al [7]. Thus, the dual-action of LpL in regulating both fatty acid and glucose uptake highlights the use of the agents that lower triglyceride-rich lipoproteins by increasing LpL activity. These might be more advantageous than those that increase the activity of LDL-receptors, such as statins or PCSK9. Although it is still under investigation, statins or PCSK9 have been linked to increased risks for diabetes. Therefore, exploring this regulatory role of LpL in fatty acid delivery may open new perspectives in the prevention and therapy of insulin resistance.

Roles of tissue-specific LpL in inflammatory pathways

Aortic LpL and macrophages in atherosclerosis—In contrast to its conventional role in catalyzing lipolysis, aortic expression of LpL is a marker of atherosclerosis that has been established by the classic genetic engineering approaches [11, 12]. Several mechanisms by which aortic LpL may promote atherosclerosis have been proposed. Macrophages within atherosclerotic lesions are a major site of LpL expression. We had previously reported that high intakes of saturated fatty acids altered aortic cell populations, particularly the accumulation of macrophages that secrete LpL, to promote arterial LDL cholesterol deposition before the development of atherosclerosis. By contrast, dietary n-3 fatty acid decreased arterial LpL and LDL cholesterol deposition in several mouse models [13, 14]. In an atherosclerosis-susceptible mouse model, our data had further demonstrated that the replacement of saturated fats with n-3 fatty acids improved plasma abnormal lipid profiling, ameliorated adverse inflammatory responses and decreased atherosclerosis. In proximal aorta, increased LpL positively correlated with aortic wall macrophage levels [14, 15]. We proposed that LpL might direct “vicious cycle” whereby increased macrophage levels increase LpL secretion, which promote further macrophage accumulation in the arterial wall.

Recent genetic studies in humans have associated heterozygous LpL deficiency with early-onset coronary heart disease [10], an effect that might reflect hypertriglyceridemia,

increased postprandial lipemia, and low HDL cholesterol levels. Results from the latest large clinical trial (REDUCE-IT™ Cardiovascular Outcomes Study) strongly support n-3 EPA-mediated cardioprotective effects in decreasing CVD risks in patients with the history of CVD and diabetes. The potential underlying mechanisms are associated with improved plasma lipid profiles and adverse inflammatory responses. Our earlier studies have reported additional new insights into the underlying mechanisms of how n-3 fatty acids interact with focal arterial LpL in modulating atherosclerosis development, providing evidence for new therapeutic approaches on lowering abnormal plasma triglyceride-rich lipoproteins, reducing arterial lipid deposition and suppressing adverse inflammatory events.

“Uncovered” functions of LpL in CNS and their implication—Despite the numerous studies on examining the roles of LpL in peripheral tissues in various cell culture systems, animal models, and humans, very limited studies have directed towards understanding the functions of LpL in brain and central nerve system (CNS). In the past few years, roles of cholesterol have been investigated extensively in neuron degenerative Alzheimer’s disease (AD), which include its potential interactions with apoE, HMG-CoA reductase, and β -amyloid metabolism. Other factors that are known to be involved in cholesterol homeostasis in the cardiovascular system also present in the CNS are now being explored in the context of AD pathophysiology, including LpL. LpL is present throughout all brain regions with the highest levels found in hippocampus. It has been suggested that LpL could serve as a transporter for cholesterol and facilitates cellular uptake of lipoproteins, lipids and lipid-soluble vitamins (e.g., vitamin E) to neurons in supporting their survival and the plasticity during regeneration of neuronal processes [16]. In addition, it has been reported that LpL significantly affects brain cholesterol levels, neurofibrillary tangles and senile plaque densities. Data from several genetic studies and meta-analyses have suggested the association of common polymorphisms in LpL in modulating AD risk [17, 18], including Asn291Ser, HindIII and Ser447Ter polymorphisms [17]. Recent reports have shown that colocalization of LpL and senile plaques may form a complex that facilitates cell surface binding and uptake in mouse primary astrocytes that directs A β to lysosomal degradation through a cell surface proteoglycan-dependent pathway [19]. LpL might affect hippocampal function and possibly dementia via its role as supplier of membrane components or antioxidants to neurons. Alternatively, LpL may play a part in plaque formation through its interaction with apoE and LRP.

Furthermore, Laperrousaz et al. have reported that neuron-specific LpL knockout led to weight gain and obesity, which is associated with insulin resistance. The potential mechanisms include the increased AgRP expression in hypothalamus [20]. The authors also noted that decreased LpL activity led to increased de novo synthesis of ceramide and neurogenesis. Interestingly, in a mouse model of obesity, knocking down LpL specifically in microglia resulted in deficient microglial lipid uptake, a shift of mitochondrial fuel preference to glutamate and decreased immune reactivity. Microglial reactivity was reduced in hypothalamus, which was accompanied by down-regulation of phagocytic capacity and increased mitochondrial dysmorphologies [21]■. Moreover, studies by Bruce et al. confirmed that lipid uptake in LpL-deficient microglial cells was decreased when compared to control wild type. These cells also had markedly reduced expression of anti-inflammatory

makers, YM1 and arginase 1 and increased expression of pro-inflammatory markers, such as iNOs [22]. Nonetheless, several genetic variant studies have also strongly suggested that LpL plays a significant role in the pathophysiological response of the brain to cerebral ischemic-reperfusion [23]. All these findings indicate the importance of LpL in regulating neuron survival and differentiation.

