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Review

# Lipoprotein lipase: Biosynthesis, regulatory factors, and its role in atherosclerosis and other diseases

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## ABSTRACT

Lipoprotein lipase (LPL) is a rate-limiting enzyme that catalyzes hydrolysis of the triglyceride (TG) core of circulating TG-rich lipoproteins including chylomicrons (CM), low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL). A variety of parenchymal cells can synthesize and secrete LPL. Recent studies have demonstrated that complicated processes are involved in LPL biosynthesis, secretion and transport. The enzyme activity of LPL is regulated by many factors, such as apolipoproteins, angiopoietins, hormones and miRNAs. In this article, we also reviewed the roles of LPL in atherosclerosis, coronary heart disease, cerebrovascular accident, Alzheimer disease and chronic lymphocytic leukemia. LPL in different tissues exerts differential physiological functions. The role of LPL in atherosclerosis is still controversial as reported in the literature. Here, we focused on the properties of LPL derived from macrophages, endothelial cells and smooth muscle cells in the vascular wall. We also explore the existence of crosstalk between LPL and those cells when the molecule mainly plays a proatherogenic role. This review will provide insightful knowledge of LPL and open new therapeutic perspectives.

## 1. Introduction

The existence of lipoprotein lipase (LPL) was first noticed in1943 when Paul et al. [1] observed that intravenous injection of heparin could cause rapid clearance of alimentary lipemia associated with the absorption of a fatty meal. Subsequently, a series of studies revealed that this so-called "clearing factor lipase" activated by heparin is a lipolytic enzyme and possesses "antichylomicronemic" characteristics [2]. Thereafter, many studies focused on LPL roles in the metabolism and transport of lipids and gradually identified the gene structure, synthesis, regulation and function of the enzyme. To gain a better understanding of LPL function, possible associated pathological events and LPL as a therapeutic target, it is important to explore its gene, its biosynthesis including factors regulating the LPL protein, and the role of LPL in various diseases.

## 2. Genetics of LPL

The LPL gene is mapped to human chromosome 8p22 and is homologous to the sequences of hepatic and pancreatic lipase. The complementary DNA of human LPL shows that the gene encodes 448 amino acids. The LPL gene is composed of 10 exons (spanning approximately 30 kb) interrupted by 9 introns (spanning 6 kb) [3,4]. The first exon encodes the long 5′-untranslated region of 188 nucleotides and the entire signal peptide plus the first two amino acid residues of the mature protein. The tenth exon encodes the long 3′-untranslated region of 1948 nucleotides, and the middle eight exons encode the remaining 446 amino acids [5]. The second exon encodes the protein domain that binds to the lipoprotein substrate. The fourth exon encodes the domain containing the serine and the flanking amino acid residues that were previously identified as the interfacial lipid-binding region. The fifth exon encodes the sequence $Gly^{154}$–$Gly^{231}$ of the mature

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protein, which is involved in the process of catalysis. The sixth and ninth exons encode for the sequences that are relatively rich in basic amino acids and, therefore, are likely involved in anchoring of the enzyme to the capillary endothelium by interaction with the acidic domain of heparan sulfate [4,6,7].

## 3. Structure and biochemistry of LPL

The LPL protein monomer is organized into a larger amino-terminal domain that contains catalytic residues and a smaller carboxyl-terminal domain with a flexible peptide connecting the two domains [8]. The amino-terminal domain contains the catalytic triad (Ser132, Asp156, and His241) responsible for lipolysis and a 22-amino acid loop or "lid" that covers the catalytic site, which is critical for the subsequent binding of the lipid substrate for hydrolysis [9–11]. The carboxyl-terminal region contains the dominant heparin-binding domain, which is important for binding lipoproteins. Active LPL is a dimeric molecule of two identical subunits with a head-to-toe configuration [12]. LPL is active only when it forms a homodimer. Dissociation from homodimers to monomers will lead to loss of the catalytic function [13,14].

LPL is the rate-limiting enzyme that facilitates the hydrolysis of triglycerides in chylomicrons (CM) and very low-density lipoproteins (VLDL) in circulation and produces chylomicron remnants and intermediate-density lipoproteins (IDL), and releases fatty acids (FFA) for tissue energy utilization or storage [3,15].

## 4. Biosynthesis, secretion and transportation

LPL is primarily synthesized and secreted in the rough endoplasmic reticulum (ER) of a variety of parenchymal cells including myocytes, adipocytes, skeletal muscle cells, macrophages and mammary gland cells. In the rough ER, LPL is still an inactive and monomeric proenzyme around the cell nucleus. Lipase maturation factor 1 (LMF1), a membrane-bound protein located in the ER, is often believed to act as a "client-specific" factor for the maturation of LPL. With the presence of chaperones, post-translational maturation of LPL first attains a proper tertiary fold, followed by its assembly into homodimers arranged in a head-to-tail orientation [16]. LMF1 not only keeps the kinetics of folding and assembly but also protects nascent chains of LPL from inappropriate intra- and inter-chain interactions. That LMF1 mutations cause lipase deficiency and hypertriglyceridemia has been identified in the combined lipase deficiency (*cld*) mouse model and human subjects [17,18]. Misfolded LPLs, such as those only partially folded in an N-terminal domain, are destined for ER-associated degradation (ERAD) [16]. ERAD is a universal quality-control system in the cell and provides safeguards against massive protein misfolding by regulating the ER stress response [19]. Sel-1 suppressor of lin-12-like (Sel1L) protein is an essential adaptor protein involved in the ERAD. Interestingly, recent studies showed that Sel1L is indispensable for the folding and secretion of LPL [20,21]. Sel1L forms a functional complex with LPL-LMF1, the Sel1L-LPL-LMF1 complex, on the ER membrane, which stabilizes nascent LPL dimers and allows its exit from the ER. If there is no Sel1L retained in the ER, LPL dimers are unstable, are trapped in the ER and form ERAD-resistant aggregates, which are then degraded primarily through autophagy [21].

