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Regulation of lipoprotein lipase-mediated lipolysis of triglycerides

Debapriya Basu, **Ira J. Goldberg**

Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, New York University Grossman School of Medicine, New York, New York, USA

Abstract

PURPOSE OF REVIEW—To discuss the recent developments in structure, function and physiology of lipoprotein lipase (LpL) and the regulators of LpL, which are being targeted for therapy.

RECENT FINDINGS—Recent studies have revealed the long elusive crystal structure of LpL and its interaction with glycosylphosphatidylinositol anchored high-density lipoprotein binding protein 1 (GPIHBP1). New light has been shed on LpL being active as a monomer, which brings into questions previous thinking that LpL inhibitors like angiopoietin-like 4 (ANGPTL4) and stabilizers like LMF1 work on disrupting or maintaining LpL in dimer form. There is increasing pharmaceutical interest in developing targets to block LpL inhibitors like ANGPTL3. Other approaches to reducing circulating triglyceride levels have been using an apoC2 mimetic and reducing apoC3.

SUMMARY—Lipolysis of triglyceride-rich lipoproteins by LpL is a central event in lipid metabolism, releasing fatty acids for uptake by tissues and generating low-density lipoprotein and expanding high-density lipoprotein. Recent mechanistic insights into the structure and function of LpL have added to our understanding of triglyceride metabolism. This has also led to heightened interest in targeting its posttranslational regulators, which can be the next generation of lipid-lowering agents used to prevent hypertriglyceridemic pancreatitis and, hopefully, cardiovascular disease.

Keywords

hypertriglyceridemia; lipase; monomer; triglyceride-rich lipoprotein

INTRODUCTION

Lipoprotein lipase (LpL)-mediated lipolysis has long been known to be the rate-limiting step in the removal of triglyceride from the blood stream. Within the past decade, LpL and its

Correspondence to Debapriya Basu, PhD, Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, New York University Grossman School of Medicine, New Science Building 623B, 435 East 30th Street, New York, NY 10016, USA. Tel: +1 646 501 0586; debapriya.basu@nyulangone.org.

Conflicts of interest

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regulators have garnered increased attention in part because genes that modulate LpL activity correlate with the risk of cardiovascular disease (CVD) events. Whether this relationship is because higher triglyceride levels are atherogenic or because LpL modulates other processes, such as HDL levels and function or coagulation, is unknown.

During the past year, new publications have focused on five major areas, which will be reviewed here. These include studies on genetics of LpL and CVD risk; structure–function relationship of LpL, its interactions with GPIHBP1 and ANGPTL4; physiology of LpL action; newer approaches to treating hypertriglyceridemia and clinical studies to reduce hypertriglyceridemia.

GENETICS OF HUMAN DISEASE

LpL variations are a risk factor for CVD events, hyperchylomicronemia and pancreatitis [1]. The relationship between LpL variants and CVD risk was strengthened by Klarin *et al.*'s [2■] report, in which they assessed single nucleotide polymorphisms associated with disease using the very large U.S. Veteran's Administration database, containing samples from more than 30,000 patients with peripheral arterial disease (PVD). They then confirmed their data by interrogating the UK Biobank of stored samples. LpL variants — along with variants in the LDL receptor (LDLR) and Lp(a) — are associated with more disease, as had been observed for coronary artery disease. In addition, a number of genetic markers of thrombogenic risk were also found to be associated with PVD. Thus, PVD is likely a pathogenic consequence of atherosclerosis as well as coagulation. What is unclear from this report, and likely to be part of further study, are the lipoprotein profiles associated with the observed genetic variations, as well as the associations between other regulators of lipolysis, such as angiopoietin-like proteins (ANGPTLs) and apoproteins, and PVD risk.

Further support for triglyceride-lowering variants in LpL and CVD risk came from Ference *et al.*'s study [3], where they studied participants enrolled in 63 cohort or case–control studies conducted in North America or Europe between 1948 and 2017. Odds ratio for coronary heart disease (CHD) was defined as coronary death, myocardial infarction or coronary revascularization-per 10-mg/dl lower concentration of apolipoprotein B-containing lipoproteins. They concluded that triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants were associated with similar lower risk of CHD per unit difference in ApoB. These data support potential clinical benefits of triglyceride lowering, although it may require concomitant ApoB lowering.

