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Lecithin:Cholesterol Acyltransferase: From Biochemistry to Role in Cardiovascular Disease

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Abstract

Purpose of review—We discuss the latest findings on the biochemistry of lecithin:cholesterol acyltransferase (LCAT), the effect of LCAT on atherosclerosis, clinical features of LCAT deficiency, and the impact of LCAT on cardiovascular disease from human studies.

Recent findings—Although there has been much recent progress in the biochemistry of LCAT and its effect on HDL metabolism, its role in the pathogenesis of atherosclerosis is still not fully understood. Studies from various animal models have revealed a complex interaction between LCAT and atherosclerosis that may be modified by diet and by other proteins that modify lipoproteins. Furthermore, the ability of LCAT to lower apoB appears to be the best way to predict its effect on atherosclerosis in animal models. Recent studies on patients with LCAT deficiency have shown a modest but significant increase incidence of cardiovascular disease consistent with a beneficial effect of LCAT on atherosclerosis. The role of LCAT in the general population, however, have not revealed a consistent association with cardiovascular disease.

Summary—Recent research findings from animal and humans studies have revealed a potential beneficial role of LCAT in reducing atherosclerosis but additional studies are necessary to better establish the linkage between LCAT and cardiovascular disease.

Keywords

LCAT; HDL; reverse cholesterol transport; atherosclerosis; cholesterol; cardiovascular disease

Introduction

Lecithin:cholesterol acyltransferase (LCAT) (EC2.3.1.43), first described in 1962 by Glomset[1], is a key enzyme for the production of cholesteryl esters in plasma and promotes the formation of high density lipoprotien (HDL). Shortly after its discovery, LCAT was proposed by Glomset[2] to promote the Reverse Cholesterol Transport (RCT), the anti-atherogenic mechanism by which excess cholesterol is removed from cells by HDL and delivered to the liver for excretion[3,4]. Although the role of LCAT in cholesterol efflux from cells has largely been substantiated, its overall role in the pathogenesis of coronary heart disease (CHD) is still not completely understood, because it appears to depend upon other genes and environmental factors. In this review, we will first briefly discuss the biochemistry of LCAT and its role in HDL metabolism. Next, we will review the effect of increasing or decreasing the expression of LCAT on lipoprotein metabolism and

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atherosclerosis in various animal models. Finally, clinical features of LCAT deficiency and evidence from recent human studies on the effect of LCAT on CHD will be discussed.

LCAT Biochemistry

The human *lcat* gene, localized at 16*q22*, is 4.5 kb in length and contains 6 exons, which contain 1.5 kb of coding sequence[5]. It is primarily expressed in the liver but is also produced in smaller amounts in the brain and testes[6–12]. LCAT gene expression is relatively insensitive to most drugs, diet modifications or other lifestyle factors; however, fibrates lower plasma LCAT activity by approximately 20%[13,14], whereas torcetrapib and atorvastatin can modestly increase LCAT levels HDL[15–17]. The mature protein contains 416 amino acids and the primary amino acid sequence of LCAT is relatively well conserved[5–8,18]. There is limited information on the tertiary structure of LCAT, but a stucutural model for LCAT based on its homology with the α/β hydrolase fold family proteins, such as the lipases, has been described[19]. The model nicely predicts the conformation of the known catalytic triad of the enzyme, which is formed by Ser181, Asp345, and His377 residues. Two disulfide bridges have been described in LCAT[20]. Residues 53 to 71, which contains the disulfide-linked Cys50-Cys74 residues, forms part of the lid-region and a lipid binding surface[21–23], which partially covers the active site of the enzyme[24]. LCAT also contains two free cysteines (Cys31, Cys184), which account for the sensitivity of the enzyme to inhibition by sulfhydryl reactive agents[25]. The mature fully processed protein is approximately 63 kDa, which is more than 20% greater than the predicted protein mass. Most of this extra mass is due to the presence of N-linked glycosylation[26,27], which are important for its biological activity [28–31].

