

# High-density lipoprotein synthesis and metabolism (Review)

LINGYAN ZHOU<sup>1</sup>, CONGCONG LI<sup>1</sup>, LING GAO<sup>1,2</sup> and AIHONG WANG<sup>3</sup>

<sup>1</sup>Department of Endocrinology, Shandong Provincial Hospital Affiliated to Shandong University, Institute of Endocrinology, Shandong Academy of Clinical Medicine, Jinan, Shandong 250021; <sup>2</sup>Central Laboratory; <sup>3</sup>Department of Cardiology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong 250021, P.R. China

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
2. Sub-types of high-density lipoproteins (HDL)
3. Factors associated with HDL synthesis
4. The function of HDL
5. HDL catabolism
6. HDL metabolism-associated transcription factors

## 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.

---

*Correspondence to:* Professor Aihong Wang, Department of Cardiology, Shandong Provincial Hospital Affiliated to Shandong University, 324 Jing 5 Road, Jinan, Shandong 250021, China  
E-mail: wah2905@sina.com

**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 acetylhydrolase, 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- $\beta$  HDL: pre- $\beta$ 1HDL (d=5.6 nm) and pre- $\beta$ 2HDL (d=12.0-14.0 nm);  $\alpha$ HDL:  $\alpha$ 1HDL (d=11.0 nm),  $\alpha$ 2HDL (d=9.2 nm),  $\alpha$ 3HDL (d=8.0 nm) and  $\alpha$ 4HDL (d=7.4 nm).

Pre- $\beta$ 1 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,  $\alpha$ 1 HDL mainly interact with the liver scavenger receptor B1 to deliver cholesterol back to the liver. Intermediate-sized  $\alpha$ 3 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  $\alpha$ -helix structure. The double  $\alpha$ -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  $\alpha$ -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- $\beta$ 1HDL. 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 restraining 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 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- $\beta$ HDL). 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 depend 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 stearoyl 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