Screening of targeted sequencing data of 632 patients with severe hypertriglyceridemia identified partial deletions of the LPL gene in four individuals (0.63%). Dron *et al.* [4] say that although relatively infrequent, LPL copy number variations are an important type of genetic variation that should be screened for when establishing the genetic basis of hypertriglyceridemia as these show severe phenotypes.

D'Erasmo *et al.* [5] screened patients with severe hypertriglyceridemia for rare and common variants using a panel of 18 triglyceride-raising genes, including LPL, APOC2, APOA5, GP1HBP1 and *LMF1*. Familial chylomicronemia syndrome (FCS) patients exhibited the most severe

clinical phenotype — resistance to medications and higher incidence of acute pancreatitis when compared to multifactorial chylomicronemia (MCS) patients. Biallelic mutations in LpL were common in FCS patients, whereas ApoA5 variants, in combination with high rare polygenic burden, were the most frequent genotype of MCS.

STRUCTURE-FUNCTION RELATIONSHIP OF LIPOPROTEIN LIPASE, GPIHBP1 AND ANGPTL4

Several new studies have focused on the structure of the LpL active protein and its interaction with its obligate endothelial cell binding protein (GPIHBP1) [6]. Studies from the Olivecrona laboratory [7] and others [8] had noted that LpL could be active as a monomer. However, when isolated during enzyme purification from either postheparin plasma or bovine milk, LpL tended to aggregate into dimers or multimers; aggregation was likely abetted by the presence of heparin used to stabilize LpL activity. Aggregates were more stable when the partially purified preparation was incubated at 37°C, leading to the assumption that in-vivo LpL activity was primarily because of dimeric LpL, in which the two subunits were arranged in a head to tail configuration.

The use of buffers or heparin to retain the more stable dimeric LpL configuration predated the discovery of GPIHBP1 or ANGPTL group of LpL inhibitors. This issue was reinvestigated by Beigneux *et al.* [9■■] who, like previous investigators, found that the addition of heparin stabilized LpL activity and led to its aggregation. Most importantly, they also found that the addition of purified GPIHBP1 led to the elution of active LpL that was monomeric. This suggests that the known lability of monomeric LpL is preserved *in vivo* by its association with GPIHBP1. In addition to a number of density gradient isolations showing the coelution of monomeric LpL protein in its active form, the investigators performed a clever coexpression study of inactive but GPIHBP1-binding LpL and active LpL that did not bind to GPIHBP1. Dimerization would have been expected to produce double tagged, more active enzyme. However, very little of this mixed dimer was found, and what was found instead was in the inactive fraction. One might wonder if non-GPIHBP1 binding LpL is less stable, and native LpL has its activity stabilized by GPIHBP1.

Kristensen *et al.* [10■■] isolated LpL monomers utilizing their high-affinity interaction with the monoclonal antibody 5D2, which recognizes the hydrophobic lipid-binding region of LpL Authors show that ANGPTL4 appears to unfold LpL monomers, rendering them inactive and this process is independent of homodimer-monomer state changes of LpL. These results imply that the previously accepted mechanism behind LpL homodimer disruption by ANGPTLs must be revisited. Moreover, the role of LMF1 has long been thought to stabilize LpL dimer formation, which again, in light of new data, will need to be clarified by future studies.

Nimonkar *et al.* [11■] fused LpL to GPIHBP1, resulting in a high yield active recombinant LpL resistant to ANGPTL3 or 4 inactivation. Previously, the poor stability of recombinant LpL had impeded the development of LpL enzyme replacement therapy. However, this stable recombinant fused protein reduced circulating triglycerides in several mouse strains without adverse effects when injected intravenously or subcutaneously.

Another novel mechanism of ANGPTL4's action on LpL was shown recently by Gutgsell *et al*. [12]. Using hydrogen–deuterium exchange MS and site-specific mutagenesis, they showed that the N terminal region of ANGPTL4 (nANGPTL4) binds LpL near its lid domain and a nearby helix. A peptide mimetic of LpL lid domain that binds nANGPTL4 could protect full length LPL from inhibition. This study suggests that the nANGPTL4 reversibly inhibits LPL by binding the lid domain to prevent substrate catalysis by the active site. Thus, LpL inhibition by ANGPTLs might involve several mechanisms.

