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ATP binding cassette transporter A-I and HDL metabolism: Effects of fatty acids

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Abstract

Ample evidence indicates that dietary fatty acids alters the plasma levels of HDL-C. However, the mechanisms underlying the effects of fatty acids still remain elusive. Recent advances in our understanding of ATP binding cassette transporter A1 (ABCA1) function and regulation have provided a valuable insight into the mechanisms by which fatty acids may affect plasma HDL-C levels. ABCA1 mediates the assembly of phospholipids and free cholesterol with apolipoprotein A-I, which is a critical step for HDL biogenesis. Studies have shown that unsaturated fatty acids, but not saturated fatty acids, repress the expression of ABCA1 in vitro. Although information on mechanisms for the fatty acid-mediated regulation of ABCA1 expression is still limited and controversial, recent evidence suggests that unsaturated fatty acids inhibit the expression of ABCA1 at the transcriptional and posttranscriptional levels. The transcriptional repression of ABCA1 expression by unsaturated fatty acids is likely LXR-dependent. Evidence also suggests that histone deacetylation may play a role in the repression. Posttranscriptionally, unsaturated fatty acids may facilitate ABCA1 protein degradation, which may involve phosphorylation of ABCA1 by protein kinases. Further studies are warranted to better understand the role of dietary fatty acids in HDL metabolism and their effects on cardiovascular health.

Keywords

ATP-binding cassette transporter AI; high density lipoprotein; fatty acids; regulation

1. Introduction

Epidemiological studies have consistently shown a strong inverse relationship between plasma high-density lipoprotein cholesterol (HDL-C) concentrations and the incident of coronary heart disease (CHD). High-density lipoproteins (HDL) are known to be antiatherogenic as they play a key role in reverse cholesterol transport (RCT), inhibit cytokine-induced expression of adhesion molecules by endothelial cells, and prevent the oxidation of low-density lipoproteins (LDL). In particular, the RCT pathway, by which excess cholesterol is delivered from the periphery to the liver for excretion, is considered to be a primary mechanism for the cardioprotective effect of HDL.

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HDL particles present in human plasma are heterogeneous and classified based on density, size, electrophoretic mobility, and apolipoprotein content. Apolipoprotein A-I (apoA-I) is a structurally and functionally important component of HDL particles and accounts for ~80% of the total protein in the particle. By functioning as an acceptor of cholesterol and phospholipid effluxed from cells and as an activator of lecithin:cholesterol acyltransferase (LCAT), apoA-I plays a critical role in RCT. Lipidation of apoA-I with phospholipid and cholesterol produces discoidal pre β -HDL particles that migrate to the pre- β position on agarose gel electrophoresis. Earlier, the pre β -HDL particles were thought to be produced in the circulation during remodeling of spherical mature HDL by cholesteryl ester transfer protein (CETP), phospholipid transfer protein (PLTP) and hepatic lipase. However, studies showed that the pre β -HDL are nascent HDL particles that are subsequently transformed into mature spherical HDL particles by the action of LCAT. The mature HDL particles are further remodeled during circulation by CETP and PLTP. Although the formation of pre β -HDL is a prerequisite step toward the formation of mature HDL particles, the process has been obscure until the discovery of ATP-binding cassette transporter AI (ABCA1).

Current evidence indicates that ABCA1 is the major determinant for the formation of pre β -HDL and hence plasma HDL-C concentrations. Among many dietary factors, dietary fat or fatty acids have long been known to alter the metabolism and circulating levels of LDL and HDL. Key and Hegsted et al. first developed predictive equations for changes in plasma total cholesterol concentrations in response to dietary fatty acids and cholesterol. The equations indicated that in general, most saturated fatty acid (SFA) are hypercholesterolemic, whereas stearic acid and monounsaturated fatty acids (MUFA) are neutral or mildly hypocholesterolemic, and polyunsaturated fatty acids (PUFA) are hypocholesterolemic. The equations also provided insight into how dietary fatty acids may alter cholesterol levels in different lipoprotein classes including LDL and HDL [22, 23]. However, the relative contributions of changes in these lipoproteins by dietary fatty acids to CHD risk have not been fully resolved. More recent studies have shown that dietary fatty acids may alter the formation and metabolism of HDL by modulating the expression of ABCA1 that facilitates the efflux of cellular phospholipid and cholesterol to extracellular acceptors such as apo A-I. This review focuses on the regulation of ABCA1 expression and potential mechanisms by which fatty acids alter ABCA1 expression and plasma HDL-C.