Most homodimers of LPL, which are folded at both the N- and C-domains and have enzymatic activity, then exit from the ER to the Golgi for further modification, sorting and transportation. LPL can then bind to SorLA (sortilin-related receptor), which mediates endocytic activity and trafficking among intracellular vesicles in the TGN (late trans-Golgi network), and is then sorted to late endosomes (LEs) [22]. From the LEs, SorLA returns to the TGN, and LPL is sent to lysosomes (LS) for degradation, which suggests that SorLA is responsible for the vesicular localization of LPL. Alternatively, LPL can be secreted from parenchymal cells in a constitutive pathway (CP) [23].

After being secreted, active LPL binds to heparan sulfate proteoglycans (HSPGs) on parenchymal cells, which are cell surface receptors important for translocation of LPL. HSPGs are proteoglycans with core proteins modified with heparan sulfate (HS) side chains that can interact with numerous proteins including LPL [24]. In fact, the HS portion of HSPGs functions as a cofactor in enzymatic reactions and is crucial for maintaining LPL activity when LPL translocates from the site of synthesis to the endothelium [25]. The interaction between positively charged heparin-binding domains of LPL and negatively charged HSPGs is very important for its intracellular/extracellular transport across the endothelial cell barrier and docking at the cell surface [26,27]. In addition, the movement of LPL across the abluminal side to the luminal side of endothelial cells involves both HSPG and VLDL receptor. In fact, HSPGs facilitate the VLDL receptor, a member of the LDL receptor family, to internalize and transfer ligands from the interstitial space to the circulation and enhances LPL transcytosis [28].

It is worth noting that through a series of recent studies, the presence of GPIHBP1, a glycosylphosphatidylinositol (GPI)-anchored glycoprotein of the lymphocyte antigen 6 (Ly6) family, has been found at both the basolateral and apical surfaces of endothelial cells, and GPIHBP1 is also responsible for the transport of LPL from the interstitial space to endothelial cell surface of the luminal capillary [29]. It was reported that LPL-HSPG interactions are transient, such that LPL can be detached and move to GPIHBP1 on endothelial cells [30]. If GPIHBP1 is absent, LPL is mislocalized to the interstitial spaces, leading to severe hypertriglyceridemia [31]. GPIHBP1 has a single Ly6 domain containing 10 cysteines, the mutation of any of which will abolish GPIHBP1's capacity to bind LPL. The acidic domain of the endothelial membrane protein GPIHBP1 stabilizes LPL activity by preventing unfolding of its catalytic domain [32]. Thus, recent research has concluded that GPIHBP1 is the critical molecule in shuttling LPL from the interstitial space to the luminal surface of capillary endothelial cells. The binding of LPL to GPIHBP1 requires only the C-terminal portion of LPL and does not depend on full-length LPL homodimers [33]. Importantly, some studies have shown that the transport of GPIHBP1 and LPL across endothelial cells in invaginations of the plasma membrane and in vesicles is bidirectional [34].

Interestingly, a series of experiments has demonstrated that GPIHBP1 is expressed in capillary endothelium, but not in large vessel endothelium or brain capillaries. Thus, LPL tethering to the luminal surface of large arteries is presumably more dependent on HSPG. However, LPL-binding to GPIHBP1, rather than HSPG, is the main determinant of triglyceride-rich lipoproteins (TRLs) margination in heart capillaries [35,36].

After LPL hydrolyzes circulating lipoproteins in capillary, sortilin (Sort1) facilitates the uptake of secreted LPL and transfers it to early endosomes and in turn late endosomes in parenchymal cells. Finally LPL ends up in lysosomes for degradation [23] (Fig. 1).

## 5. Physiological function of LPL

LPL is primarily expressed in the heart, skeletal muscle, adipose tissues, nervous system, liver, mammary gland, kidney, adrenals, pancreatic islet cells, lungs and spleen [37–40]. LPL in these tissues exerts differential physiological functions. It plays key roles in some physiological and pathophysiological conditions. Abnormal LPL expression and/or function are directly or indirectly associated with various diseases, such as hypertriglyceridemia, atherosclerosis, obesity, diabetes, Alzheimer's disease (AD), stroke and chronic lymphocytic leukemia (CLL) [41–43].

## 6. Regulatory factors of LPL

Since LPL is so critical to the hydrolysis of triglycerides in CM and VLDL and the storage of energy, its expression is highly controlled by some regulatory factors (Table 1).

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