HDL and Lipid Metabolism

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Qi Zhang, Yilang Ke, and Huashan Hong

Abstract

Mediating reverse cholesterol transport (RCT) is the most classic function of HDL. HDL and HDL-C participate in the entire process of RCT, including cholesterol removal from cells, cholesterol transport in circulation, and cholesterol excretion. As cholesterol is a component of lipid rafts and lipid droplets in cells, HDL and RCT can influence cell activity. HDL has also been shown to be related to the metabolism of some other biological lipids, such as S1P and ox-PL. Here we will introduce in detail the molecular mechanism of HDL participation in RCT and its significance.

Q. Zhang
The Institute of Cardiovascular Sciences and Institute of Systems Biomedicine, School of Basic Medical Sciences, Key Laboratory of Molecular Cardiovascular Science of Ministry of Education, NHC Key Laboratory of Cardiovascular Molecular Biology and Regulatory Peptides, Beijing Key Laboratory of Cardiovascular Receptors Research, Health Science Center, Peking University, Beijing, China
e-mail: 1410305226@bjmu.edu.cn

Y. Ke
Fujian Key Laboratory of Vascular Aging, Department of Geriatrics, Fujian Institute of Geriatrics, Fujian Medical University Union Hospital, Fuzhou, Fujian, China
e-mail: keyilang@fjmu.edu.cn

H. Hong (✉)
Fujian Key Laboratory of Vascular Aging, Department of Geriatrics, Fujian Institute of Geriatrics, Fujian Heart Disease Center, Fujian Medical University Union Hospital, Fuzhou, Fujian, China

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4.1 HDL Mediates Reverse Cholesterol Transport

Mediating RCT is the most classic function of HDL. Early in the 1960s, Dobbins et al. [1] proved the presence of cholesterol acyltransferase in HDL, and then the pathway of RCT was identified. Now RCT is defined as the process by which cholesterol moves out of cells in peripheral tissues, enters the circulation, and is excreted in the feces [2]. HDL is both the acceptor of cholesterol from cells and the carrier of cholesterol in circulation, and, therefore, plays an important role in RCT (Fig. 4.1).

4.1.1 HDL Participates in Cholesterol Removal from Cells

Cellular cholesterol homeostasis is essential for normal cell function. As it was said, HDL acts as the specific cholesterol acceptor that transports excess cholesterol stores within peripheral tissues to the plasma [2]. ABCA1 and ABCG1 are critical receptors for the initial step of RCT, which mediate cholesterol efflux out of cells. Combined

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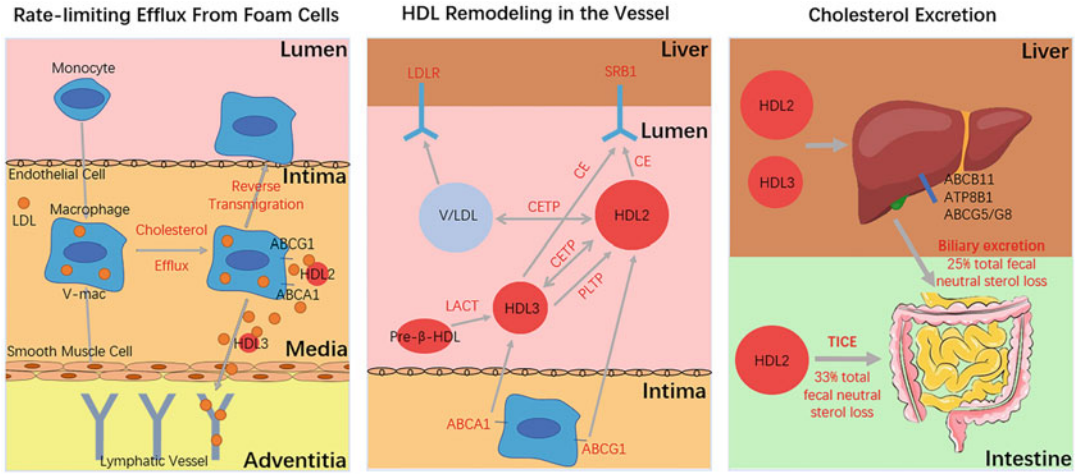