2. Dietary fatty acids and HDL-C

Studies with non-human primates and humans showed that isocaloric substitution of n-3 PUFA for SFA decreased plasma total cholesterol, LDL-C, and HDL-C. Also, in African green monkeys fed atherogenic diets containing PUFA, the plasma levels of total cholesterol and HDL-C as well as apoA-I were significantly decreased, compared with animals fed SFA and MUFA. A meta-analysis of 60 controlled trials with human subjects indicated that SFA, MUFA and PUFA significantly increased plasma HDL-C when they replaced carbohydrate. However, the increase was the least with PUFA. Predictive equations based on several meta-analyses of human studies also support the similar effect of fatty acid classes on plasma HDL-C. Additionally, a recent study with human subjects showed that plasma HDL-C levels were decreased in subjects consuming a PUFA-rich diet, compared with a SFA-rich diet. Thus, the above-cited studies support the notion that in general, PUFA lower HDL-C relative to SFA and MUFA and are least effective in raising HDL-C with its isocaloric substitution for carbohydrates. However, further studies are needed to evaluate effects of individual fatty acids on plasma HDL-C using a fatty acid as a reference for comparison. This is an important area that requires further evaluation, particularly, in relation to their effects on mechanisms of HDL assembly/biogenesis and, ultimately, plasma HDL-C.

3. ABCA1 and HDL metabolism

3.1. Role of ABCA1 in HDL formation

In 1961, Fredrickson et al. reported a new malady discovered in Tangier island of Chesapeake Bay in Virginia and the disease was named as Tangier disease. Individuals with Tangier disease have severe HDL deficiency with less than 5% of normal plasma HDL-C levels and higher incidence of premature CHD. Etiology of the disease was identified in the late 1990's that mutations in the gene encoding ABCA1 present in Tangier patients are responsible for the extremely low plasma HDL-C. Subsequent studies with mice [39, 40] and chickens lacking ABCA1 [41, 42] demonstrated that the animals also exhibit HDL and apoA-I deficiencies, substantiating a pivotal role of ABCA1 in HDL formation.

ABCA1 is an integral membrane protein consisting of twelve transmembrane domains and two ATP-binding domains. The primary function of ABCA1 is to facilitate the efflux of cellular phospholipid and cholesterol to extracellular acceptors. Interaction of apoA-I, the major protein in HDL particles, with ABCA1 produces pre β -HDL. Lipid-free or lipid-poor apoA-I is the initial acceptor of cellular phospholipid and cholesterol in ABCA1-mediated efflux.

In several studies, the formation of heterogeneous nascent pre β -HDL particles was observed during incubation of apoA-I with Chinese hamster ovary (CHO) cells and THP-1 macrophages, presumably by the interaction of apoA-I with cell surface binding sites or through retroendocytosis. In J774 macrophages, in which ABCA1 expression was up regulated by cAMP, the presence of extracellular apoA-I induced formation of 9 and 12 nm sizes of particles containing ~3:1 and 1:1 phospholipid/free cholesterol (mol/mol), respectively. The interaction of apoA-I with ABCA1 under in vitro conditions produces pre β migrating nascent HDL subpopulations (pre β_1 to pre β_4) that vary in size, lipid and apoA-I content. The differing sizes of pre β HDL have different metabolic fates depending on the degree of lipidation; less lipidated pre β_1 HDL are destined to be rapidly removed from the circulation by kidney, whereas other pre β HDL with more lipid are able to participate in the maturation process. The studies suggest that lipidation of apoA-I via the interaction with ABCA1 is an essential initial step for the formation of HDL that ultimately determines plasma HDL-C levels.