In the last year, two groups have solved the crystal structure of LpL bound to GPIHBP1. Birrane *et al*. [13■■] crystallized an LpL–GPIHBP1 complex, where GPIHBP1's Ly6/uPAR domain binds to LpL's C-terminal domain, largely by hydrophobic interactions. Arora *et al*. [14■■] coexpressed LpL with a soluble GPIHBP1and LMF1 to create a stable and homogenous LpL/GPIHBP1 complex suitable for X-ray crystal structure at 2.5–3.0 Å resolution. Binding of a novel inhibitor resulted in ordering of the LPL lid and lipid-binding regions and thus enabling determination of the first crystal structure of LPL that includes these important regions of the protein. The derived structure was similar to that reported by Birrane *et al*.

CLINICAL ASPECTS OF LIPOPROTEIN LIPASE

Although human data associate genetic variations that modify triglyceride levels with CVD, data showing that triglyceride reduction decreased events have been controversial. Only nonsignificant subgroup data from fibrate trials show that individuals with increased triglyceride levels (~>200mg/dl, 2.3 mM) and low levels of HDL cholesterol appear to benefit [15]. This lack of clarity might have resulted from trial designs that enrolled individuals without consideration of baseline triglyceride levels.

The shortest route to market for triglyceride-reducing therapies has been the development of treatment strategies to reduce markedly increased triglyceride levels, an accepted way to prevent hyperchylomicronemia-induced pancreatitis. However, data to support the hypothesis that reducing triglyceride levels actually leads to less pancreatitis had been lacking. Witztum *et al*. [16■■] reported the results of a trial of volanesorsen, an antisense oligonucleotide inhibitor of ApoC3 production. In a double blind study of 66 patients carefully screened to have genetic hyperchylomicronemia syndrome, volanesorsen reduced circulating ApoC3 levels 84% and reduced average triglyceride levels 77%. Many of these patients had LpL mutations, confirming that volanesorsen supports a non-LpL requiring pathway for the removal of circulating triglycerides. The authors note that there were four episodes of pancreatitis in the control group and only one in the treated group. Unfortunately, volanesorsen was also associated with increased numbers of local injection site reactions and, more importantly, reductions in circulating platelet counts. Newer, antisense formulations are being developed to hopefully overcome these issues.

The incentives to reduce circulating ApoC3 levels were increased when Kanter *et al*. [17■] reported that ApoC3, exclusive of circulating triglyceride levels, was a risk factor for developing CVD in patients with type 1 diabetes. They went on to show that ApoC3 antisense therapy in a mouse model reduced atherosclerosis and suggest a toxic effect of this

apoprotein exclusive of its actions to modulate LpL and liver lipoprotein uptake. Thus, reducing ApoC3 might be protective by mechanisms in addition to reducing triglyceride levels. Moreover, ApoC3 circulating levels or their levels within LDL or remnant lipoproteins could be an additional marker of clinical CVD risk. Ramms *et al.* [18] determined the role of ApoE in ApoC3's action on hepatic clearance of TRL via syndecan 1 (SDC1). In mice lacking hepatic SDC1 and apoE, both apoE-mediated TRL clearance through LDLR/LRP1 and SDC1-mediated TRL clearance are absent. They found that ApoC3 lowering in the absence of apoE expression robustly decreased plasma triglycerides because of greater LpL activity in white adipose tissue.

Ashraf *et al.* [19] described a 15-year-old female with intermittent chylomicronemia and concomitant intermittent rises in GPIHBP1 autoantibodies, which dangerously lowered her plasma LpL levels. The episodes of chylomicronemia were accompanied by acute pancreatitis, so the patient had to be treated with immunosuppressive drugs, which lowered GPIHBP1 autoantibodies and normalized plasma triglyceride levels. The authors suggest testing for GPIHBP1 autoantibodies in patients with unexplained acquired cases of chylomicronemia.

