Endothelial Lipase Promotes the Catabolism of ApoB-Containing Lipoproteins

Uli C. Broedl, Cyrille Maugeais, John S. Millar, Weijun Jin, Ryan E. Moore, Ilia V. Fuki, Dawn Marchadier, Jane M. Glick, Daniel J. Rader

Abstract—Endothelial lipase (EL) has been found to be a key enzyme in high-density lipoprotein (HDL) metabolism in mice, leading to the concept that inhibition of EL could be a novel strategy for raising HDL cholesterol levels. However, mice are “HDL animals” and the effect of EL on atherogenic apoB-containing lipoproteins has not been elucidated. We previously found that EL is capable of hydrolyzing very low-density lipoprotein (VLDL) and LDL lipids ex vivo. To investigate the role of EL in the metabolism of apoB-containing lipoproteins in vivo, we expressed human EL in three mouse models of elevated apoB-containing lipoproteins: apoE-deficient, LDL receptor–deficient, and human apoB transgenic mice. Unexpectedly, hepatic expression of EL resulted in markedly decreased levels of VLDL/LDL cholesterol, phospholipid, and apoB accompanied by significantly increased LDL apolipoprotein and phospholipid catabolism. To determine whether lipolytic activity is required for this effect, we also expressed a catalytically inactive form of human EL (ELS149A); unexpectedly, expression of EL S149A did not lower and in fact increased plasma lipids. Coexpression and coimmunoprecipitation studies suggested that catalytically inactive EL S149A inhibits endogenous mouse EL, accounting for the increased lipid levels. We conclude that (1) in addition to its known effects on HDL metabolism, EL influences the metabolism of apoB-containing particles; (2) catalytic activity of EL is required for its effects on apoB-containing lipoproteins; and (3) overexpressed catalytically inactive EL inhibits endogenous mouse EL, resulting in increased levels of plasma lipids. In light of these results, inhibition of EL has the potential to raise levels of atherogenic lipoproteins in addition to HDL-C levels. (*Circ Res.* 2004;94:1554-1561.)

Key Words: lipase ■ lipids ■ lipoproteins

Endothelial lipase (EL), a new member of the triglyceride lipase gene family,1,2 has been recently shown to be a key enzyme affecting high-density lipoprotein (HDL) metabolism. Hepatic overexpression of EL using adenoviral vectors resulted in markedly reduced HDL cholesterol (HDL-C) levels in mice.1 Transgenic overexpression of EL under the control of the endogenous promoter resulted in modestly reduced HDL-C levels.3 Conversely, inhibition of mouse EL activity in wild-type, apoA-I, and hepatic lipase (HL) knockout mice using a specific antibody resulted in significantly increased HDL-C and phospholipid levels.4 In the EL knockout mouse model, total cholesterol, HDL-C, and phospholipids were significantly increased.3,5 Therefore, EL is considered to be an attractive target for pharmacological inhibition as a novel approach to raising HDL cholesterol levels.

Surprisingly little data, however, are currently available about the potential effects of EL on the metabolism of apoB-containing lipoproteins in vivo. In vitro, EL has been shown to be capable of hydrolyzing chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL6 and of bridging VLDL and LDL to heparan sulfate proteoglycans (HSPGs).7 In vivo studies of EL overexpression and loss-of-function have been largely performed in mice that have very low levels of apoB-containing lipoproteins, making it difficult to assess the effects of EL on the metabolism of this class of lipoproteins. Conflicting results have been reported for the EL knockout mouse models. In one report, LDL cholesterol (LDL-C) levels in male (but not female) EL knockout mice were increased,8 but in another, there was no significant difference in levels of apoB-containing lipoproteins, even when fed a high-cholesterol diet.4

The present study was therefore designed to (1) investigate the effects of EL on the metabolism of apoB-containing lipoproteins in appropriate mouse models and (2) to determine whether catalytic activity of EL is required for its possible effects on apoB-containing lipoproteins. We used recombinant adenovirus to express both wild-type EL and catalytically inactive EL in apoE-deficient, LDL receptor knockout, and human apoB transgenic mice. Overexpression of EL resulted in significantly increased postheparin plasma phospholipase activity associated with significantly reduced VLDL/LDL cholesterol and phospholipid as well as apoB levels, a shift to smaller lipid poor LDL particles, and...
accelerated catabolism of LDL apolipoprotein and LDL phospholipids. Unexpectedly, overexpression of catalytically inactive EL resulted in increased levels of VLDL/LDL cholesterol and phospholipid and decreased catabolism of LDL-phospholipids, possibly because of inhibition of endogenous mouse EL.