The LCAT reaction occurs in two steps (Fig. 1). After binding to a lipoprotein, LCAT cleaves the fatty acid in sn-2 position of phosphatidylcholine and transfers it onto Ser181. Next, the fatty acid is transesterified to the 3-β-hydroxyl group on the A-ring of cholesterol to form cholesteryl ester. Because cholesteryl esters are more hydrophobic than free cholesterol, it migrates into the hydrophobic core of lipoprotein particles. Approximately 75% of plasma LCAT activity is associated with HDL, but LCAT is also able to bind and produce cholesteryl esters on LDL and other apoB-containing lipoproteins[32,33]. Human LCAT preferentially acts on phospholipids containing 18:1 or 18:2 fatty acids, whereas rat and mouse LCAT prefer phospholipids containing 20:4 fatty acids[34,35]. Other phospholipids, such as phosphatidylethanolamine, can also participate in the LCAT reaction[36], whereas other lipids, such as sphingomyelin, can inhibit LCAT [37–40].

In vitro, many different apolipoproteins can activate LCAT[41,42], but compared to apoA-I, they appear to be less effective and are not as abundant as apoA-I in plasma., They may still, however, play a physiologic role, particularly apoE, in activating LCAT on apoB-containing lipoproteins [43]. The exact mechanism by which apoA-I activates LCAT is not known[44–47], but one proposal is that it stabilizes an active conformation of LCAT, similar to the way colipase activates pancreatic lipase[48,49]. In several recent HDL structural studies, the regions of apoA-I that activate LCAT appear to be more surface exposed compared to most other parts of apoA-I[44,50,51].

LCAT in HDL metabolism

Figure 2 shows where LCAT fits into the RCT pathway[3]. This pathway promotes the removal of excess cellular cholesterol from peripheral tissues and its delivery to the liver[52,53] for excretion into the bile. It begins with the formation of HDL largely in the liver[54–56] and the transfer of phospholipid and cholesterol by various transporters[57–60] to HDL and its eventual uptake into the liver. According to this model, LCAT plays two important roles. First, as originally proposed by Glomset[3], LCAT has been shown to

promote the efflux of cholesterol from peripheral cells[61]. The esterification of cholesterol on HDL increases the concentration gradient for free cholesterol between cell membranes and HDL. Without the ongoing esterification of cholesterol, the capacity of HDL to remove and bind additional cholesterol would eventually be diminished over time. CETP may further enhance this process by transferring cholesteryl esters formed by LCAT from HDL onto LDL[62,63], creating additional capacity for HDL to bind cholesterol. The esterification of cholesterol also transforms the discoidal shaped nascent HDL with a pre-beta migration position on agarose gels into spherical shaped HDL, which is called alpha-HDL. Because cholesteryl esters are much more hydrophobic than cholesterol, the other consequence of LCAT is that it prevents the spontaneous back exchange of cholesterol from HDL to cells and thus promotes the net cellular removal of cholesterol [61]. Cholesteryl esters on HDL and LDL are essentially trapped on these lipoproteins until they can be removed from the circulation by the liver.

Analysis of LCAT in animal models

An important experimental system for testing the role of LCAT in the RCT pathway and its effect on atherosclerosis has been the development of various animal models with either increased or decreased expression of LCAT (Table 1).

One of the first LCAT transgenic mice produced had a relatively high level of expression, (10–200 fold), which was associated with an increase in total cholesterol, LDL-C and HDL-C[9,69]. Mice with the highest level of LCAT were found to produce heterogeneous size HDL, which contained a mixture of apoA-I and apoA-II, as well as apoE, particularly on the larger HDL particles that were enriched in cholesteryl esters. ApoE-rich HDL in these mice was found to be dysfunctional, at least in regard to the delivery of cholesterol to the liver[69,70]. LCAT has also been overexpressed in transgenic rabbits[11], which unlike mice express CETP. As observed in mice, overexpression of LCAT in rabbits also increased HDL-C but unlike mice it decreased LDL-C[71]. Transient expression of hLCAT in squirrel monkeys with adenovirus also raised HDL-C and decreased apoB-lipoproteins, due to increased catabolism[66].