Fig. 4.1 Key steps of reverse cholesterol transport (RCT). The first step of RCT is the removal of cholesterol from macrophages or vascular smooth muscle cells. In this step, free cholesterol efflux to acceptors such as HDL. This is the rate-limiting step of RCT. In macrophages, ABCA1/ABCG1 (ATP-binding cassette proteins A1/G1) is required to pump out cholesterol, but the efflux mechanisms in vascular smooth muscle cells are not well understood. In the next step, the cholesterol on HDL is transported to the liver. SR-B1 (scavenger receptor class B type 1) is responsible for binding HDL and selective cholesterol intake. Another part of cholesteryl ester is transferred to VLDL or LDL by CETP (cholesterol ester transfer protein) and PLTP (phospholipid transfer protein) and cleared by LDLR. Finally, cholesterol is excreted into the feces. Biliary cholesterol excretion mediates about 25% of total fecal neutral sterol loss, while transintestinal cholesterol efflux (TICE) mediates about 33% under normal circumstances. *LCAT* lecithin-cholesterol acyltransferase, *OSBP* oxysterol-binding protein. Adapted from Ouimet, M. et al. [2]

ABCA1 and ABCG1 deficiency in macrophages resulted in impaired cholesterol efflux to HDL and decreased apoE secretion in vitro. This deficiency also increased secretion of inflammatory cytokines and chemokines. Mouse models showed the same trend [3, 4]. ABCA1 preferentially synthesizes small HDL particles, specifically apoA-I to form nascent HDL [5], at the same time ABCG1 stimulates net cholesterol efflux to larger HDL but not to lipid-poor apoA-I [2, 6]. The classical hypothesis is that free cholesterol generated by lipid lipolysis reaches the ABCA1 and ABCG1 by vesicular or non-vehicular trafficking pathways and then becomes effluxed [7]. In fact, ATP-binding cassette transporters themselves can be motile. ABCA1-mediated cholesterol efflux to apo A-I was found to take place in endosomes [8]. ABCA1 can also shuttle between the plasma membrane and late endosomes, and between the endolysosomal compartments and plasma membrane [9]. ABCG1 relocalizes from the Golgi and ER to the plasma membrane following LXR activation to stimulate efflux to HDL [2, 10].

Another cholesterol trafficking pathway is mediated by a conserved family of lipid-binding/transfer proteins, which is constituted by oxysterol-binding proteins (OSBPs) and its related protein homologs, OSBP-related proteins (ORPs). ORPs are ubiquitously expressed in eukaryotes, and their ligand-binding domain accommodates cholesterol and oxysterols [11]. Thus, ORPs facilitate non-vesicular transfer of cholesterol between lipid bilayers and coordinate lipid signals with a variety of cellular regimes. Recent study found ORP6 may contribute to HDL homeostasis and regulate cholesterol efflux, although the mechanism is not clear [12]. Other proteins related to lipid trafficking could also influence cholesterol efflux to HDL,

such as steroidogenic acute regulatory protein (StAR) and Niemann-Pick type C (NPC) [13].

4.1.2 HDL-C Mediates Cholesterol Transport in Circulation

After cholesterol transferred to HDL particles, the next step is the esterification to form cholesteryl ester (CE), which depends on lecithin-cholesterol acyltransferase (LCAT). Overexpression of LCAT in mice raises HDL-C levels, though results in unaffected atherosclerosis [14]. Similarly, LCAT knockout mice showed extremely low levels of HDL-C, but the influence on atherosclerosis remained unclear [15, 16]. Studies have found that the capacity of cholesterol transport is also related to the functional status of HDL itself [17, 18]. Although LCAT has long been believed to be critical for promoting RCT by maintaining a free cholesterol gradient between cells in the periphery and plasma HDL, some current data are inconsistent with it [19]. The clearance of HDL-C is much faster than its esterification. Within the halftimes of HDL-C, only about 2% of free cholesterol is esterified, which means that over 95% of HDL-FC is cleared without esterification, and LCAT may play only a minor role in RCT [20, 21]. Consistently, LCAT knockout mice showed little damage in macrophage RCT [22]. Interestingly, overexpression of LCAT reduced macrophage RCT by reducing the level of lipid poor apoA-1 and the cholesterol efflux via ABCA1, although the HDL-C level was increased in this model [22].