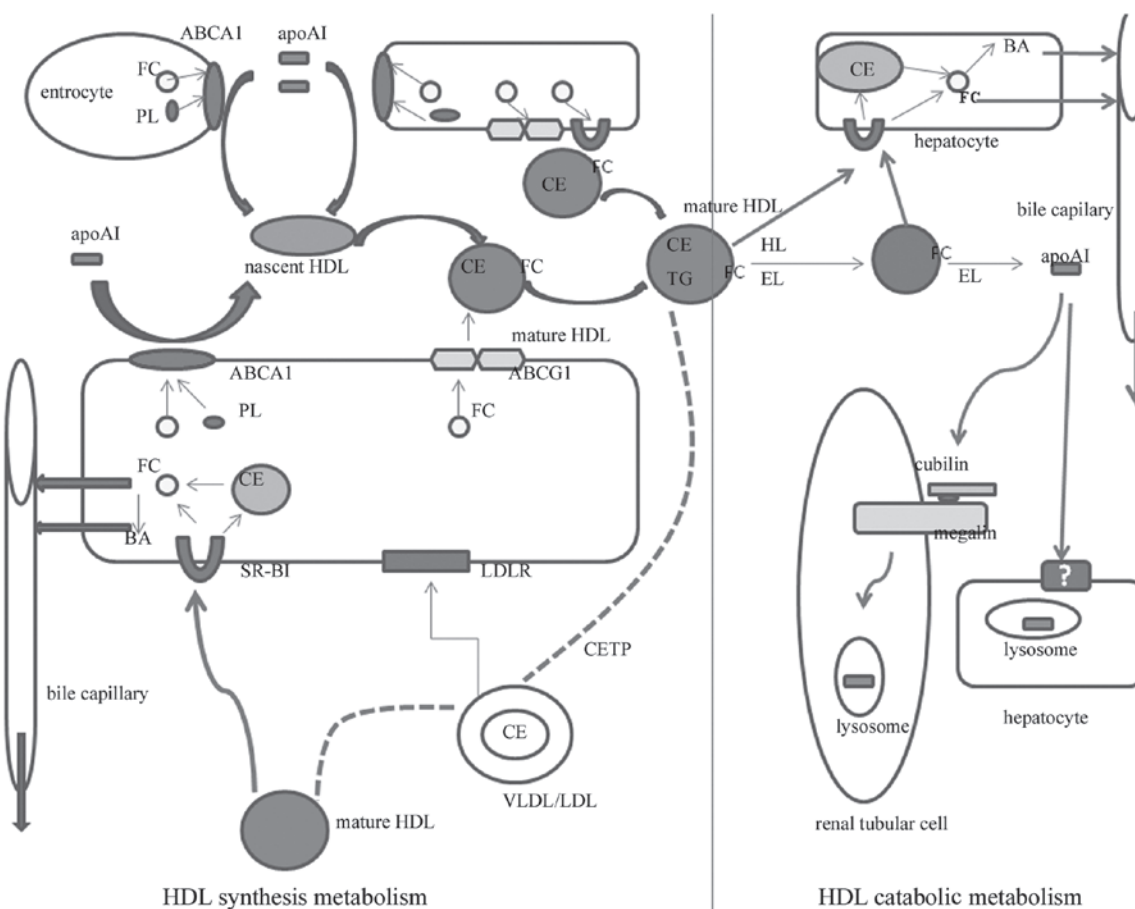


Figure 1. Biosynthesis and catabolic metabolism of HDL. Left: Biosynthesis of HDL begins with the interaction of ABCA1 with lipid-poor apoAI to form nascent HDL (discoidal HDL). ABCG1 can introduce FC to specific receptors (including discoidal HDL, PL-apoAI and mature HDL) with contains PL. In peripheral 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 HDL is metabolized into lipid-poor apoAI by lipases (eg. HL or EL). ApoAI can be degraded 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  $\beta$ HDL into spherical  $\alpha$ HDL 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  $\alpha$  to activate nuclear factor- $\kappa$ B 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) is filtered 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 LXR $\alpha$  and LXR $\beta$ . 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 PPAR $\alpha$ , PPAR $\beta/\delta$  and PPAR $\gamma$  sub-types. PPAR $\alpha$  can upregulate ABCA1 expression by inducing LXR $\alpha$ , promoting cellular cholesterol efflux to lipid-poor apoAI to boost HDL generation (69). PPAR $\gamma$  is a pleiotropic transcription factor. Caveolin-1, ABCA1, ABCG1, SR-BI and apoE are target genes of PPAR $\gamma$ . PPAR $\gamma$  can also regulate downstream molecules by adjusting the LXR/FXR nuclear receptor family (70). PPAR $\delta$  is widely expressed in the body, but is also the least studied PPAR sub-type. It has been confirmed that PPAR $\delta$  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.

