High-density lipoprotein synthesis and metabolism (Review)

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Received September 3, 2014; Accepted March 26, 2015

DOI: 10.3892/mmr.2015.3930

Abstract. High density lipoproteins (HDL) are heterogeneous particles regarding their size and composition. They have vital functions in reverse cholesterol transport (RCT). RCT occurs when lipid-free apolipoprotein AI recruits cholesterol and phospholipid to form nascent HDL particles. Adenosine triphosphate-binding cassette transporters and scavenger receptor class B type I were found to be associated with the synthesis of HDL. Experimental studies have identified several potential anti-atherogenic effects of HDL, including promotion of macrophage cholesterol outflow as well as anti-inflammatory and anti-thrombotic effects. HDL can also transport microRNAs. This review mainly summarizes the present knowledge of HDL synthesis and metabolism.

Contents

1. Introduction

HDL are heterogeneous particles regarding their size and composition. Compared with other lipoproteins, they have the highest relative density while being smallest in size. HDL have an important role in carrier in reverse cholesterol transport (RCT) and act as a carrier of cholesterol back to the liver. They effectively function in homeostasis and lipid metabolism.

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Key words: high-density lipoprotein, scavenger receptor class B type I, adenosine triphosphate-binding cassette sub-family A member 1, reverse cholesterol transport

2. Sub-types of high-density lipoproteins

HDL is mainly secreted by the liver and small intestines. The liver, which secretes ~70-80% of the total HDL in plasma, is the main source of HDL in the circulation. Apolipoprotein (apo)AI is the major structural protein and constitutes the framework of HDL to bear phospholipids and cholesterol. In addition to apoAI, several other apolipoproteins (for example, apoAII, apoAIV, apoB, apoCI and apoCII) contribute to the composition of HDL (1-3). HDL particles are highly uniform and can be divided into several sub-types based on their composition proteins or bulk density.

Classification by apoAII content. In HDL, the content of apoAII content is lower than that of apoAI. HDL particles can be divided into two sub-types according to whether they contain apoAII. HDL of the LPAI category contain apoAI but not apoAII, while HDL of the LPAI:AII category contain apoAI as well as apoAII.

To date, the difference between the two HDL subtypes regarding their function has remained to be fully elucidated. In human HDL, the small and dense apoAII-enriched HDL can stimulate paraoxonase1, platelet-activating factor acetyl-hyokolase, lipoprotein-associated phospholipase A2 and lecithin cholesterol acyltransferase (LCAT) activity and exert a higher anti-LDL-oxidative effect, as compared with HDL that does not contain apoAII (4). In human apoAII transgenic mice, apoAII-rich HDL was shown to reduce very low density protein (VLDL) oxidation to enhance the anti-oxidant effects of HDL (5).

Classification by buoyant density. Mature HDL can be divided into two subtypes, based on their buoyant density: HDL2 (1.063 g/ml<d<1.125 g/ml) and HDL3 (1.125 g/ml<d<1.210 g/ml) (6). Using the method of gradient gel electrophoresis, they can be divided into five sub-types: HDL2a (8.8-9.7 nm), HDL2b (9.7-12.9 nm), HDL3a (8.2-8.8 nm), HDL3b (7.8-8.2 nm) and HDL3c (7.2-7.8 nm). They can also be classified using non-denaturing two-dimensional gel electrophoresis: pre-β HDL: pre-β1HDL (d=5.6 nm) and pre-β2HDL (d=12.0-14.0 nm); αHDL: α1HDL (d=11.0 nm), α2HDL (d=9.2 nm), α3HDL (d=8.0 nm) and α4HDL (d=7.4 nm).

Pre-β1 HDL particles are most efficient in interacting with adenosine triphosphate-binding cassette sub-family A member 1 (ABCA1) to promote cholesterol efflux from cells

to form nascent HDL. By contrast, α1 HDL mainly interact with the liver scavenger receptor B1 to deliver cholesterol back to the liver. Intermediate-sized α3 HDL mostly interact with ABCG1 to induce cellular cholesterol efflux onto spherical HDL particles which contain apoAI and apoAII (7,8).