3.2. Sites of HDL formation

ApoA-I is primarily synthesized in the liver and intestine that highly express ABCA1. Thus, it is reasonable to expect that liver and intestine have a major role in producing nascent HDL and modulating plasma HDL-C levels. Several strategies have been tried to determine the contribution of hepatic ABCA1 to plasma HDL-C levels. When human ABCA1 was overexpressed in mouse liver and macrophages under the control of apolipoprotein E promoter, plasma HDL-C and apoA-I were increased in the transgenic mice with an elevation in pre β -HDL particles. Given the minimal effect of macrophage ABCA1 on HDL-C levels, the human ABCA1 overexpressed in the mouse liver was likely responsible for the increased HDL-C levels. To further define the role of hepatic ABCA1 expression on plasma HDL-C, Basso et al. infused adenovirus expressing ABCA1 into mice. The hepatic overexpression of ABCA1 by this method induced apoA-I-dependent cholesterol efflux from primary hepatocytes and also increased plasma HDL-C and apoA-I levels. Another study employing adenoviral-mediated overexpression of human ABCA1 in the liver also showed an increase in plasma HDL-C. To examine the role of the intestine in HDL biogenesis, Murthy et al. demonstrated that in Caco-2 cells, ABCA1 mRNA expression and cholesterol efflux from the basolateral membrane to apoA-I or HDL particles were enhanced by liver X receptor (LXR)/retinoid X receptor (RXR) activation, suggesting that ABCA1

plays an important role in intestinal HDL production. The role of ABCA1 in the formation of HDL particles was further studied by using mice with tissue-specific deletion of *Abca1* gene [57]. Mice with liver-specific *Abca1* knockout (*Abca1*^{-/-}) mice exhibited marked reductions in plasma HDL-C and apoA-I by ~80% and 98%, respectively, compared with the wild-type. The deletion of intestinal *Abca1* gene elicited ~30% reduction in plasma HDL-C and the mice without functional ABCA1 in both liver and intestine had only ~10% of the wild-type plasma HDL-C levels. These studies strongly suggest that liver and intestine are quantitatively the most important sites for producing and modulating plasma HDL-C levels (Figure 1).

Macrophages were presumed to play a role in HDL formation. However, the role of macrophage ABCA1 in maintaining the plasma HDL-C pool is considered minimal. Mice expressing ABCA1 only in macrophages and those with selected inactivation of ABCA1 in macrophages were generated using bone marrow transplantation. Restoration of macrophage ABCA1 by transplantation of the wild-type bone marrow into in *Abca1*^{-/-} mice minimally increased plasma HDL-C and apoA-I levels, whereas mice with the selective inactivation of ABCA1 in macrophages had normal HDL-C levels. Furthermore, *Abca1* deletion in macrophages did not alter plasma HDL-C levels in mice, supporting that macrophage ABCA1 is not a major contributor to plasma HDL-C levels. Thus, it is evident that the liver and intestine produce nascent pre β -HDL particles that function as an acceptor of cellular cholesterol in the RCT pathway and that ABCA1-mediated efflux from macrophages to lipid-free apoA-I plays a quantitatively less important role in RCT.

3.3. Role of ABCA1 in HDL catabolism

As discussed above, a large body of evidence has shown that ABCA1 plays a pivotal role in HDL formation, particularly, in the liver and small intestine. In addition, hepatic ABCA1 is thought to be involved in the catabolism of HDL particles as well. An *in vivo* kinetic study demonstrated that liver-specific *Abca1*^{-/-} mice has a significantly higher fractional catabolic rate of ¹²⁵I-radio labeled mature HDL as well as lipid-free apoA-I than the wild-type counterparts, suggesting that HDL catabolism occurs at a faster rate in the absence of hepatic ABCA1. The tracer uptake by the liver was not different between liver specific *Abca1*^{-/-} mice and the wild type, where as a significantly higher tracer up take by the kidney was noted in the liver specific *Abca1*^{-/-} mice. Based on the observations, it is presumed that ABCA1 is critical in lipidating not only newly-synthesized apoA-I, but also apoA-I released from mature HDL. Thus, in the absence of ABCA1, apoA-I generated in the liver would fail to acquire lipid and consequently be rapidly cleared by the kidney without being recycled.