## References

1. Timmins JM, Lee JY, Boudyguina E, Kluckman KD, Brunham LR, Mulya A, Gebre AK, Coutinho JM, Colvin PL, Smith TL, *et al*: Targeted inactivation of hepatic Abca1 causes profound hypoalphalipoproteinemia and kidney hypercatabolism of apoA-I. *J Clin Invest* 115: 1333-1342, 2005.
2. Vaisar T, Pennathur S, Green PS, Gharib SA, Hoofnagle AN, Cheung MC, Byun J, Vuletic S, Kassim S, Singh P, *et al*: Shotgun proteomics implicates protease inhibition and complement activation in the antiinflammatory properties of HDL. *J Clin Invest* 117: 746-756, 2007.
3. Davidsson P, Hulthe J, Fagerberg B and Camejo G: Proteomics of apolipoproteins and associated proteins from plasma high-density lipoproteins. *Arterioscler Thromb Vasc Biol* 30: 156-163, 2010.
4. Boisfer E, Stengel D, Pastier D, Laplaud PM, Dousset N, Ninio E and Kalopissis AD: Antioxidant properties of HDL in transgenic mice overexpressing human apolipoprotein A-II. *J Lipid Res* 43: 732-741, 2002.
5. Kontush A, Chantepie S and Chapman MJ: Small, dense HDL particles exert potent protection of atherogenic LDL against oxidative stress. *Arterioscler Thromb Vasc Biol* 23: 1881-1888, 2003.
6. Rosenson RS, Brewer HB Jr, Chapman MJ, *et al*: HDL measures, particle heterogeneity, proposed nomenclature, and relation to atherosclerotic cardiovascular events. *Clin Chem* 57: 392-410, 2007.
7. Sankaranarayanan S, Oram JF, Asztalos BF, Vaughan AM, Lund-Katz S, Adorni MP, Phillips MC and Rothblat GH: Effects of acceptor composition and mechanism of ABCG1-mediated cellular free cholesterol efflux. *J Lipid Res* 50: 275-284, 2009.
8. de la Llera-Moya M, Drazul-Schrader D, Asztalos BF, Cuchel M, Rader DJ and Rothblat GH: The ability to promote efflux via ABCA1 determines the capacity of serum specimens with similar high-density lipoprotein cholesterol to remove cholesterol from macrophages. *Arterioscler Thromb Vasc Biol* 30: 796-801, 2010.
9. Saito H, Dhanasekaran P, Nguyen D, Deridder E, Holvoet P, Lund-Katz S and Phillips MC:  $\alpha$ -helix formation is required for high affinity binding of human apolipoprotein A-I to lipids. *J Biol Chem* 279: 20974-20981, 2004.
10. Duong PT, Weibel GL, Lund-Katz S, Rothblat GH and Phillips MC: Characterization and properties of pre beta-HDL particles formed by ABCA1-mediated cellular lipid efflux to apoA-I. *J Lipid Res* 49: 1006-1014, 2008.
11. Wang N and Tall AR: Regulation and mechanisms of ATP-binding cassette transporter A1-mediated cellular cholesterol efflux. *Arterioscler Thromb Vasc Biol* 23: 1178-1184, 2003.
12. McNeish J, Aiello RJ, Guyot D, Turi T, Gabel C, Aldinger C, Hoppe KL, Roach ML, Royer LJ, de Wet J, *et al*: High density lipoprotein deficiency and foam cell accumulation in mice with targeted disruption of ATP-binding cassette transporter-1. *Proc Natl Acad Sci USA* 97: 4245-4250, 2000.
13. Voloshyna I and Reiss AB: The ABC transporters in lipid flux and atherosclerosis. *Prog Lipid Res* 50: 213-224, 2011.
14. Brooks-Wilson A, Marcil M, Clee SM, Zhang LH, Roomp K, van Dam M, Yu L, Brewer C, Collins JA, Molhuizen HO, *et al*: Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency. *Nat Genet* 22: 336-345, 1999.
15. Bodzioch M, Ors o E, Klucken J, Langmann T, B ottcher A, Diederich W, Drobnik W, Barlage S, B uchler C, Porsch-Ozcur omez M, *et al*: The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease. *Nat Genet* 22: 347-351, 1999.
16. Voloshyna I, Reiss AB: The ABC transporters in lipid flux and atherosclerosis. *Prog Lipid Res* 50: 213-224, 2011.
17. Mendez AJ, Lin G, Wade DP, Lawn RM and Oram JF: Membrane lipid domains distinct from cholesterol/sphingomyelin-rich rafts are involved in the ABCA1-mediated lipid secretory pathway. *J Biol Chem* 276: 3158-3166, 2001.
18. Drobnik W, Borsukova H, B ottcher A, Pfeiffer A, Liebisch G, Sch utz GJ, Schindler H and Schmitz G: Apo AI/ABCA1-dependent and HDL3-mediated lipid efflux from compositionally distinct cholesterol-based microdomains. *Traffic* 3: 268-278, 2002.
19. Sun Y, Hao M, Luo Y, Liang CP, Silver DL, Cheng C, Maxfield FR and Tall AR: Stearoyl-CoA desaturase inhibits ATP-binding cassette transporter A1-mediated cholesterol efflux and modulates membrane domain structure. *J Biol Chem* 278: 5813-5820, 2003.