It is generally believed that high plasma HDL-C concentration represents a better rate of cholesterol metabolism and is therefore associated with a reduced incidence of cardiovascular events [23]. Studies such as the Helsinki Heart Study and the Veterans Administration HDL Intervention Trial (VA-HIT) also support this view, which showed that increased plasma HDL-C levels in patients receiving gemfibrozil versus placebo are associated with fewer coronary heart disease events [24, 25]. However, these studies cannot completely rule out the effects of other risk factors, like insulin resistance and plasma triglyceride levels, and other studies showed different results. Especially, high plasma HDL-C level and no CVD incidence reduction were found in patients with cholesteryl ester transfer protein (CETP) deficiency. CETP inhibitors, which profoundly increase plasma HDL-C levels, can't reduce CVD events either [26]. In genetic studies, the Copenhagen City Heart Study showed patients with genetically elevated plasma levels of HDL-C did not have a reduced atherosclerotic cardiovascular disease (ASCVD) risk [27]. According to a Mendelian randomization study, an HDL-C-raising endothelial lipase variant was not associated with reduced myocardial infarction [28]. In fact, new views hold that HDL's functional changes are more important than its quantitative changes, and the abnormal high HDL-C level is caused by HDL dysfunction. Moreover, some epidemiological studies in humans showed the correlation between plasma HDL-C levels and ASCVD hazard ratio is U-shaped, with the extremes of high and low HDL-C concentrations being associated with more all-cause and ASCVD mortality [29–31], suggests that HDL may derive its dysfunctionality from both high free cholesterol content and high plasma HDL concentration.

Recently, a lot of evidences support that the most important site from which HDLs act to promote cholesterol efflux from cells is in the extracellular matrix of tissues, rather than in plasma [32]. Since one of the major roles of the lymphatic system is to drain macromolecules from the interstitial space back to the circulation, it is generally believed that the return of lipoproteins from the interstitium to plasma may occur mainly via the lymphatic system and less via the venous capillaries [33]. Analysis of animal and human lymph fluid composition showed that lymph fluid was rich in cholesterol and HDL [34]. The major apolipoprotein of HDL is apoA1, and approximately half of all apoA1 in the body is extravascular and found within interstitial fluid of peripheral organs [35]. Total cholesterol level in lymph HDL was about 30% higher than plasma, indicating that periphery cholesterol clearance has relevance to lymph and extravascular compartment [34]. Whereas plasma

mainly contains α-HDL particles that are the predominant carriers of CE to hepatocytes, interstitial fluid provides a metabolic environment that drives the conversion of α-HDL to pre-β-HDL, the main acceptor of free cholesterol from peripheral tissues [2, 36]. And this conversion may due to the high specific activity of phospholipid transfer protein (PLTP) in lymph, along with the absence of cholesterol esterification [15]. Furthermore, studies have found mice with impaired lymphatic drainage showed impaired RCT, and lymphatic endothelial cells could express functional HDL transporters such as SR-BI, which directly demonstrated that lymphatic drainage is required for RCT and HDL function [37].

4.1.3 CE in HDL Can Be Transferred into Cells

In humans, CE in HDL can be transferred to triglyceride-rich lipoproteins by cholesteryl ester transfer protein (CETP) for elimination via hepatic clearance in the liver through the LDLR, or selectively taken up via scavenger receptor class B type 1 (SR-B1) acting as a hepatic receptor for CE on HDL [2]. Notably, this process in mice differs from that in humans.

CETP is a 74-kDa hydrophobic plasma glycoprotein that has an established role in mediation of neutral lipid transport among lipoproteins [38]. The main effect of CETP activity is a transfer of CEs from HDLs to apo B containing lipoproteins in exchange for triglycerides. People with loss-of-function mutations in both CETP alleles have extremely high levels of HDL-C, indicating the importance of this pathway in humans [20]. Indeed, studies in humans have indicated that the majority of CEs are transferred to the liver by apo B containing lipoproteins and not HDL, which was shown by injection of HDL labeled with a CE tracer [20]. As said before, CETP is a therapeutic target for inhibition to raise plasma levels of HDL-C. Mice overexpressing CETP experience a substantial reduction in HDL-C levels, as well as increased macrophage RCT rate, consistent with the concept that CETP promotes the delivery of HDL-C to the liver [39]. Besides, the function of CETP is also influenced by LDL receptors and the clearance of apoB-lipoproteins [19].