Materials and Methods

Generation of Adenoviral Constructs

The catalytically inactive EL (EL\(^{S149A}\)) was generated by mutation of the catalytic triad (Ser149-Asp173-His254) replacing the active serine 149 by alanine as previously described.\(^3\) Recombinant adenoviral vectors encoding human EL (AdEL), catalytically inactive human EL (AdEL\(^{S149A}\)), and mouse EL (AdmEL) were constructed as previously described.\(^1,4,8\)

Animals

Apoe\(^{−/−}\) (n=4/group) and LDL receptor knockout mice (n=4/group) were obtained from the Jackson Laboratory (Bar Harbor, Maine). The protocols for mice have been approved by the University of Pennsylvania Animal Care and Use Committees (IACUC) and meet their standard guidelines. Human apoB transgenic mice (n=5/group) were originally obtained as a gift from S.G. Young (Gladdiston Institute of Cardiovascular Disease, San Francisco, Calif). All mice were fed a chow diet. \(1 \times 10^{11}\) particles of AdEL, AdEL\(^{S149A}\), or a control virus (Adnull) were administered via the tail vein on day 0 of the study. For blood sampling, mice were fasted for 4 hours. Mice were bled from the retroorbital plexus 1 day before and several time points after virus injection. Postheparin plasma samples were obtained at day 3 after virus injection 5 minutes after tail-vein injection of heparin (100 U/kg). EDTA (Invitrogen) to a final concentration of 8 mmol/L was added to the tubes as an anticoagulant.

In Vivo LDL Metabolic Studies

LDL apolipoprotein and phospholipid turnover studies were performed by injecting LDL receptor knockout mice (n=4/group) with a doubly labeled human LDL. Human LDL (d=1.019 to 1.063 g/mL) was prepared by ultracentrifugation as previously described.\(^8\) Dialyzed human LDL was labeled with \(^{3}H\) by the iodine monochloride method as described.\(^8\) Dialyzed \(^{3}H\)-LDL was subsequently labeled with \(^{125}I\)methionine-di-palmitoyl phosphatidylcholine (DPPC) as previously described.\(^8\) Briefly, 50 \(\mu\)Ci of \(^{125}I\)methionine-DPPC (PerkinElmer Life Sciences) was dried under nitrogen in a glass tube and resuspended in 50 \(\mu\)L of ethanol. Two mg of LDL protein were mixed with approximately 100 mg of heat-inactivated lipoprotein-deficient plasma (d’=1.21 g/mL) in a glass tube, and the \(^{125}I\) methionine-DPPC was added dropwise with intermittent vortexing. The tube was purged with nitrogen, sealed, and placed in a shaking water bath at 37°C for 24 hours. After incubation, labeled LDL was reisolated at the original density, dialyzed against PBS, and filter sterilized before injection into mice. LDL receptor knockout mice (n=4/group) were injected with \(1 \times 10^{11}\) particles of AdEL, AdEL\(^{S149A}\), or control. On day 5 after virus injection, an LDL turnover study was performed using \(3 \times 10^{10}\) particles of AdEL or control adenovirus. Blood was obtained from the retroorbital plexus at baseline and at days 3, 5, 7, and 10 after injection. Lipoprotein subclass profiles were determined on 100 \(\mu\)L of pooled plasma by proton NMR spectroscopy at LipoScience as previously described.\(^12\)

NMR Lipoprotein Analysis

Human apoB transgenic mice (n=4/group) were injected with \(3 \times 10^{10}\) particles of AdEL or control adenovirus. Blood was obtained from the retroorbital plexus at baseline and at days 3, 5, 7, and 10 after injection. Lipoprotein subclass profiles were determined on 100 \(\mu\)L of pooled plasma by proton NMR spectroscopy at LipoScience as previously described.\(^8\)

Gel Filtration Analysis

Pooled plasma samples from mice of the same experimental group were subjected to fast protein liquid chromatography (FPLC) gel filtration by using 2 Superose 6 columns (Amersharm Pharmacia Biotech). Samples were chromatographed at a flow rate of 0.5 mL/min, and fractions of 500 \(\mu\)L each were collected. Individual fractions were assayed for cholesterol and phospholipid concentrations by using commercially available enzymatic kits (Wako Pure Chemical Industries).