20. Yamauchi Y, Abe-Dohmae S and Yokoyama S: Differential regulation of apolipoprotein A-I/ATP binding cassette transporter A1-mediated cholesterol and phospholipid release. *Biochim Biophys Acta* 1585: 1-10, 2002.
21. Wang N, Lan D, Chen W, Matsuura F and Tall AR: ATP-binding cassette transporters G1 and G4 mediate cellular cholesterol efflux to high-density lipoproteins. *Proc Natl Acad Sci USA* 101: 9774-9779, 2004.
22. Vaughan AM and Oram JF: ABCG1 redistributes cell cholesterol to domains removable by high density lipoprotein but not by lipid-depleted apolipoproteins. *J Biol Chem* 280: 30150-30157, 2005.
23. Gelissen IC, Harris M, Rye KA, Quinn C, Brown AJ, Kockx M, Cartland S, Packianathan M, Kritharides L and Jessup W: ABCA1 and ABCG1 synergize to mediate cholesterol export to apoA-I. *Arterioscler Thromb Vasc Biol* 26: 534-540, 2006.
24. Langmann T, Klucken J, Reil M, Liebisch G, Luciani MF, Chimini G, Kaminski WE and Schmitz G: Molecular cloning of the human ATP-binding cassette transporter 1 (hABCG1): Evidence for sterol-dependent regulation in macrophages. *Biochem Biophys Res Commun* 257: 29-33, 1999.
25. Liu W, Qin L, Yu H, Lv F and Wang Y: Apolipoprotein A-I and adenosine triphosphate-binding cassette transporter A1 expression alleviates lipid accumulation in hepatocytes. *J Gastroenterol Hepatol* 29: 614-622, 2014.
26. O'Connell BJ, Denis M and Genest J: Cellular physiology of cholesterol efflux in vascular endothelial cells. *Circulation* 110: 2881-2888, 2004.
27. Terasaka N, Wang N, Yvan-Charvet L and Tall AR: High-density lipoprotein protects macrophages from oxidized low-density lipoprotein-induced apoptosis by promoting efflux of 7-ketocholesterol via ABCG1. *Proc Natl Acad Sci USA* 104: 15093-15098, 2007.
28. Rye KA: Biomarkers associated with high-density lipoproteins in atherosclerotic kidney disease. *Clin Exp Nephrol* 18: 247-250, 2014.
29. Simonelli S, Tinti C, Salvini L, Tinti L, Ossoli A, Vitali C, Sousa V, Orsini G, Noll ML, Franceschini G, *et al*: Recombinant human LCAT normalizes plasma lipoprotein profile in LCAT deficiency. *Biologicals* 41: 446-449, 2013.
30. Larrede S, Quinn CM, Jessup W, Frisdal E, Olivier M, Hsieh V, Kim MJ, Van Eck M, Couvert P, Carrie A, *et al*: Stimulation of cholesterol efflux by LXR agonists in cholesterol-loaded human macrophages is ABCA1-dependent but ABCG1-independent. *Arterioscler Thromb Vasc Biol* 29: 1930-1936, 2009.
31. Brundert M, Ewert A, Heeren J, Behrendt B, Ramakrishnan R, Greten H, Merkel M and Rinninger F: Scavenger receptor class B type I mediates the selective uptake of high-density lipoprotein-associated cholesteryl ester by the liver in mice. *Arterioscler Thromb Vasc Biol* 25: 143-148, 2005.
32. Pagler T A, Rhode S, Neuhofer A, Laggner H, *et al*: SR-BI-mediated high density lipoprotein (HDL) endocytosis leads to HDL resecretion facilitating cholesterol efflux. *J Biol Chem* 281: 11193-11204, 2006.
33. Gillotte-Taylor K, Boullier A, Witztum JL, Steinberg D and Quehenberger O: Scavenger receptor class B type I as a receptor for oxidized low density lipoprotein. *J Lipid Res* 42: 1474-1482, 2001.
34. Barter P and Rye KA: Cholesteryl ester transfer protein: Its role in plasma lipid transport. *Clin Exp Pharmacol Physiol* 21: 663-672, 1994.
35. Tall AR: Plasma cholesteryl ester transfer protein and high-density lipoproteins: New insights from molecular genetic studies. *J Intern Med* 237: 5-12, 1995.
36. Zhang L, Yan F, Zhang S, Lei D, Charles MA, Cavigliolo G, Oda M, Krauss RM, Weisgraber KH, Rye KA, *et al*: Structural basis of transfer between lipoproteins by cholesteryl ester transfer protein. *Nat Chem Biol* 8: 342-349, 2012.
37. Beisiegel U: New aspects on the role of plasma lipases in lipoprotein catabolism and atherosclerosis. *Atherosclerosis* 124: 1-8, 1996.
38. Olivecrona G and Olivecrona T: Triglyceride lipases and atherosclerosis. *Curr Opin Lipidol* 6: 291-305, 1995.
39. Lamarche B, Uffelman KD, Carpentier A, Cohn JS, Steiner G, Barrett PH and Lewis GF: Triglyceride enrichment of HDL enhances in vivo metabolic clearance of HDL apo A-I in healthy men. *J Clin Invest* 103: 1191-1199, 1999.
40. Cappel DA, Palmisano BT, Emfinger CH, Martinez MN, McGuinness OP and Stafford JM: Cholesteryl ester transfer protein protects against insulin resistance in obese female mice. *Mol Metab* 2: 457-467, 2013.