3. Factors associated with HDL synthesis

ApoAI. ApoAI has a pivotal role in the HDL assembly process. ApoAI is the structural protein of HDL, which constitutes the skeleton of HDL and accounts for ~70% of HDL. ApoAI is the major carrier of HDL and, importantly, acts as the acceptor of cholesterol from cells. The apoAI molecule is a single-chain polypeptide of 243 amino acid residues, consisting of a series of tandem-repeated amino acid fragments containing 22 polymers or 11 polymers of amino acids, and has a double α-helix structure. The double α-helix structure has a high affinity to lipids and is the structural foundation of ABCA1 and scavenger receptor class B type I (SR-BI) to identify apoAI. A study confirmed that the apoAI molecule's hydrophobic α-helix is indispensable for apoAI to form high-affinity adducts with lipids (9).

The monomeric form of apoAI is present in the plasma, which is called lipid-poor apoAI or pre-β1HDL. It can be esterified with lipids discarded by cells to form nascent HDL particles. Esterification of ApoAI with the lipids, whose efflux is mediated by ABCA1, is the rate-limiting step of HDL formation in body. Like mature HDL, the nascent HDL is heterogeneous in size and lipid content. Each new particle contains 2, 3 or 4 apoAI molecules and is disc-shaped. The nascent HDL is subsequently transformed into mature HDL (10).

ApoAI is necessary for HDL assembly. Only in the presence of apoAI, ABCA1 can mediate the efflux of cholesterol in hepatocytes effectively. In C57/BL mice overexpressing human apoAI, which were fed a methionine-choline deficiency diet (MCD) for 1 week, lipid accumulation in the liver was alleviated compared with that in control mice injected an empty vector (1). ApoAI overexpression significantly reduced lipid deposition in the liver, inhibiting the formation and development of fatty liver.

Extracellular lipid-poor apolipoprotein (mainly apoAI) is a essential for ABCA1-induced lipid efflux. ApoAI can stabilize ABCA1 by inhibiting the proline-, glutamic acid-, serine- and threonine- (PEST) dependent proteolysis of calpain. Following combination of apoAI with ABCA1, ABCA1 undergoes conformational changes. These changes reduce calpain proteolysis by restrainting the cohesion of calpain and PEST to steady the structure of ABCA1 and to mediate lipid efflux (11).

ABCA1. ABCA1 has an important role in the formation of HDL. In In the plasma of ABCA1 knockdown mice, HDL cannot be detected at all (12). After liver-specific ABCA1 knockout in mice, HDL was decreased by almost 83% in the blood, which shows that the liver is the major source of HDL in the circulation (1).

ABCA1 is a member of the ABC superfamily, which includes a total of seven subfamilies termed ABCA-G. In cells, ABCA1 mainly localizes on the cellular membrane, which is the requirement for ABCA1 to act as a lipid efflux carrier. In fact, ABCA1 has a symmetrical structure with a transmembrane domain, and which is a tandem repeat sequence containing six transmembrane segments and a nucleotide-binding domain. In this domain, the ATP binding site is a nucleotide domain providing the energy required for transmembrane transport. ABCA1 also has an N terminal and two large extracellular loops. 40 amino acid sequences of the N terminal are highly conserved (13). An ABCA1 mutation is present in patients with Tangier disease (TD) and familial HDL deficiency. These mutations occur in the N-terminal binding region of ABCA1 and ultimately lead to a significant decrease of HDL levels in the blood of patients (14,15).

The main role of ABCA1 is to transport intracellular free cholesterol and phospholipids to extracellular lipid-poor apolipoprotein (primarily apoAI) to assemble nascent HDL (i.e. pre-βHDL). LCAT can convert free cholesterol in nascent HDL into cholesterol ester (CE) in order to ultimately form mature HDL. Mature HDL, under the effect of cholesterol ester transfer protein (CETP), exchanges nuclear CE with triglyceride (TG) from LDL and VLDL, turning into TG-rich HDL (16).

At present, the concrete mechanisms of ABCA1-mediated lipid efflux are elusive. Certain studies have suggested that ABCA1 is localized in and promotes lipid efflux from a membrane lipid domain distinct from cholesterol- and sphingomyelin-rich rafts (17). ABCA1-mediated lipid efflux does not dependent on the density of raft and nonraft domains, but on the cell type. In different cell types, ABCA1-mediated cholesterol efflux and phospholipid efflux are not parallel (18,19). Studies have shown that stearyol CoA desaturase (SCD) can adjust ABCA1-mediated lipid efflux in cells (20). When ABCA1 and SCD are co-expressed in cells, ABCA1-mediated free cholesterol efflux decreases, while ABCA1-mediated phospholipid efflux to apoAI does not change; however, high SCD also increases non-ABCA1-dependent free cholesterol efflux to HDL2.