PHYSIOLOGY of LIPOPROTEIN LIPASE ACTION

Miyamoto *et al.* [20] show that acetoacetate regulates LpL activity via adipose GPR43 in ketogenic conditions. They investigated the signaling partner for acetoacetate, which is generated during energy deficit or metabolic crisis, and found that it is a direct agonist for GPR43. GPR43 is a short-chain fatty acid (FA) receptor involved in energy homeostasis, also known to regulate LpL activity. Using *Gpr43*$^{-/-}$ mice and GPR43 transgenic mice (*Gpr43TG*) mice in combination with acetoacetate, they found that the effects of acetoacetate on LpL activation were less in *Gpr43*$^{-/-}$ mice compared to wild type, and more in the *Gpr43TG* mice compared to wild type.

The regulation of LpL has been extensively studied in diabetes; however, many controversies remain, because of its complex regulation and differential expression in various tissues. Epicardial adipose tissue (EAT) surrounds myocardium and coronary arteries and has a higher volume in type 2 diabetic (DM2) patients [21–23]. As LpL can supply Free fatty acid (FFA) to adipose tissue, Barchuk *et al.* collected EAT from patients undergoing coronary by-pass graft (CABG), divided it into CABG-DM2 (with type 2 diabetes) and CABG-noDM2 (without type 2 diabetes), and patients without CABG (no CABG) [24]. They reported that in DM2, LpL activity was increased, which also correlated with increased GPIHBP1 and decreased ANGPTL4 expression. They discuss that increased LpL activity in DM2 may contribute to higher EAT volume; however, further studies will be needed to confirm this.

In a study on diabetic rats, Puri *et al.* [25] show that the severity of experimental type 1 diabetes in rats resulted in differential FA partitioning and gene expression profile in hearts. Rats were injected with a low (55 mg/kg) or a high (100 mg/kg) dose of streptozotocin. Although both doses led to similar hyperglycemia, insulin and LpL activity were much lower in the high-dose group. There was minimal change in plasma FA in low-dose rats but an increase in saturated, monounsaturated and polyunsaturated FA in the plasma of the high-

dose treated rats. The authors conclude that with increasing severity of diabetes, the heart is unable to control its own FA supply using LpL and it undergoes reprogramming to handle excess FA coming from adipose tissue. This transition results in a cardiac metabolic gene signature showing mitochondrial FA overload, oxidative stress, triglyceride storage and cell death.

FA uptake and oxidation characterize the metabolism of alternatively activated macrophage polarization *in vitro*, but the in-vivo biology is less clear. Our group investigated the role of LpL-mediated lipid uptake in macrophage polarization *in vitro* and *in vivo* using both global and myeloid cell-specific LpL deficiency [26■]. *In vitro*, lack of LpL altered lipid uptake in bone marrow macrophages and caused an increase in some anti-inflammatory and proinflammatory markers. However, LpL deficiency did not alter lipid accumulation or gene expression in circulating monocytes in mice. In adipose tissue, less macrophage lipid accumulation was found with global but not myeloid-specific LpL deficiency. Neither deletion affected the expression of inflammatory genes in adipose tissue macrophages. When we assessed macrophage gene signatures from regressing atherosclerotic lesions in mice, LpL deficiency did not affect the polarity of plaque macrophages. We concluded that phenotypic changes observed in macrophages upon deletion of *Lpl in vitro* are not mimicked in tissue macrophages.

ANGPTL4 is a well-studied posttranslational inhibitor of LpL. Many groups have shown that inhibiting ANGPTL4, in mice on high saturated fat diet, causes severe inflammatory phenotypes presenting with mesenteric lymphadenopathy, marked elevation of acute-phase proteins in plasma like serum amyloid A and ultimately, death [27,28]. As a result, therapeutic prospects of whole-body ANGPTL4 inactivation are not being pursued. Oteng *et al*. [29■] characterized *Angptl4*-hypomorphic mice with partial expression of a truncated N-terminal ANGPTL4, which had lower plasma triglycerides, cholesterol and FA, similar to full body ANGPTL4 knockout mice (*Angptl4*$^{-/-}$) mice. After high-fat diet feeding, *Angptl4*-hypomorphic mice had slower and much more attenuated inflammatory phenotype than *Angptl4*$^{-/-}$ mice, despite similar abundance of lipid-laden giant cells in mesenteric lymph nodes.