Analysis of mEL RNA Expression In Vivo

Liver RNA was extracted using the RNeasy Mini kit (Qiagen) according to the manufacturer’s protocol. After DNase digest (Invitrogen), 500 ng of total RNA was converted into cDNA using the SuperScript first-strand synthesis system for reverse-transcription polymer chain reaction (PCR; Invitrogen). Real-time PCR was performed using the ABI Prism 7700 Sequence Detector System (Applied Biosystems). The sequences of primers and TaqMan probes for mEL and mGAPDH cDNA were as follows: mEL, 5’-AGCGTCTCCTTTGGCGTTA-3’ (forward primer), 5’-CAGCCGACCCATTCAGAGAG-3’ (reverse primer), and 5’-GCTGTTGAGCATACAC-3’ (TaqMan probe); mGAPDH, 5’-GCTGTTGAGCATACAC-3’ (forward primer), 5’-GGTGCACATGCGGAGGAG-3’ (reverse primer), and 5’-GCTGTTGAGCATACAC-3’ (TaqMan probe). Quantitation of mEL was performed using the standard curve method. Determination of mouse GAPDH mRNA was used to standardize the amount of sample RNA added to the reaction.

In Vitro Tissue Culture Experiments

A Cos-7 cell line stably expressing mouse EL (mEL) protein was generated by transfecting mEL cDNA into Cos-7 cells using lipofectamine (Invitrogen) according to the manufacturer’s protocol. The cells were then selected in the presence of 1000 \(\mu\)g/mL G418 (Invitrogen). Expression of mEL protein was determined by Western blot analysis. The clone with the highest expression level of mEL was selected for further study. Stably transfected Cos-7 cells in 60-mm dishes were infected in duplicates with \(8 \times 10^{5}\) particles of AdEL\(^{S149A}\), AdGFP, or AdlacZ. Heparin to a final concentration of 10 U/mL was added 47.5 hours after infection. Media for Western blot analysis and phospholipase activity assay was harvested 48 hours after infection and stored at \(-80\)°C.
Commmunoprecipitation of Mouse and Human EL
Conditioned media from Cos-7 cells coinjected with AdmEL and AdELmyc (myc-tagged human EL), AdmEL and AdGFP, or AdELmyc and AdGFP (1×10^{11} particles of each adenvirus) and a 1:1 mixture of media from Cos-7 cells infected with AdmEL/AdGFP or AdELmyc/AdGFP were incubated with mouse anti-myc IgG at 4°C in the presence of 0.1% Triton X-100 (Fisher Scientific International) for 2 hours. Protein A magnetic beads (New England Biolabs) were added to each sample, and samples were incubated overnight at 4°C. Samples were washed three times with PBS and eluted from the beads with 4X loading buffer and 10X DTT (Invitrogen). Western blot analysis of samples was performed using a rabbit anti-mouse EL antibody as described later.

Immunoblotting
Postheparin plasma samples after heparin-Sepharose treatment or conditioned media from Cos-7 cells were mixed with 4X loading buffer (Invitrogen), subjected to 10% SDS-PAGE (Invitrogen) under reducing conditions and electroblotted to Hybond-P (PVDF) membrane (Amersham Pharmacia Biotech). The detection of EL and ELs149A was performed using a (species-specific) rabbit anti-human EL antibody at 1:3000 dilution as primary antibody as previously described. Detection of mEL in homogenized liver lysate (30 µg total protein) or conditioned media was performed using a (species-specific) rabbit anti-mouse EL antibody at 1:2500 dilution as primary antibody as previously described. A goat anti-rabbit antibody at 1:5000 dilution was used as the secondary antibody. Detection was performed by the ECL protocol (Amersham Pharmacia Biotech) according to the manufacturer’s instruction.