ABCG1. ABCG1 is also a member of the ABC superfamily. In contrast to ABCA1, ABCG1 is half transporter and equivalent to half of the ABCA1 structure, which is a functional dimer (21). ABCG1 alone cannot transport free cholesterol to apoAI, but requires phospholipid (PL)-containing receptors, such as HDL or PL-apoAI disk-like structures. ABCG1 in peripheral tissues and cells can cooperate with ABCA1 to complete the reverse cholesterol transport (22,23).

According to the current understanding, the role of ABCG1 is to induce free cholesterol efflux from cells and to inhibit excessive lipid accumulation in hepatocytes and macrophages (24,25); furthermore, ABCG1 inhibits the transport of acetylated LDL into monocytes and the differentiation of monocytes into macrophages (26), which has a synergistic effect with HDL and delays oxidative LDL-mediated macrophage apoptosis, therefore exerting a protective function (27).

LCAT. LCAT is a key enzyme in lipoprotein metabolism, which also has acyltransferase and phospholipase A2 activity. It has an important role in maintaining cholesterol homeostasis and regulating cholesterol transport in the circulation. LCAT is mostly synthesized by the liver and then secreted into the blood. In the circulation, LCAT is present as a free molecule

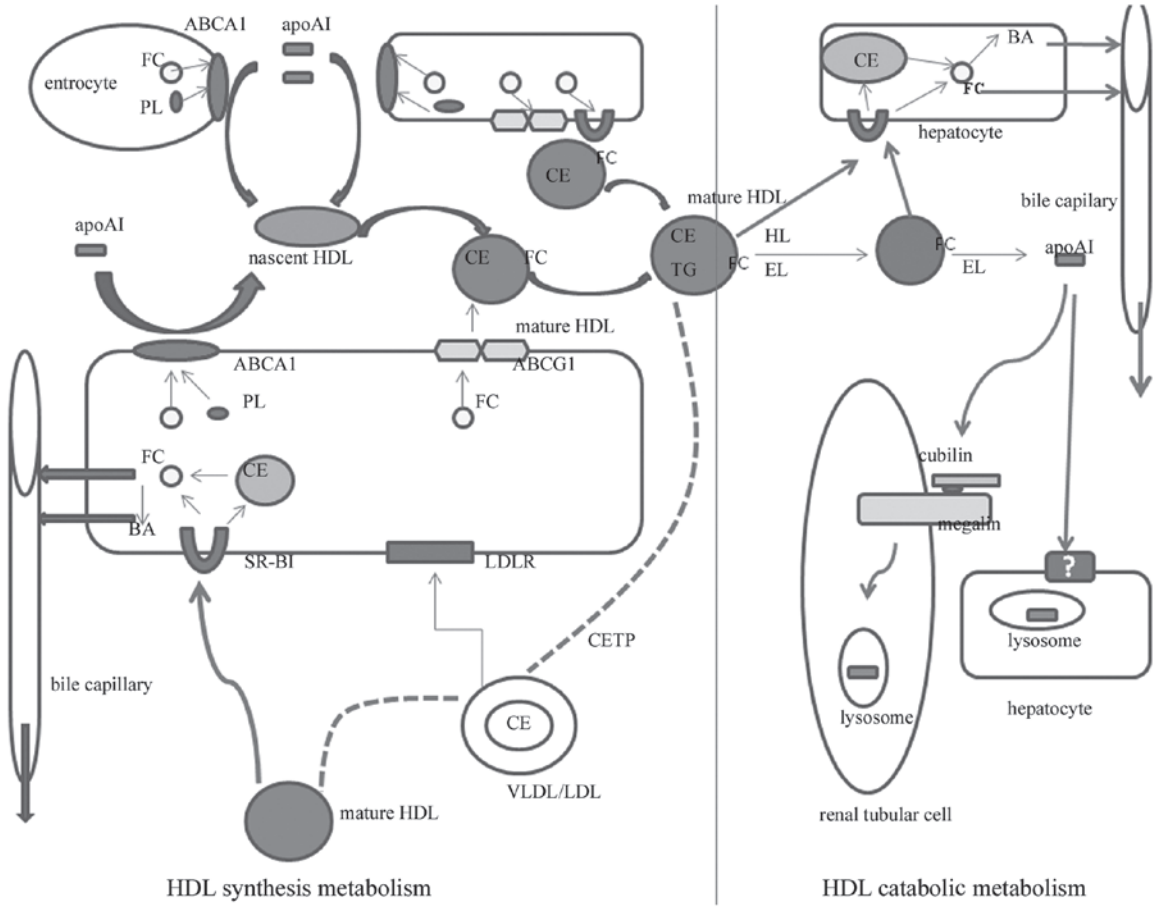

Figure 1. Biosynthesis and catabolic metabolism of HDL. Left: Biosynthesis of HDL begins with the interaction of ABCA1 with lipid-poor apoAI to from nascent HDL (discoidal HDL). ABCG1 can introduce FC to specific receptors (including discoidal HDL, PL-apoAI and mature HDL) with contains PL. In peripheric cells, SR-BI mainly mediates cholesterol efflux to HDL, while in hepatocytes and steroidogenic cells, it mainly takes up CE. Nascent HDL acquires more lipid from other peripheral tissues and from lipoproteins, and LCAT generates CE, forming mature HDL (spherical HDL). CETP promotes the transfer of CE from HDL to VLDL and LDL. Right: HDL catabolism includes lipids of HDL catabolism and apolipoprotein (primarily apoAI) catabolism. The CE of HDL can be transferred to the liver, mediated by SR-BI, and can then be metabolized into bile acids or neutral sterol to be excreted. ApoAI is catabolized mainly in the liver and kidney. In the circulation, mature is HDL metabolized into lipid-poor apoAI by lipases (eg. HL or EL). ApoAI can be degradated by lysosomes in renal tubular epithelial cells. HDL, high-density lipoproteins; ABCA1, adenosine triphosphate-binding cassette sub-family A member 1; Apo, apolipoprotein; FC, free cholesterol; PL, phospholipid; CE, cholesterol ester; SR-BI, scavenger receptor class B type I; LCAT, lecithin cholesterol acyltransferase; CETP, cholesterol ester transfer protein; VLDL, very low-density lipoprotein; EL, endothelial lipase; HL, hepatic lipase; BA, bile acid.