LCAT transgenic rabbits had 50–60% lower levels of pro-atherogenic apo B lipoprotiens[71] and were protected against diet-induced atherosclerosis[10]. LCAT transgenic rabbits crossed with LDL-receptor deficient rabbits showed that the LDL-receptor is necessary for the ability of LCAT to lower apoB-lipoproteins and for reducing atherosclerosis[72]. In contrast, LCAT overexpression in mice did not protect against diet-induced atherosclerosis[70,73,74], and in fact, in some cases, increased atherosclerosis mice with very high levels of LCAT [70]. Crossbreeding of LCAT and CETP transgenic mice led, however, to an approximate 50% reduction of diet-induced atherosclerosis compared to LCAT transgenic mice, although it was still increased above control mice[69]. The HDL produce by these mice in the presence of CETP was found to be more functional. In addition, these mice had lower levels of apoB containing lipoproteins[69].

Studies of LCAT-knockout (K/O) mice have also advanced our knowledge of the effect of LCAT on HDL metabolism. LCAT-K/O mice have markedly reduced plasma total cholesterol, cholesteryl esters, HDL-C, apoA-I, and an increase in plasma triglycerides[67,68]. The amount of alpha-HDL was strikingly decreased and the residual HDL was mostly pre-beta type HDL. When LCAT-K/O mice were placed on high cholesterol/cholate diet, it induced the formation of LpX-like lipoprotein particles, which can also be produced in cholestatic liver disease. Unlike normal lipoproteins, which have a micellar-like structure with a single monolayer of phospholipids and neutral lipid core, these abnormal particles, are multilamellar phospholipid vesicles that contain a minimum amount

of neutral lipids but can contain common plasma proteins like albumin entrapped within the particle. Similar to LCAT-deficient patients, LCAT-K/O mice on a high fat diet developed proteinuria and glomerulosclerosis, characterized by mesangial cell proliferation, sclerosis, and lipid accumulation, which may be the consequence of the renal deposition of LpX [75]. Another mouse model of LCAT deficiency that spontaneously developed glomerulopathy on a normal chow diet was created by crossing LCAT-K/O mice with SREPB1a transgenic mice[76], which have increase production of apoB containing lipoproteins. These mice also had lower levels of paraoxonase and platelet-activating factor acetylhydrolases[77], two anti-oxidant enzymes that normally reside on HDL.

Unexpectedly, LCAT deficiency in mice significantly reduced diet-induced atherosclerosis when on a high cholesterol/cholate diet, despite causing a marked decrease of HDL-C[75]. This protection was also observed for LCAT deficiency when present in LDL-receptor-K/O and CETP-transgenic mice placed on high-cholesterol/cholate diet, as well as in apoE-K/O knockout mice on normal chow diet[75]. In all these cases, LCAT deficiency was associated with a significant decrease of apoB-containing lipoproteins. In another study, LCAT-K/O × apoE-K/O mice placed on a high fat diet but without cholate showed instead an increase of atherosclerosis[78]. On this diet, apoB levels increased and cholesteyl esters were enriched in pro-atherogenic saturated fatty acids. In contrast, LCAT-K/O × apoE-K/O mice on a normal chow diet had lower apoB levels and developed less atherosclerosis compared to just apoE-K/O mice[79]. Interestingly, these mice have higher paraoxonase 1 activity and decreased markers of oxidative damage compared to just apoE-K/O mice, presumably because in the absence of LCAT, paraoxonase 1, can relocate from HDL to the abnormal apoB-containing lipoproteins that accumulate with LCAT deficiency. Overall the results from the various animal models, indicate that there is a complex interaction between LCAT and atherosclerosis, which depends on the diet and can be modulated by the other proteins in the RCT pathway, such as CETP and the LDL-receptor. It appears, however, that the anti-atherogenic effect of LCAT more closely correlates with its ability to lower plasma levels of apoB-lipoproteins than on its ability to raise HDL-C.