Emerging roles of LpL in modulating immune cell biology—Although LpL is highly expressed in bone marrow, few studies have assessed the relationship between LpL and bone marrow hematopoiesis or blood leukocyte parameters. As hematopoietic stem and progenitor cells (HSPC) arise during embryonic development and occupy a series of niches in fetal tissues, they localize primarily to the bone marrow postnatally where they expand in number and initiate hematopoiesis in adult mammals under normal circumstances. When responding to severe hematopoietic stresses, hematopoiesis can transiently expand into extramedullary organs, including liver and spleen.

Employing a transgenic LpL knockout mouse model, our recent data has demonstrated that LpL-deficiency mice have decreased blood leukocytes and leukocyte subsets, including macrophage precursors – monocytes, which led to substantial reductions in aortic macrophage levels [24]. Reconstitution of LpL-expressing bone marrow was able to replenish arterial macrophage density. LpL deficiency significantly decreased bone marrow macrophage-associated pro-inflammatory markers, and was associated with the reduced expression of hematopoietic master transcription factors (PU.1 and C/EBP α) and colony-stimulating factors (CSFs) and their receptors (CSF-Rs), which are required for myeloid cell proliferation and differentiation. As a result, bone marrow-derived monocyte progenitor or monocyte differentiation to macrophages was significantly decreased in LpL-deficient mice. We have also reported that defective bone marrow triglyceride lipid metabolism induced by LpL deficiency may contribute to decreased bone marrow myelopoiesis via regulating expression of M-CSF and M-CSF-R in bone marrow macrophage precursor cells. Our studies are the first to indicate that LpL, in addition to being a lipolytic enzyme, also influences peripheral and bone marrow immune cell responses, and this modulates both the number and function of macrophages in the arterial wall.

Zebrafish models have been emerged as a new powerful model to study lipid metabolism and atherosclerosis [25]. Zebrafish express many important genes involved in lipid transport system, including LpL, hepatic lipase and apoCII. Recent studies on zebrafish embryos have visualized the interactions of HSCs with vascular and perivascular cells in vivo. Imaging of the vasculature in apoCII $^{-/-}$ mutants reveals accumulation of lipids and lipid-laden macrophages that resemble the early stages of atherosclerosis in humans [25]. Mutant zebrafish deficient in functional apoCII became severely hypertriglyceridemic on a normal diet, which can be rescued by the injection of normal fish serum or by an apoCII mimetic peptide. Liu et al. utilized the CRISPR-Cas9 gene editing technique to mutate LpL gene in zebrafish with 2 nucleotides (nt) deletion in exon 4 of the LpL gene, resulting in the truncated mRNA or in-frame exon skipping and alternative splicing. LpL-knockout zebrafish shared the same hypertriglyceridemia phenotypes with apoCII mutants. Interestingly, apoCII and LpL mutant fish also display profound anemia and defects in HSPC maintenance and differentiation during definitive hematopoiesis. Parabiosis of apoCII and LpL mutants

rescued the defective HSPC expansion in both mutants, suggesting the importance of circulating free fatty acids [26]■■■. The authors have further characterized LpL expression pattern in both zebrafish and mouse bone marrow and found that LpL is highly expressed in stromal cells, but not in HSPC. These findings suggest that LpL might play a crucial role in the specialized vascular niches in supporting the maintenance of stem cells and their functions.

Similar to our findings on the defective lipid metabolism in the hematopoietic origin in LpL-deficient mice, apoCII mutant fish have altered lipid composition with reduced DHA levels. Injection of DHA fatty acid but not DHA triglycerides rescued HSPC defects in both apoCII and LpL mutants. Injection of human VLDL (+ apoCII), but not LDL (– apoCII) also rescued the defective hematopoiesis in apoCII mutant 2 days post-fertilization. However, it did not rescue the similar defects in LpL mutant fish, as there is no functional LpL present even in the presence of apoCII. The exact cellular mechanism of DHA-mediated HSPC maintenance remains to be elucidated. The authors suggest that DHA might be involved in the activation of PPAR α / δ or upregulation of other genes involve in fatty acid oxidation and mitochondrial biogenesis. In addition, the derivatives of DHA have been shown to regulate HSPC homing and engraftment [26, 27].

Taken together, these studies provide novel insights into the regulation of immune cell biology and may have therapeutic applications for a number of metabolic and blood cell diseases. It is likely that, in some situations, decreased myelopoiesis via selective LpL deletion could have translational applications for various inflammatory and metabolic diseases to inhibit pathways important to CVD.

CONCLUSIONS

Recent advances in identifying functional cell populations by systematic screening of the expression patterns of target markers, genetic engineering tools, advanced imaging techniques and new experimental model systems, indicate that functions and activities of the “old” enzyme – LpL need to be updated and re-defined. Findings outlined in this review suggest the feasible therapeutic translation of activating systemic LpL activity in ameliorating elevated plasma triglyceride levels and potentially, regulating insulin sensitivity, that are attributed to atherosclerotic CVD. New roles of focal expression of LpL in influencing hematopoiesis and brain regenerative processes have been delineated, which provide new mechanistic insights into the interaction of lipid metabolisms and inflammatory pathways. Further studies will shed more light on these newly identified characteristics of LpL. A better understanding of the focal action of LpL with its corresponding microenvironment in regulating multifaceted cellular responses will lead to novel treatment strategies for CVD or tissue degenerative processes.

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KEY POINTS:

- Enhancing systemic LpL enzymatic activity can offer appealing advantages in ameliorating atherosclerotic CVD and insulin resistance.
- LpL can now be recognized not only as a key player in directing arterial lipid deposition, but also a potential regulator in influencing blood and peripheral inflammatory responses.
- Growing understanding of the roles of LpL in mediating immune cell biology has uncovered new mechanisms that can be part of strategic approaches to decrease risks for CVD using n-3 fatty acids and related molecules in humans.