Lipase Assays
Phospholipase activity was determined as previously described. Briefly, an emulsion of cholesteryl oleate (150 mg) and DPPC (8.88 mg unlabeled and 17.15 µCi [1,2-14C]-DPPC, 110 µCi/mmol) was prepared by sonication in 2.5 mL glycerol. The assay tubes contained, in a total volume of 0.3 mL, 0.05 mol/L Tris-HCl, pH 8.0, 0.75% bovine serum albumin, 4.6 mmol/L cholesteryl oleate, 245 µmol/L DPPC, 0.15 mol/L NaCl, conditioned media or postheparin plasma samples. Samples were incubated for 15 minutes at 37°C. Reactions were stopped and products were extracted by the method of Belfrage and Vaughan using 100 µg lysopatimoylphosphatidylcholine per mL as carrier in the organic extraction mix.

Statistical Analysis
Values are presented as mean±SD. Turnover study data were subjected to a 1-way ANOVA and the Newman-Keuls multiple comparison test. Statistical significance for all comparisons was assigned at P<0.05.

Results
EL Expression Markedly Reduces VLDL and LDL Levels
To study the effect of wild-type EL and catalytically inactive ELs149A on the metabolism of apoB-containing particles, we injected apoE-deficient, LDL receptor knockout, and human apoB transgenic mice with 1×10^{11} particles of AdEL, AdELs149A, or control (Adnull) (2 slots for each type of injection). Unexpectedly, overexpression of catalytically inactive ELs149A resulted in significantly increased levels of total cholesterol, HDL-C, non–HDL-C, and phospholipids 5 to 7 days after virus injection in all 3 mouse models examined (Figures 2 through 4).

FPLC analysis of lipoprotein distribution demonstrated that overexpression of EL dramatically lowered VLDL/IDL cholesterol in the apoE-deficient mice (data not shown) as well as LDL-C in the LDL receptor knockout (data not shown) and human apoB transgenic mice (Figure 5A), in addition to its known effects on HDL levels in all three models. Consistent with the lipid data, the FPLC profile of ELs149A expressing mice showed increased levels of VLDL/IDL cholesterol with a shift toward larger LDL particles compared with control (Figure 5A).

EL Expression Generates Lipid-Depleted, Smaller LDL Particles
LDL isolated from human apoB transgenic mice 7 days after injection of AdEL showed a significant decrease in the percentage of phospholipids and triglycerides compared with control whereas the free and esterified cholesterol content was not changed and the percentage of protein increased (data not shown). The change in the ratio of LDL core (cholesterol esters, triglycerides) to surface constituents (free cholesterol, phospholipids, protein) (ratio_{core}, 0.75 versus ratio_{Adnull}, 0.96) suggests a shift in LDL size toward smaller LDL particles. The FPLC profile of human apoB transgenic mice expressing EL confirms this shift in LDL size (Figure 5A). NMR analysis of mouse plasma from human apoB transgenic mice injected with 3×10^{10} particles of AdEL and control adenovirus demonstrates that overexpression of EL resulted in reduced LDL-C levels, and decreased LDL size and particle number (Figure 5B through 5E).
EL Expression Accelerates LDL Apolipoprotein and Phospholipid Turnover

To determine the mechanism by which EL can reduce apoB-containing particles, we performed a kinetic study in LDL receptor knockout mice using $^{[125]}$I apoB and $[^3H]$ phospholipid (PL) doubly radiolabeled human LDL 5 days after injection of $1 \times 10^{11}$ particles of AdEL, AdEL$^{S149A}$, and Adnull. $^{[125]}$I-LDL was cleared significantly faster in the EL-expressing mice compared with both AdEL$^{S149A}$ and Adnull-injected mice (0.200±0.036 versus 0.066±0.010 pools per hour; $P<0.001$). No significant difference was observed for the fractional catabolic rates of apoB in EL$^{S149A}$- and Adnull-injected mice (0.060±0.007 versus 0.066±0.010 pools per hour; $P>0.05$) (Figure 6A). Furthermore, $[^3H]$-PL-LDL was cleared significantly faster in EL-expressing mice compared with control mice (0.250±0.098 versus 0.484±0.017 pools/hour; $P<0.05$) (Figure 6B).