or combined with lipoproteins. In the plasma, LCAT can easily bind to HDL and be activated by apoAI of HDL. LCAT converts HDL cholesterol and lecithin into CE and lysolecithin by acyl transfer. It mainly has the following two functions: 1) Cholesterol esterification, therefore being the main source of CE in human plasma; and 2) HDL maturation, converting disc-shaped nascent βHDL into spherical αHDL by adjusting HDL remodeling to affect the extracellular cholesterol transport system (28).

LCAT deficiency is a common autosomal recessive hereditary disease, which is characterized by a significant reduction in HDL and apoAI. LCAT deficiency leads to the lack of HDL-CE formation, consequently inhibiting the assembly of mature HDL and thereby, promoting the catabolism of apoAI (29).

SR-BI. SR-BI, a member of the scavenger receptor class B family, is primarily expressed in the liver and steroidogenic tissues, and is also widely expressed in other cell types, if at lower levels. SR-BI is located in a part of the plasma membrane, namely in particular microvilli channels, which facilitates the exertion of its physiological functions.

SR-BI regulates the transport of free cholesterol in cells. The orientation of this transport mediated by SR-BI is bidirectional, depending on the gradient direction of cholesterol. In addition, SR-BI also mediates the selective uptake of other lipoprotein-lipids, including CE, phospholipids and triglycerides. A study showed that SR-BI does not induce free cholesterol efflux to extracellular apoAI in hepatocytes, indicating that hepatocellular SR-BI is not involved in the process of the formation of nascent HDL (30).

In hepatocytes and steroidogenic cells, SR-BI as an HDL receptor facilitates the selective uptake of CE. This SR-BI-mediated selective uptake of CE is divided in two steps: 1) Combination of HDL with SR-BI and 2) diffusion of CE molecules into the cell plasma membrane. This process requires a high affinity of SR-BI for HDL to warrant transport of CE to the membrane. SR-BI transports CE to its localization

region in the membrane, where CE hydrolase converts CE into free cholesterol (31).