Lupien *et al*. [30■] describe a novel role of LpL for internalizing whole lipoproteins via receptor-mediated endocytosis in breast cancer cells. Breast cancer cells depend on FA via de-novo lipid synthesis, and uptake via CD36. They demonstrated that breast cancer cells and clinical breast cancer tissues robustly express LpL. Expression of genes in lipid acquisition pathways was altered in response to the availability of lipoproteins in media, as well as LPL expression status. This study hints that pharmaceutical targeting of FA synthesis or uptake inhibition in breast cancer may elicit compensatory upregulation of lipid uptake.

NEWER APPROACHES TO REDUCE HYPERTRIGLYCERIDEMIA

For the many patients with hyperchylomicronemia syndrome who either have recurrent pancreatitis or are sentenced to a lifetime of very restricted diets, there will be new approaches to treatment in the next few years. Aside from the reduction of ApoC3, two additional therapies are in development for patients who do not have LpL genetic mutations.

Wolska *et al.* [31■] have shown that a novel ApoC2-like peptide reduces circulating triglyceride levels. This effect is associated with the displacement of ApoC3 from circulating lipoproteins and not surprisingly, like volanesorsen, the reduction of triglyceride levels in LpL-deficient model as well.

Although genetic studies in mice had defined ANGPTL3, 4 and 8 as modulators of LpL activity, establishing the association that humans with hypolipoproteinemia and reduced levels of all ApoB lipoproteins were due to a defect in ANGPTL3 has driven major pharmaceutical interests toward this target. Both monoclonal antibodies and antisense oligonucleotides and silencing RNAs (in development) targeting ANGPTL3 tested in humans show reductions in LDL and also triglyceride levels. Clinical trials with Evinacumab, a monoclonal antibody targeting ANGPTL3, have shown promising reductions in plasma lipids in patients. Last year, two phase 1 trials in hypertriglyceridemic individuals were reported [32■]. There were no adverse events linked to Evinacumab and circulating lipids were decreased in hypertriglyceridemic individuals, similar to what has been seen with antisense oligonucleotides targeting ANGPTL3 [33].

The larger issue is whether reductions in triglyceride levels will affect atherosclerosis and CVD events, an issue most pressing in patients with diabetes who are often hypertriglyceridemic and have a greater risk of CVD events even after LDL cholesterol reduction. Aside from fibrates, the usual treatment for severe hypertriglyceridemia has been the use of 4 g of purified omega 3 FA: Docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) or a combination of both. Following a series of suboptimal clinical trials, which failed to show that 1 g of omega 3 FA supplements affects CVD events (some of these trials did not even include triglyceride levels), a randomized trial named REDUCE-IT showed a reduction in CVD events from 22 to 17.2% over a mean followup of 4.9 years using 4 g of icosapent ethyl per day in individuals with diabetes, a known CVD, or high risk [34■■]. This reduction was similar for individuals with triglycerides under or over 200 mg/dl. On average, triglyceride levels in the statin-treated group of individuals decreased by 18.3%. The control group received mineral oil, which surprisingly was associated with an increase in LDL and hsCRP. Along with a number of other clinical outcome trials using fibrates and other omega 3 FA, the results of this study cry out for confirmation and additional studies to understand the mechanism behind this clinical benefit.

CONCLUSION

Driven both by the desire to fully understand a fundamental biological process, the hydrolysis of triglyceride levels and delivery of FA to tissues, and the relationships of increased triglyceride levels and human diseases, there has been intense focus on the molecular details of LpL and the molecules that affect its activity. Greater biological knowledge coupled with increased pharmaceutical development promises to lead to new therapies in the clinical field within the next decade.

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KEY POINTS

- LpL is the major regulator of plasma triglyceride metabolism and is active as a monomer and stable when bound to GPIHBP1.
- Crystal structure of LpL bound to GPIHBP1 has been solved, providing more information on the effects of clinical mutations in LpL as well as its functions.
- Posttranslational regulators of LpL like ANGPTL3, ApoC3 and ApoC2 have garnered pharmaceutical interest to treat hypertriglyceridemia and lower risk of CVD.