Human Genetic Disorders of LCAT

Over 60 different mutations in the LCAT gene have been described[80–82], which can lead to two rare autosomal recessive disorders, namely Familial LCAT Deficiency[83,84] (FLD) or Fish-Eye Disease[85] (FED). Both conditions are characterized by low HDL-C and corneal opacities, but FLD subjects have a more severe deficiency of LCAT and can develop other signs and symptoms (Table 2).

FED subjects were first described to have reduced LCAT activity on HDL (alpha-LCAT) but near normal activity on LDL (beta-LCAT), whereas LCAT is nearly absent on both lipoproteins in FLD[86]. Some LCAT mutations have been shown to selectively affect LCAT activity on HDL[87], but not all mutations can be neatly categorized as affecting only the esterification of cholesterol on HDL or LDL, suggesting that some patients with FED may differ from FLD by having more residual LCAT activity on both HDL and LDL[88,89].

FED and FLD subjects can have normal to elevated total cholesterol and triglycerides, and they both present with a similar low level of HDL-C (Table 3).

Although also low in FED subjects, FLD subjects have a much lower ratio of CE/TC because of their greater reduction in LCAT activity. This is consistent with the much lower cholesterol esterification ratio (CER) typically found in FLD compared to FED[86]. The CER assay, which is a measure of LCAT activity based on endogenous lipoproteins, is performed by adding radiolabeled cholesterol to plasma and then determining the rate of

cholesteryl ester formation. LCAT mass can be highly variable, because some mutations will primarily affect enzyme activity but not mass.

Many of the clinical features of these two diseases can be partially explained by the underlying defect in LCAT. As with other disorders of the RCT pathway, such as Tangier disease and apoA-I deficiency[94], cholesterol can accumulate in the cornea of these patients[80,91], most likely as a consequence of decreased cholesterol efflux. A physical examination of the eyes of these subjects will typically reveal a pale cloudy cornea, with a whitish ring around the periphery that is similar to arcus senilis. Typically the corneal deposits do not significantly interfere with vision, but some patients have required corneal transplantation[80]. Hepatosplenomegaly may be a consequence of increased lipid accumulation, possibly from decreased cholesterol efflux but also because of accelerated red blood cell removal. FLD subjects can have normocytic normochromic anemia and abnormal red blood cells shapes, most likely because of a disturbance in the exchange of lipids between red blood cells and the abnormal level and type of lipoproteins in these subjects. Renal disease is the major cause of morbidity and mortality in patients with FLD. Proteinuria can develop in childhood and progresses to nephrotic syndrome typically by the fourth to fifth decade of life[95]. Eventually these patients can develop hypertension and end-stage renal disease, which can be treated by renal transplantation, but the disease can reoccur in the renal allograft[95]. A recent report has suggested that angiotensin-converting enzyme inhibitors, which reduces proteinuria, may be useful in these patients for delaying the progression of the renal disease[96].

LCAT and Cardiovascular Disease

Although CHD has been reported in FLD and FED patients[82,87,90,91,97–101], in many cases they do not develop clinically apparent disease[102] and hence the role of LCAT in the pathogenesis of atherosclerosis has been controversial. Recently, a relatively large study of carriers of LCAT defects have reported not only reduced HDL-C but also a marked increase in C-reactive protein and in intima media thickness (IMT) of the carotid artery. No significant change in IMT was observed in homozygotes, but an increased incidence of CHD was reported when heterozygotes were compared with controls[90–92,103–105]. Similar findings for heterozygous subjects were observed in a 25 years follow-up study of a large Canadian LCAT deficient family and in 13 unrelated Italian families with FLD and FED[81,93]. These results suggest that while heterozygosity for LCAT deficiency is associated with increased IMT and CHD, this may not be true for homozygous subjects, but this could potentially be explained by the low number of homozygous subjects studied. An alternative explantion is that homozygous FLD and FED patients may be partially protected from their low HDL, because they often also have reduced levels of LDL-C compared to heterozygotes and controls[80].