41. Fisher EA, Feig JE, Hewing B, Hazen SL and Smith JD: High-density lipoprotein function, dysfunction, and reverse cholesterol transport. *Arterioscler Thromb Vasc Biol* 32: 2813-2820, 2012.
42. Rosenson RS, Brewer HB Jr, Davidson WS, Fayad ZA, Fuster V, Goldstein J, Hellerstein M, Jiang XC, Phillips MC, Rader DJ, *et al*: Cholesterol efflux and atheroprotection: Advancing the concept of reverse cholesterol transport. *Circulation* 125: 1905-1919, 2012.
43. Groen AK, Oude Elferink RP, Verkade HJ and Kuipers F: The ins and outs of reverse cholesterol transport. *Ann Med* 36: 135-145, 2004.
44. Ono K and Ono K: Current concept of reverse cholesterol transport and novel strategy for atheroprotection. *J Cardiol* 60: 339-343, 2012.
45. Freeman SR, Jin X, Anzinger JJ, Xu Q, Purushothaman S, Fessler MB, Addadi L and Kruth HS: ABCG1-mediated generation of extracellular cholesterol microdomains. *J Lipid Res* 55: 115-127, 2014.
46. Zhang Y, Da Silva JR, Reilly M, Billheimer JT, Rothblat GH and Rader DJ: Hepatic expression of scavenger receptor class B type I (SR-BI) is a positive regulator of macrophage reverse cholesterol transport in vivo. *J Clin Invest* 115: 2870-2874, 2005.
47. Chen W, Silver DL, Smith JD and Tall AR: Scavenger receptor-BI inhibits ATP-binding cassette transporter 1-mediated cholesterol efflux in macrophages. *J Biol Chem* 275: 30794-30800, 2000.
48. Yvan-Charvet L, Pagler TA, Wang N, Senokuchi T, Brundert M, Li H, Rinninger F and Tall AR: SR-BI inhibits ABCG1-stimulated net cholesterol efflux from cells to plasma HDL. *J Lipid Res* 49: 107-114, 2008.
49. Gromelski S and Brezesinski G: DNA condensation and interaction with zwitterionic phospholipids mediated by divalent cations. *Langmuir* 22: 6293-6301, 2006.
50. Lu D and Rhodes DG: Binding of phosphorothioate oligonucleotides to zwitterionic liposomes. *Biochim Biophys Acta* 1563: 45-52, 2002.
51. Vickers KC, Palmisano BT, Shoucri BM, Shamburek RD and Remaley AT: MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. *Nat Cell Biol* 13: 423-433, 2011.
52. Yvan-Charvet L, Wang N and Tall AR: Role of HDL, ABCA1, and ABCG1 transporters in cholesterol efflux and immune responses. *Arterioscler Thromb Vasc Biol* 30: 139-143, 2010.
53. Barter PJ, Puranik R and Rye KA: New insights into the role of HDL as an anti-inflammatory agent in the prevention of cardiovascular disease. *Curr Cardiol Rep* 9: 493-498, 2007.
54. Schmidt A, Geigenmüller S, Völker W and Buddecke E: The antiatherogenic and antiinflammatory effect of HDL-associated lysosphingolipids operates via Akt- $\rightarrow$ NF-kappaB signalling pathways in human vascular endothelial cells. *Basic Res Cardiol* 101: 109-116, 2006.
55. Mineo C, Deguchi H, Griffin JH and Shaul PW: Endothelial and antithrombotic actions of HDL. *Circ Res* 98: 1352-1364, 2006.
56. Landmesser U: High density lipoprotein - should we raise it? *Curr Vasc Pharmacol* 10: 718-719, 2012.
57. Kozarsky KF, Donahee MH, Rigotti A, Iqbal SN, Edelman ER and Krieger M: Overexpression of the HDL receptor SR-BI alters plasma HDL and bile cholesterol levels. *Nature* 387: 414-417, 1997.
58. Rigotti A, Trigatti BL, Penman M, Rayburn H, Herz J and Krieger M: A targeted mutation in the murine gene encoding the high density lipoprotein (HDL) receptor scavenger receptor class B type I reveals its key role in HDL metabolism. *Proc Natl Acad Sci USA* 94: 12610-12615, 1997.
59. Rader DJ: Molecular regulation of HDL metabolism and function: Implications for novel therapies. *J Clin Invest* 116: 3090-3100, 2006.
60. Glass C, Pittman RC, Weinstein DB and Steinberg D: Dissociation of tissue uptake of cholesterol ester from that of apoprotein A-I of rat plasma high density lipoprotein: Selective delivery of cholesterol ester to liver, adrenal, and gonad. *Proc Natl Acad Sci USA* 80: 5435-5439, 1983.
61. Christensen EI and Gburek J: Protein reabsorption in renal proximal tubule-function and dysfunction in kidney pathophysiology. *Pediatr Nephrol* 19: 714-721, 2004.
62. Luo Y and Tall AR: Sterol upregulation of human CETP expression in vitro and in transgenic mice by an LXR element. *J Clin Invest* 105: 513-520, 2000.