Inhibition of Endogenous Mouse EL May Account for the Effects of Catalytically Inactive EL

To determine the mechanism by which expression of catalytically inactive EL resulted in increased lipid levels and decreased LDL-phospholipid catabolism compared with control, we tested whether expression of catalytically inactive EL$^{S149A}$ reduces the expression or function of endogenous mouse EL. Real-time PCR and Western blot analysis of mouse EL expression in the liver of LDL receptor knockout mouse mice 5 days after injection with $1 \times 10^{11}$ particles of AdEL, AdEL$^{S149A}$, or control did not reveal any differences in EL mRNA or protein abundance among the groups (data not shown). To determine whether EL$^{S149A}$ may affect mouse EL activity at a posttranslational level, COS-7 cells, stably transfected with mouse EL, were infected with AdEL$^{S149A}$ or controls.
(AdGFP, AdlacZ) (Figure 7A and 7B). Interestingly, despite similar mouse EL protein expression levels, phospholipase activity in ELS149A-expressing cells was significantly reduced compared with control (Figure 7C). Furthermore, human and mouse EL could be coimmunoprecipitated when coexpressed in vitro, yet could not be coimmunoprecipitated when conditioned media from cells expressing either mouse or human EL were mixed together (Figure 7D), suggesting that human and mouse EL form specific protein–protein interactions, possibly as heterodimers. Therefore, inhibition of endogenous mEL by ELS149A may be the cause of the decreased LDL-phospholipid turnover and increased lipid levels.

Discussion

EL has been shown to influence HDL metabolism and levels in mice, yet its role in the metabolism of apoB-containing lipoproteins remained to be elucidated. In the present study, we demonstrate that expression of EL in mouse models with elevated levels of apoB-containing lipoproteins significantly reduced VLDL/LDL cholesterol, phospholipid, and apoB levels. Expression of EL resulted in increased phospholipase activity in vivo, thus generating phospholipid depleted, smaller LDL particles that were more rapidly catabolized. Unexpectedly, expression of catalytically inactive EL resulted in increased levels of VLDL/LDL cholesterol and phospholipid as well as reduced catabolism of LDL-phospholipids, possibly because of inhibition of endogenous mouse EL activity. These data suggest that in addition to its role in HDL metabolism, EL may have a role in the metabolism of apoB-containing lipoproteins.
Overexpression of EL resulted in major changes in the structure of LDL particles. EL-modified LDL had a decreased content of phospholipids and triglycerides, whereas the protein content was increased. The shift in the ratio of LDL core to surface constituents and in the FPLC profile as well as the NMR analysis of lipoprotein distribution and size suggest that expression of EL may contribute to the generation of small dense LDL. HL is hypothesized to play a critical role in the generation of small dense LDL.14 HL activity in normolipidemic subjects was reported to be significantly positively correlated with plasma triglyceride, apoB, and mass of large VLDL and small dense LDL.15 Transgenic overexpression of HL in rabbits was shown to reduce levels of IDLs with a shift toward smaller, denser LDL particles.16 Conversely, buoyant, triglyceride-rich LDL particles accumulate in patients with HL deficiency.17,18 We speculate that HL might act primarily on the TG-enriched LDL particle resulting in the reduction of LDL size, whereas EL may primarily act on LDL phospholipids as a critical step in the formation of small dense LDL.

To determine whether the EL-mediated decrease of LDL phospholipids and apoB levels was because of increased catabolism, we performed a turnover study using doubly labeled human LDL in LDL receptor knockout mice. The fractional catabolic rates of both LDL phospholipids and apoB were significantly increased in EL-expressing mice compared with control. We propose that the phospholipase activity of EL depletes the LDL particle of phospholipids, resulting in smaller LDL particles that are more rapidly cleared from plasma. The major cellular pathway for tissue catabolism of LDL particles is that of the LDL receptor.19 Still, up to 50% of LDL is removed from the plasma by LDL receptor–independent pathways.20,21 It has been suggested that the intermediate size LDL subspecies constitute the optimal ligand for the LDL receptor among the human LDL particle subpopulations,22 whereas small, dense LDL are cleared from plasma to a large extent by LDL receptor–independent pathways,23 a process mediated, in part, by cell surface proteoglycans.24 LDL cell binding to LDL receptor–independent binding sites could also be related to other cell surface binding sites such as LDL receptor–related protein (LRP) or scavenger receptor class B type I (SR-BI). Interaction of small, dense LDL and HDL₃ particles with consecutive enrichment in apoE may lead to uptake of LDL by LRP. Ueda et al25 reported a significant reduction of non–HDL-C and apoB levels along with increased LDL-apoB clearance in transgenic mice overexpressing SR-BI. Recent in vitro studies by Rhainds et al26 highlight the importance of SR-BI in selective LDL cholesterol ester (CE) and phospholipid uptake as well as possibly LDL holoparticle uptake: inhibition of SR-BI function using a specific blocking antibody as well as inhibition of SR-BI expression using RNA antisense strategy suggested that SR-BI mediated up to 87% of LDL-CE uptake and 75% of LDL-PL uptake in HepG2 cells.