4. Regulation of ABCA1 by fatty acids

4.1. Regulation of ABCA1 expression

Transcription of ABCA1 is primarily under the control of liver X receptors (LXR), a major transcription factor that senses high cellular cholesterol levels and triggers the expression of genes involved in the removal of excess cholesterol from the cells. Considering the critical role of ABCA1 in the efflux of cellular cholesterol, it is not surprising that the expression of ABCA1 is under control of LXR at the transcriptional level. LXR is a ligand-activated transcription factor that forms a heterodimer with retinoid X receptor (RXR) to transactivate gene expression. Evidence shows the presence of a *cis*-element for LXR/RXR heterodimer binding in the *Abca1* promoter and up-regulation of ABCA1 expression by LXR results in a concomitant increase in cellular cholesterol efflux to apoA-I.

ABCA1 protein levels do not always correlate with ABCA1 mRNA, suggesting the presence of posttranscriptional regulation. The turnover of ABCA1 protein is rapid with a half-life of

less than 1 hr in macrophages, which indicates posttranscriptional regulation of ABCA1 could be an important determinant for its function. Binding of helical apolipoproteins, e.g. apoA-I and apoA-II, but not HDL, to ABCA1 retarded the degradation of ABCA1 protein in THP-1 cells by protecting ABCA1 from degradation by a thiol protease. Wang et al. identified a sequence rich in proline, glutamic acid, serine and threonine (PEST) present in the cytoplasmic region of ABCA1, which facilitated ABCA1 protein degradation by calpain protease. The presence of extracellular apoA-I abolished the effect of calpain protease and increased efflux of phospholipids and cholesterol. The finding suggests that a positive feedback regulation of ABCA1 protein expression exists where the interaction of apoA-I with ABCA1 inhibits PEST sequence-mediated calpain proteolysis, consequently increasing the efflux of cellular phospholipid and cholesterol to apoA-I. Subsequently, the same research group reported that phosphorylation of the PEST sequence in ABCA1 protein directed the protein to calpain proteolysis whereas extracellular apoA-I diminished the phosphorylation of PEST sequence, resulting in increased cell surface expression of ABCA1. Although phosphorylation of Thr-1286 and Thr-1305 in the PEST sequence of ABCA1 increases the protein degradation by calpain, ABCA1 protein levels are positively correlated with its phosphorylation in THP-1 cells. Therefore, the regulation of ABCA1 protein levels via phosphorylation likely depends on the sites of phosphorylation in the protein.

4.2. Transcriptional regulation of ABCA1 by fatty acids

Considerable evidence exists that fatty acids modulate the expression of ABCA1 and potentially influence plasma HDL-C levels. In LXR or RXR ligand-treated HepG2 cells and RAW264.7 macrophages, unsaturated fatty acids reduced the expression of ABCA1 mRNA and protein with a concomitant decrease in cholesterol efflux, where as palmitic acid failed to diminish ABCA1 expression and activity. Also, in human monocyte-derived macrophages, ABCA1 mRNA abundance was significantly decreased by linoleic acid whereas palmitic acid significantly increased its expression compared with control. In mouse small intestinal epithelial cells, MUFA and PUFA such as oleic, linoleic, linolenic and docosahexaenoic acids significantly reduced ABCA1 mRNA abundance, where as SFA such as palmitic and stearic acids did not alter its expression. The repressive effect of unsaturated fatty acids on ABCA1 mRNA was also observed in vivo. In duodenal mucosal cells of dogs, PUFA-rich diet significantly down-regulated ABCA1 mRNA expression. Similarly, ABCA1 mRNA levels were significantly reduced in the small intestines of SV129 mice gavaged with triacylglycerols of unsaturated fatty acids.