SR-BI induces endocytosis and secretion of HDL particles. Apart from selectively transporting CE into cells, SR-BI also mediates endocytosis of HDL particles in hepatocytes and steroidogenic cells. CE is isolated from the HDL particles and is hydrolyzed in the cell. The remaining part of the HDL particle is then re-secreted into the circulation, where it continues to carry peripheral cholesterol (32).

In addition to sequestration of cholesterol from HDL, SR-BI can also mediate cholesterol ester uptake from LDL into the cells, which can affect the metabolism of apoB-containing lipoproteins (33).

CETP. CETP is mainly produced by the liver and adipose tissue (34). Its main function is to replace neutral lipids in HDL, including cholesterol ester, with triglyceride from LDL and VLDL to form triglyceride-rich HDL (35). In the process of lipid exchange, the N-terminal domain of CETP penetrates into HDL and its C-terminal domain enters the LDL or VLDL to assemble a ternary complex (HDL-CETP-VLDL or HDL-CETP-LDL). CE is moved along hydrophobic channels from the N-terminus to the C-terminus and exchanged with triglyceride (36). Triglyceride-rich HDL is the natural substrate of hepatic lipase (HL), which promotes HDL clearance in the blood. In addition, triglyceride-rich HDL also boosts the dissociation of HDL-associated apoAI and promotes the clearance of circulating HDL (37-39).

4. The function of HDL

Carrier in RCT. A large number of epidemiological studies have found that low levels of high-density lipoprotein cholesterol (HDL-C) are an independent risk factor for atherosclerotic vascular disease (CVD) (40). High levels of HDL-C were shown to lower the incidence of CVD, and low HDL-C levels increased the incidence of CVD in mice. When levels of HDL-C were reduced by 1 mg/dl in the circulation, the incidence of coronary artery disease (CAD) increased by 2-3%.

According to the traditional view, HDL carries free cholesterol from peripheral cells, including macrophages and endothelial cells. Free cholesterol from HDL can be esterified into CE in the blood. After HDL reaches the liver, HDL receptors in the hepatocellular surface, such as SR-BI, transport CE from HDL into the liver, and CEs are then metabolized into bile acid or neutral lipids, which are excreted as bile and feces in the RCT process. This mechanism explains for the anti-atherosclerotic effect of HDL (41-43).

The RCT process includes free cholesterol efflux from macrophages, which requires various carriers, including ABCA1, ABCG1 and SR-BI (30,44). ABCA1 is located on the cell membrane and mediates cholesterol and phospholipid efflux to apoAI to form disc-shaped nascent HDL. The nascent HDL is then transformed into spherical mature HDL by the regulation of LCAT, CETP, phospholipid transfer protein and other factors. ABCG1 is not involved in the assembly of nascent HDL. It only promotes free cholesterol efflux to mature HDL, which increases cholesterol contents of HDL (45); The function of SR-BI differs depending on the cell type: In macrophages, SR-BI also mediates intracellular free cholesterol efflux to mature HDL (i.e. in the SR-BI-dependent pathway) (46), while in the liver and steroidogenic tissue, SR-BI mainly functions as a receptor to selectively uptake cholesterol esters of HDL.

A study on the association between ABCA1, ABCG1 and SR-BI-mediated free cholesterol efflux using a murine macrophage cell line showed that elevated SR-BI expression reduced the ABCA1-mediated free cholesterol efflux, but did not affect the phospholipid efflux (47). Another study showed that increasing the cellular SR-BI expression inhibited ABCG1-induced free cholesterol efflux to plasma HDL (48).

Transportation of micro (mi)RNAs. HDL is also involved in the transport process of miRNAs in the cell. Biological studies have shown that HDL can combine with miRNAs by divalent cation binding (49,50). HDL purified by fast protein liquid chromatography was shown to contain smallRNAs, while smallRNAs and high levels of miRNA were identified using the bioanalyzer smallRNA characterization method. A study has shown that HDL is able to transport endogenous miRNAs to recipient cells (51). However, the specific loading mechanism of miRNAs onto HDL and the biological significance of the process remain to be elucidated.

Anti-inflammatory effects. In addition to anti-atherosclerotic effects, HDL also has an anti-inflammatory role in macrophages and endothelial cells by inhibiting the expression of adhesion molecules (52,53). HDL activates Akt protein kinase to reduce the expression of E-selectin, intercellular cell adhesion molecule-1 and vascular cell adhesion protein 1, and thereby inhibits the function of tumor necrosis factor α to activate nuclear factor-κB in the nucleus, which has an anti-inflammatory role (54).