LCAT is not a very polymorphic protein and only a few studies examining genetic variants of the LCAT gene in the general population have been described. A novel P143L SNP with a frequency of about 6% was identified in a Chinese patients with coronary artery disease and was found to be linked with low HDL-C[106]. In contrast, a study of type 2 diabetes found no association between CHD and two other LCAT variants, Arg147Trp and Tyr171Stop[107]. Another LCAT variant, rs2292318, which was initially associated with lower HDL-C in a patient population with CHD, could not be subsequently validated in an independent population sample[108]. The lack of a clear association of LCAT SNPs with CHD may simply be due to lack of prevalent SNPs in the population, the possibility that the SNPs do not alter LCAT activity, and because total variation of HDL-C explained by LCAT SNPs appears to be relatively small[109].

Recently, a study reported greater IMT and elevated LCAT activity in subjects with metabolic syndrome, suggesting that higher LCAT activity may not be beneficial[110]. A similar positive association of LCAT was also observed in patients with angiographically proven CHD[111]. These results are in contrast, however, to multiple earlier papers describing either a negative or no association between LCAT activity and CHD[112–114]. These seemingly contradictory results may potentially be explained by the fact that most of these studies are relatively small and do not examine the other proteins and enzymes in the RCT pathway, which can potentially alter the effect of LCAT on atherosclerosis. For example, low LCAT activity when also linked with elevated levels of pre-beta HDL was associated CHD[115]. Another possible explanation for the contradictory results is that there may be other biochemical markers for the cholesterol esterification process that are better than the *in vitro* LCAT activity assay for assessing the HDL maturation process, such as the fractional esterification rate of apoB-depleted plasma (FER_{HDL})[116,117]. Finally, it is important to note that it is impossible to p determine from epidemiologic studies whether LCAT is playing a causal role in promoting or decreasing atherosclerosis or instead may be being up or down regulated by some sort of compensatory response.

Summary

Although LCAT has been a subject of great interest in cardiovascular research for several decades, we still do not have a clear answer on its role in the pathogenesis of CHD. The preponderance of evidence appears to support the original contention by Glomset[3] that LCAT is an anti-atherogenic factor, but its effect is dependent upon other factors that modulate the RCT pathway, such as CETP. As was observed in mice[70], it is possible that LCAT could be pro-atherogenic for a subset of patients, with a particular lipoprotein disorder or profile that may alter the normal affect of LCAT on CHD. Our incomplete understanding of LCAT has discouraged efforts by drug companies to develop agents to modulate LCAT activity for the treatment of CHD. A small molecule that activates LCAT, however, has recently been described, but it is only in pre-clinical testing[118]. There may also be utility in increasing LCAT levels when reconstituted forms of HDL are infused in patients for the rapid stabilization of patients with acute coronary syndrome[4]. Under these circumstances, LCAT may perhaps become rate limiting and the addition of extra LCAT may potentiate the beneficial effects of the infused HDL. Besides using small molecule activators of LCAT or drugs that may increase the transcription of LCAT, the use of recombinant LCAT protein may be a good strategy for acutely raising LCAT, during HDL therapy[4]. Although it is a rare disorder, recombinant LCAT protein may also be useful as an enzyme replacement therapy agent for the prevention of renal disease in FLD subjects, particularly because of its relatively long half-life[119,120], and the fact that LCAT acts in the plasma compartment and does not need to be delivered to a specific tissue or cellular compartment. Finally, once the complex interaction between LCAT and atherosclerosis is better understood, the measurement of some aspect of LCAT activity could potentially also aid in cardiovascular risk assessment.