Further, mutations or deletion of direct repeat 4, a *cis*-acting element for LXR/RXR heterodimer binding, in *Abca1* promoter abolished the suppressive effects of unsaturated fatty acids on its expression in RAW 264.7 macrophages, suggesting that unsaturated fatty acids inhibit ABCA1 expression in an LXR-dependent manner. However, their precise modes of action are not well understood. In our recent study, we observed that unsaturated fatty acids significantly reduced ABCA1 mRNA levels in RAW 264.7 macrophages but the repression was completely abolished in the presence of an LXR agonist. This finding further supports that the effect of unsaturated fatty acids on ABCA1 expression is likely LXR-dependent.

In addition, our recent finding suggests the possibility that histone acetylation/deacetylation may be involved in the transcriptional regulation of ABCA1. We observed that trichostatin A, a pan-histone deacetylase (HDAC) inhibitor, reversed the linoleic acid-induced reduction in ABCA1 mRNA in macrophages. Histone is a component of nucleosome, a unit of chromatin, and its posttranslational modifications, e.g., acetylation and methylation, largely influence gene expression. In general, transcriptionally active DNA regions are associated with hyperacetylated histone 3 and 4, resulting in local expansion of chromatin for increased

accessibility of regulatory proteins to DNA. Certain HDACs, HDAC3 in particular, have shown to be actively involved in transcriptional regulation of genes as a component of a corepressor complex, commonly consisting of nuclear hormone receptor corepressor (NCoR) or silencing mediator of retinoid and thyroid hormone receptors (SMRT). Interestingly, LXR is one of the transcription factors that have been shown to interact with the corepressor complex for the transcriptional repression. HDACs are subject to posttranslational modifications, such as acetylation, phosphorylation, ubiquitination, and sumoylation, that determine stability, localization, activity, and protein-protein interaction. As such, the modifications are important determinants for HDAC activity. Our preliminary data [73], together with the available information above cited, suggest that the LXR-dependent transcription repression of ABCA1 by unsaturated fatty acids may be mediated at least partly via posttranslational modifications in an HDAC as a component of a corepressor complex associated with a LXR/RXR heterodimer in the promoter of *Abca1*. Further studies are warranted to identify a specific HDAC isoform(s) involved and to determine the modes of action for the regulation of HDAC activity by fatty acids and consequently ABCA1 expression. Hypothetical regulatory mechanisms for the transcriptional repression of ABCA1 by unsaturated fatty acids are summarized in Figure 2.

4.3. Posttranscriptional regulation of ABCA1 by fatty acids

Wang et al. first showed that in cAMP-activated murine macrophages, unsaturated fatty acids decreased ABCA1 protein levels, lowering the efflux of free cholesterol and phospholipid to lipid-free apoA-I, whereas SFA did not. The decrease in ABCA1 by unsaturated fatty acids was attributed to increased ABCA1 protein turnover, but not to the modulation of transcription, mRNA decay, or impaired translation efficiency. Wang et al. further demonstrated that when macrophages were incubated with LXR/RXR agonists, treatment with SFA also increased ABCA1 protein degradation and reduced the efflux of cholesterol and phospholipid to apoA-I to a similar extent to that observed with unsaturated fatty acids. Facilitated ABCA1 protein degradation by SFA in the presence of LXR agonists was due to the increased expression of stearyl-CoA desaturase that converts SFA to MUFA. In HepG2 cells, MUFA such as palmitoleic and oleic acids as well as linoleic acid, significantly reduced ABCA1 protein levels and cholesterol efflux compared with palmitic acid, but without altering mRNA abundance. In Caco-2 cells incubated with LXR agonists, PUFA decreased the efflux of cholesterol from the basolateral membrane and the effects of fatty acids were mediated primarily by decreased ABCA1 protein with minimal change in mRNA levels. In HepG2 cells as well as FHs 74 Int cells, a human small intestine cell line, we observed ABCA1 protein levels were diminished by unsaturated fatty acids without a change in mRNA levels, compared with SFA (unpublished data). The reduction was greater with PUFA, such as linoleic acid and eicosapentaenoic acid (EPA), than with MUFA.