Anti-thrombotic function. HDL exerts vascular protective effects by upregulating endothelial nitric oxide synthase (eNOs) expression and maintaining the caveolae lipid environment, which eNOs are located in. Furthermore, HDL can boost the blood flow to resist thrombosis and inhibit platelet activation by inhibiting platelet-activating factor/cyclooxygenase A2. HDL can also lower APC protein and thrombomodulin to reduce the formation of thrombin in endothelial cells and exerts an anti-thrombotic effect by inhibiting endothelial cell apoptosis and activities of tissue factors and endothelial cells (55,56). Apart from these functions, HDL can exert anti-atherosclerotic effects by inhibiting LDL oxidation.

5. HDL catabolism

HDL catabolism includes lipids of HDL catabolism and apolipoprotein (primarily apoAI) catabolism.

Catabolism of HDL-CE. The CE of HDL is transported by SR-BI into liver cells, where it is metabolized into bile acids or neutral sterol to be excreted. Studies have shown that with high expression of SR-BI in hepatocytes, HDL clearance was significantly increased in plasma, leading decreased HDL levels, while serum levels of HDL-C were significantly increased in mice with mutations in the SR-BI gene (57,58).

The dissociation rate of apolipoproteins that assemble HDL, is lower than that of CE that assembles HDL, and the

variability of the dissociation rate is markedly higher than that of the association rate. Overall, the reduction of apolipoprotein levels in HDL-C is an important determinant for HDL clearance (59).

Catabolism of ApoAI. ApoAI is catabolized mainly in the liver and kidney, with 2/3 being catabolized in the liver and 1/3 in the kidney (60). At present, the mechanisms of apoAI uptake and degradation in the liver are yet to be fully elucidated. In the blood circulation, mature HDL is metabolized into lipid-poor apoAI by lipase (e.g., HL or endothelial lipase). ApoAI (but not HDL) it filtrated by glomerules and is then internalized and degraded in renal tubular epithelial cells. Cubulin is synthesized by distal renal tubular cells and is located on the apical surface. Cubulin has a high affinity for apoAI and mediates apoAI uptake and degradation by megalin (61).

6. HDL metabolism-associated transcription factors

Liver X receptor (LXR) signaling pathway. LXR is a type of ligand which is inducible by transcription factors and is a member of nuclear hormone receptor protein superfamily. According to the structure and function, it can be classified into LXRα and LXRβ. These are constituted by a DNA-binding domain (DBD) and a ligand-binding domain (LBD), which can combine with retinoid X receptor (RXR) to form the heterodimer LXR/RXR. LXR/RXR binding to specific ligands causes the heterodimer to combine with a target gene-specific DNA element, liver X receptor element, to regulate the expression of the target gene at the transcriptional stage. The target genes associated with cholesterol metabolism are ABC family members, SR-BI, ApoE, CETP, lipoprotein lipase, cytochrome P450 and sterol regulatory element binding protein 1c (62-68). The most potent endogenous LXR agonists are 22(*R*)-hydroxylated cholesterol, 24(*S*)-hydroxylated cholesterol and 24,25-epoxy cholesterol.

Peroxisome proliferator-activated receptor (PPAR) signaling pathway. PPAR is a ligand-inducible transcription factor and belongs to the nuclear receptor family. PPAR and RXR combine to form a heterodimer, and the complex binds to a specific DNA sequence named peroxisome proliferators' response element of the target gene promoter, which can directly regulate the transcription of its downstream genes. The PPAR family includes PPARα, PPARβ/δ and PPARγ sub-types. PPARα can upregulate ABCA1 expression by inducing LXRα, promoting cellular cholesterol efflux to lipid-poor apoAI to boost HDL generation (69). PPARγ is a pleiotropic transcription factor. Caveolin-1, ABCA1, ABCG1, SR-BI and apoE are target genes of PPARγ. PPARγ can also regulate downstream molecules by adjusting the LXR/FXR nuclear receptor family (70). PPARδ is widely expressed in the body, but is also the least studied PPAR sub-type. It has been confirmed that PPARδ can promote the process of apoAI-mediated RCT (71).

In conclusion, HDL are markedly heterogenous and intricate particles. The physiochemical and functional heterogeneity of HDL presents a challenge to researchers exploring HDL.

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