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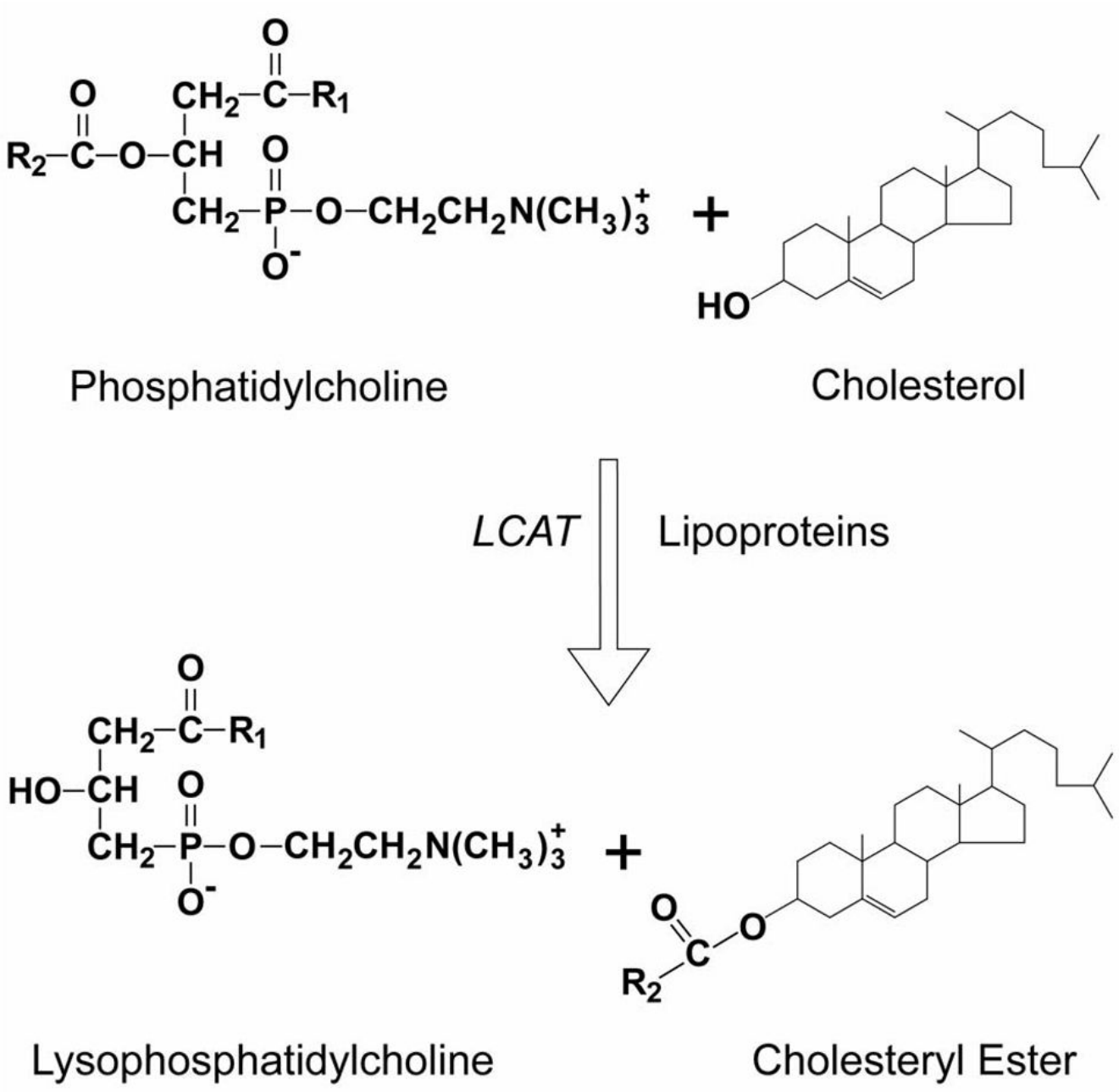