![Figure 6](http://circres.ahajournals.org/)

**Figure 6.** Plasma clearance of human ¹²⁵I-LDL (A) and human ³H-PL-LDL (B) in LDL receptor knockout mice 5 days after injection of AdEL (▲), AdEL⁵¹⁴⁹A (■), and control (●).

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**Figure 7.** Mouse (A) and human EL (B) protein expression in stably mouse EL expressing Cos-7 cells after infection with AdEL⁵¹⁴⁹A (lanes 1 and 2), AdGFP (lanes 3 and 4), or AdlacZ (lanes 5 and 6). Lanes 7 through 9 represent Western blot controls (7, GFP; 8, human EL; 9, mouse EL). Experiments were performed in duplicates. Phospholipase activity (nmol/mL·h) (C) in stably mouse EL-expressing Cos-7 cells after infection with AdEL⁵¹⁴⁹A, AdGFP, or AdlacZ. Experiments were performed in duplicates. Immunoprecipitation (D) of human EL with subsequent determination of mouse EL protein in conditioned media from Cos-7 cells coexpressing mouse and human EL (lane 1), expressing either mouse (lane 2), or human EL (lane 3), and in a mixture of media from cells expressing either mouse or human EL (lane 4). Lanes 6 and 7 represent Western blot controls (5, blank lane; 6, mouse EL; 7, human EL).
Independent of their catalytic activity, lipoprotein lipase (LPL) and HL can act in cellular lipoprotein metabolism as ligands that mediate the binding and uptake of lipoproteins via proteoglycans and/or receptor pathways. 27–31 Overexpression of catalytically inactive LPL in transgenic mice resulted in increased triglyceride-rich lipoprotein particle uptake and reduced triglyceride levels. 27–28 Overexpression of catalytically inactive HL significantly lowered apoB-containing lipoproteins.29,30 To determine whether catalytic activity of EL was required for its effects on apoB-containing particles, a catalytically inactive form of EL was overexpressed in apoE-deficient, LDL receptor knockout, and apoB transgenic mice. EL was previously shown to mediate binding of VLDL and LDL to cell surface HSPGs in vitro.7 Unexpectedly, expression of catalytically inactive EL did not reduce VLDL/LDL cholesterol and phospholipid levels but instead resulted in a significant increase of these parameters. This increase was associated with a decreased LDL-phospholipid catabolism and a shift of LDL particle size toward larger LDLs. Our in vitro data suggest that catalytically inactive EL may interfere with the function of endogenous active mouse EL at a posttranslational level, thus reducing the activity of endogenous mouse EL, resulting in decreased LDL phospholipid turnover and increased LDL cholesterol and phospholipid levels as well as larger, buoyant LDL particles. Radiation inactivation analysis as well as sedimentation equilibrium studies of LPL and HL revealed that both enzymes are functionally active as dimers.32 In light of the finding that human and murine EL coimmunoprecipitate, we may also be functionally active as a dimer. In light of the finding that human and murine EL coimmunoprecipitate, we speculate that catalytically inactive EL may form a heterodimer with endogenous hepatic mouse EL, thus reducing its function. Studies in EL-deficient mice will be needed to verify the effect of endogenous mouse EL on catalytically inactive EL in vivo.

In summary, hepatic expression of EL resulted in significantly increased posthepatic plasma phospholipase activity associated with reduced VLDL/LDL cholesterol and phospholipids, reduced apoB levels, a shift toward smaller lipid poor LDL particles, and accelerated catabolism of LDL apolipoprotein and phospholipids. These results suggest that in addition to its role in HDL metabolism, EL plays a significant role in the metabolism of apoB-containing lipoproteins. Unexpectedly, hepatic expression of catalytically inactive EL resulted in increased VLDL/LDL cholesterol and phospholipid levels associated with reduced catabolism of LDL-phospholipids, possibly because of inhibition of endogenous active mouse EL.

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