The enhanced degradation of ABCA1 protein by unsaturated fatty acids was shown to be mediated through serine phosphorylation of ABCA1 by intracellular unsaturated acyl-CoA derivatives generated by the activation of phospholipase D2. Also, chemical inhibition with rottlerin and genetic inhibition using small interfering RNA (siRNA) of protein kinase C delta (PKC δ) abolished the ABCA1-destabilizing effects of unsaturated fatty acids, suggesting that serine phosphorylation of ABCA1 by PKC δ may be partly responsible for the facilitated degradation of ABCA1 protein by unsaturated fatty acids. However, in RAW 264.7 macrophages, we were not able to observe the similar role of PKC δ in the reduction of ABCA1 protein by unsaturated fatty acids. In our study, knock down of PKC δ by ~80% using siRNA did not reverse the linoleic acid-induced reduction in ABCA1 protein. Rather, when PKC δ was knocked down, ABCA1 protein was reduced in control, palmitic acid and linoleic acid-treated cells, suggesting that PKC δ may not be involved in the fatty acid regulation of the protein, but play a role in stabilization of ABCA1 protein. A potential

involvement of protein kinase A (PKA) in the regulation has also been suggested. EPA was shown to significantly destabilize ABCA1 protein and reduce ABCA1-dependent cholesterol efflux without altering ABCA1 mRNA expression in THP-1 cell-derived macrophages, but the activation of PKA attenuated the repressive effect of EPA without affecting ABCA1 degradation rate. Interestingly, in contrast to RAW 264.7 macrophages in which unsaturated fatty acids reduced ABCA1 expression at the transcriptional as well as posttranscriptional level, only ABCA1 protein levels were reduced by unsaturated fatty acids with a minimal effect on mRNA abundance in HepG2 cells. Therefore, cell type-specific regulation of ABCA1 expression by fatty acids is likely present. Although the mechanisms still remain unclear, evidence thus far suggests that the degradation/stabilization of ABCA1 protein involves several protein kinases. Further studies are necessary to identify types of kinases and phosphorylation sites in ABCA that are sensitive to the regulation by fatty acids.

4. Conclusion

Current evidence indicates that ABCA1, particularly in the liver and intestine, plays a critical role in the formation and metabolism of HDL. Newly secreted apoA-I from the liver and small intestine acquires phospholipid and cholesterol via the interaction with ABCA1, producing nascent HDL particles that subsequently undergo the process of maturation. As such, nascent HDL formation via ABCA1 is critical in RCT. Although the mechanisms involved in the regulation of ABCA1 are not well understood, considerable evidence from in vitro studies indicates that unsaturated fatty acids reduce ABCA1 expression at the transcriptional as well as posttranscriptional levels as depicted in Figure 2. The inhibitory effect of unsaturated fatty acids, PUFA in particular, on ABCA1 expression and HDL formation is contradictory to a well-known atheroprotective effect of oleic acid and PUFA compared with SFA. Atheroprotection imparted by MUFA and PUFA, however, may be attributable to their favorable effects on very-low density lipoproteins, LDL, plasma triglyceride, anti-inflammation, and anti-thrombosis. These benefits could outweigh the inhibition of ABCA1 expression by these fatty acids in protecting against atherosclerosis. Further studies are needed to verify the inhibition of ABCA1 expression by individual unsaturated fatty acids under in vivo conditions and to elucidate the mechanisms involved. Nonetheless, the diminished ABCA1 expression by unsaturated fatty acids could account at least in part for lower HDL-C levels by unsaturated fatty acid than SFA.

Abbreviations

ApoA-I	apolipoprotein A-I
ABCA1	ATP binding cassette transporter A1
CETP	cholesterol ester transfer protein
CHD	coronary heart disease
EPA	eicosapentaenoic acid
HDAC	histone deacetylase
HDL	high-density lipoprotein
HDL-C	HDL cholesterol
LCAT	lecithin:cholesterol acyltransferase
LDL	low-density lipoprotein
LDL-C	LDL cholesterol

LXR	liver X receptor
MUFA	monounsaturated fatty acids
NCoR	nuclear hormone receptor corepressor
PEST	proline, glutamic acid, serine and threonine
PKA	protein kinase A
PKCδ	protein kinase C δ
PLTP	phospholipid transfer protein
PUFA	polyunsaturated fatty acids
RCT	reverse cholesterol transport
RXR	retinoid X receptor
SFA	saturated fatty acids
siRNA	small interfering RNA
SMRT	silencing mediator of retinoid and thyroid hormone receptors
SR-BI	scavenger receptor type B, class I