Figure 1. Diagram of the Reverse Cholesterol Transport Pathway

Pre-beta HDL produced, as a consequence of the interaction of apoA-I with the ABCA1 transporter on the liver, obtains additional phospholipid and cholesterol from ABCA1 transporters on peripheral cells, such as macrophages. In addition, HDL can acquire more lipid by other mechanisms, such as from the ABCG1 transporter, the SR-BI receptor or by an aqueous diffusion process. Cholesterol removed from cells by HDL is converted to cholesteryl esters by LCAT, which transforms pre-beta HDL to alpha-HDL. Cholesterol can be directly returned to the liver after uptake by the SR-BI receptor or after transfer to apoB-containing lipoproteins by CETP. Phospholipid transfer protein (PLTP) and hepatic lipase (HL) promote the interconversion alpha-HDL and pre-beta HDL.

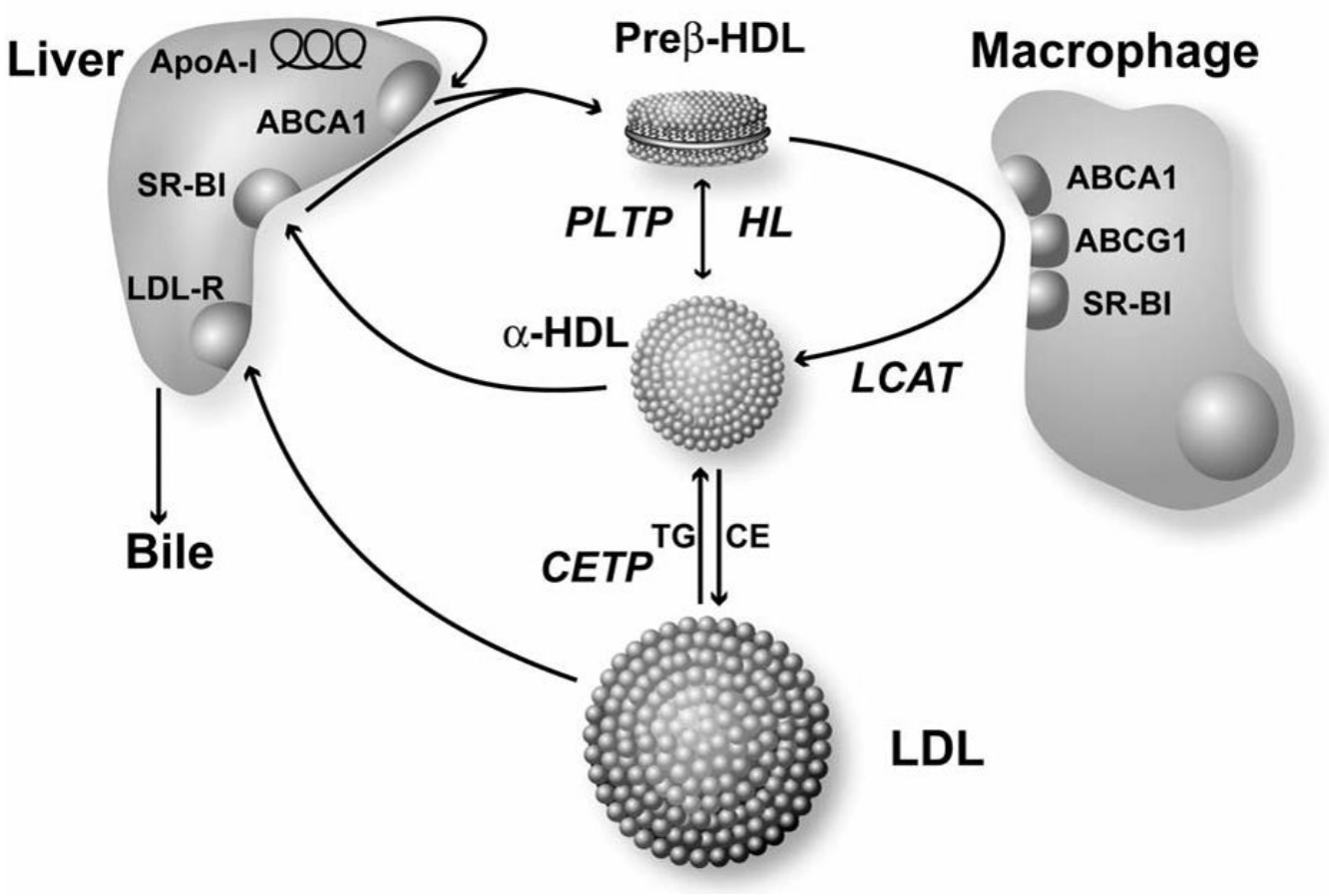

Figure 2. Diagram of the LCAT Reaction

LCAT cleaves the fatty acid (R2) from the sn-2 position of phosphatidylcholine and then transesterifies it to the A-ring of cholesterol, producing lysophosphatidylcholine and cholesteryl ester.

Table 1

Animal models of overexpression or deficit of LCAT.

Species	Model	Construct	Reference
Mice	Transgenic	Genomic hLCAT with its own promoter and 3′-flank	10
Mice	Transgenic	Genomic hLCAT with albumin enhancer and promoter	85
Mice	Transgenic	Genomic hLCAT with its own promoter and 3′-flank	82
Rabbits	Transgenic	hLCAT with its own promoter and 3′-flank region	11
Squirrel monkey	Viral infection	hLCAT in adenovirus	88
Mice	Knockout	Homologous recombination replacement vector	92