63. Lehmann JM, Kliewer SA, Moore LB, Smith-Oliver TA, Oliver BB, Su JL, Sundseth SS, Winegar DA, Blanchard DE, Spencer TA, *et al*: Activation of the nuclear receptor LXR by oxysterols defines a new hormone response pathway. *J Biol Chem* 272: 3137-3140, 1997.
64. Peet DJ, Turley SD, Ma W, Janowski BA, Lobaccaro JM, Hammer RE and Mangelsdorf DJ: Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR alpha. *Cell* 93: 693-704, 1998.
65. Repa JJ, Liang G, Ou J, Bashmakov Y, Lobaccaro JM, Shimomura I, Shan B, Brown MS, Goldstein JL and Mangelsdorf DJ: Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXRalpha and LXRbeta. *Genes Dev* 14: 2819-2830, 2000.
66. Costet P, Luo Y, Wang N and Tall AR: Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor. *J Biol Chem* 275: 28240-28245, 2000.
67. Schwartz K, Lawn RM and Wade DP: ABC1 gene expression and ApoA-I-mediated cholesterol efflux are regulated by LXR. *Biochem Biophys Res Commun* 274: 794-802, 2000.
68. Malerød L, Juvet LK, Hanssen-Bauer A, Eskild W and Berg T: Oxysterol-activated LXRalpha/RXR induces hSR-BI-promoter activity in hepatoma cells and preadipocytes. *Biochem Biophys Res Commun* 299: 916-923, 2002.
69. Xu X, Li Q, Pang L, Huang G, Huang J, Shi M, Sun X and Wang Y: Arctigenin promotes cholesterol efflux from THP-1 macrophages through PPAR- $\gamma$ /LXR- $\alpha$  signaling pathway. *Biochem Biophys Res Commun* 441: 321-326, 2013.
70. Rigamonti E, Chinetti-Gbaguidi G and Staels B: Regulation of macrophage functions by PPAR-alpha, PPAR-gamma, and LXRs in mice and men. *Arterioscler Thromb Vasc Biol* 28: 1050-1059, 2008.
71. Briand F, Naik SU, Fuki I, Millar JS, Macphee C, Walker M, Billheimer J, Rothblat G and Rader DJ: Both the peroxisome proliferator-activated receptor delta agonist, GW0742, and ezetimibe promote reverse cholesterol transport in mice by reducing intestinal reabsorption of HDL-derived cholesterol. *Clin Transl Sci* 2: 127-133, 2009.