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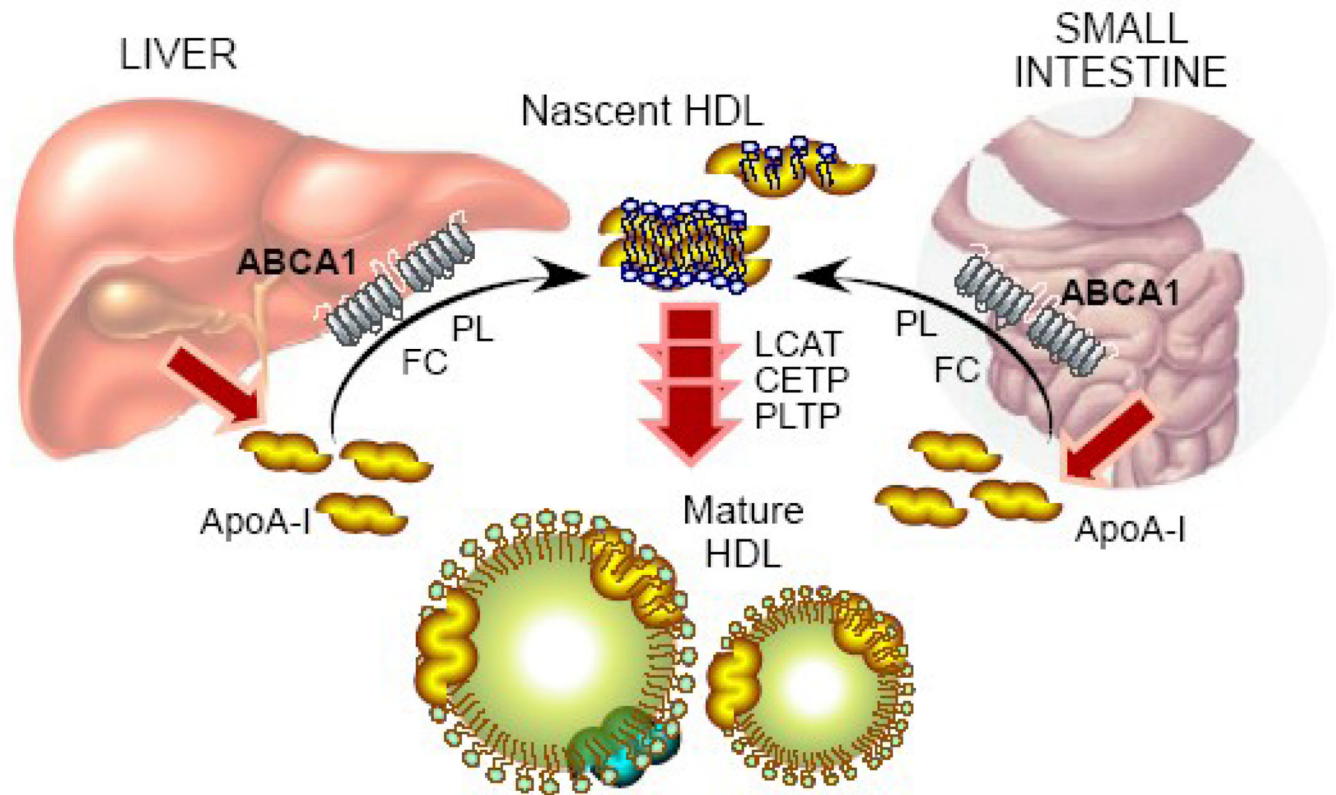


Figure 1. Role of ABCA1 in HDL formation

Newly secreted apoA-I from the liver and small intestine interacts with ABCA1 and acquires phospholipids (PL) and free cholesterol (FC). The lipidation of apoA-I produce nascent HDL that subsequently undergoes maturation process by several factors including LCAT, CETP and PLTP to become spherical HDL.