Mice	Knockout	Homologous recombination replacement vector	93

Table 2

Clinical Findings in Patients with FLD and FED

Clinical Features	FLD	FED
Corneal opacities	+	+
Anemia	+	−
Target cells in blood	+	−
Proteinuria	+	−
Renal Failure	+	−
Atherosclerosis	−/+	−/+
Hepatosplenomegaly	+	−/+
Lympnadenopathy	+	−/+

Table 3

Plasma Lipids and Lipoprotein Profile in Patients with FED

	FED (range)	Reference Range
TC (mg/dL)	186 (64–253)	120–280
TG (mg/dL)	146 (60–408)	40–250
HDL-C (mg/dL)	9 (0–27)	30–85
Apo A-I (mg/dL)	42 (29–45)	90–190
CE/TC	0.46 (0.57–0.65)	0.67–0.71
CER (nmoL/mL/h)	51 (25–74)	40–80
LCAT mass (μg/mL)	3.5 (0–4)	3.8–6.6

TC: total cholesterol; TG: triglycerides; CE/TC: cholesteryl ester/total cholesterol ratio; LCAT: lecithin:cholesteryl acyltransferase; CER: cholesteryl esterification rate. Data from approximately 15 FLD subjects are shown as mean with range in parenthesis. Modified from re,f 95 with additional data from ref. [105] and 127.

Table 4

Plasma Lipids and Lipoprotein Profile in Patients with FLD

	FLD (range)	Reference Range
TC (mg/dL)	173 (89–323)	120–280
TG (mg/dL)	605 (85–1480)	40–250
HDL-C (mg/dL)	8 (0–16)	30–85
Apo A-I (mg/dL)	39 (36–48)	90–190
CE/TC	0.06 (0.06–0.49)	0.67–0.71
CER (nmoL/mL/h)	1 (0–16)	40–80
LCAT mass (μg/mL)	0.5 (0–2.6)	3.8–6.6

TC: total cholesterol; TG: triglycerides; CE/TC: cholesteryl ester/total cholesterol ratio; LCAT: lecithin:cholesteryl acyltransferase; CER: cholesteryl esterification rate. Data from approximately 50 FLD subjects are shown as mean with range in parenthesis. Modified from ref. [95] with additional data from ref. [105] and 127.