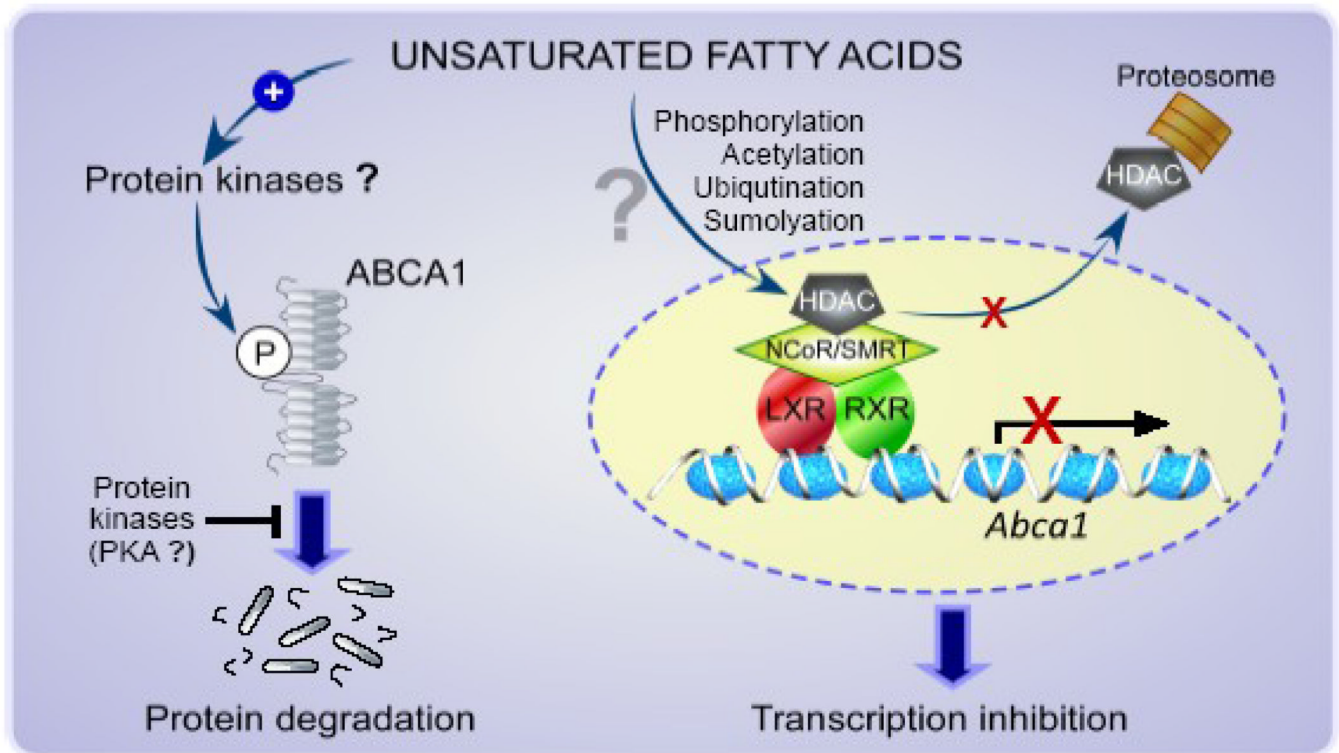


Figure 2. Hypothetical mechanisms for the regulation of ABCA1 expression by unsaturated fatty acids

Post-transcriptional regulation of ABCA1 by unsaturated fatty acids may also occur via mechanisms involving protein kinases that phosphorylate (P) ABCA1 to facilitate the protein degradation. In contrast, other types of kinases such as PKA may inhibit the action of unsaturated fatty acids and stabilize the protein. Unsaturated fatty acids may also repress ABCA1 transcription in a LXR-dependent manner. Activity or recruitment of an HDAC as a component of NCoR/SMRT corepressor complex that is associated with a LXR/RXR heterodimer in the promoter of *Abca1* may be altered by unsaturated fatty acids via post transcriptional histone modifications, such as phosphorylation, acetylation, ubiquitination and sumoylation.