SR-BI is a high affinity receptor for HDL, and it also binds LDL, VLDL, and phospholipids [40]. Studies by Pagler et al. have shown that SR-BI can transfer cholesterol from lipoproteins to cells through whole particle uptake/endocytosis [41]. However, SR-BI can also uptake cholesteryl esters without parallelly uptaking the entire lipoprotein particles, which is the mainly known function of SR-BI [42]. In this selective uptake process, HDL-C firstly binds to the loop domain of SR-BI, and then cholesterol esters transfer to the plasma membrane, finally HDL releases back to the circulation [43, 44]. Large population-based studies revealed that heterozygous carriers of the P376L variant of SR-BI have significantly high levels of plasma HDL-C [45]. SR-BI expressed in both hepatocytes and liver endothelial cells may mediate the uptake of HDL-C into the liver [46–48]. In fact, the highest relative expression level of SR-BI was found in steroid hormones producing cells despite the major focus on SR-BI in the liver, as cholesterol is a substrate for steroid hormone synthesis [49]. Interestingly, along with its classical function of cholesterol transcellular transport, SR-BI initiates signaling in some cell types [50]. For example, the binding of HDL to SR-BI will activate endothelial NO synthase (eNOS) in endothelial cells [51].

Although immune cells like most cells can utilize intricate feedback mechanisms of cholesterol uptake and synthesis, they also express numerous unregulated scavenger receptors [52, 53]. Macrophage foam cells have been a sign of early atherosclerosis in humans and animal models. These cells contain numerous droplets of CE, which could be marked by lipid stain such as Oil red O [54]. The imbalance in the rate of cholesterol uptake and efflux results in CE accumulation in immune cells [52].

How cholesterol internalized from HDL is made available to the cell for storage or modification is poorly understood. Aster proteins are ER-resident proteins that bind cholesterol and facilitate its removal from the plasma membrane,

providing a new mechanism to mobilize HDL-derived cholesterol. Mice lacking aster-B are deficient in adrenal cholesterol ester storage and steroidogenesis because of an inability to transport cholesterol from SR-BI to the ER [55].

4.1.4 Cholesterol Is Excreted Through the Liver and Intestines

Although cholesterol itself can be secreted into the bile for excretion from the body, synthesis and excretion of bile acids comprise the major cholesterol catabolism pathway in mammals [2, 56]. Studies in healthy normolipidemic humans in vivo show that unesterified cholesterol in HDL can be rapidly and directly taken up by the liver and targeted to bile [20]. Biliary cholesterol excretion is driven by the two half ABC transporters, Abcg5 and Abcg8, which form an active heterodimer [57]. Mice lacking either Abcg8 or Abcg5 have an 80% reduced biliary cholesterol output, indicating that Abcg5/8 is essential for the largest part of biliary cholesterol excretion [58, 59]. And many other factors have been found taking part in regulating the classic biliary pathway of RCT. For example, ATP8B1, a phosphatidylserine flippase in the canalicular membrane, is demonstrated to inhibit biliary cholesterol excretion, which is independent of Abcg5/8 activity [60].

However, there is now evidence that HDL-driven movement of cholesterol back to the liver can't fully correlate with how much cholesterol is lost in bile or the feces [61, 62]. Similarly, mice genetically lacking apoA-I or ABCA1 have normal biliary and fecal cholesterol loss [63, 64], indicating that there exist cholesterol excretion pathways not through bile. RCT can also proceed through a non-biliary pathway known as transintestinal cholesterol excretion (TICE), which involves the direct secretion of plasma lipoprotein-derived cholesterol by the small intestine [65]. Current evidence suggests that the non-biliary branch of RCT can be initiated by either re-uptake of biliary cholesterol via the canalicular sterol transporter Niemann-Pick C1-like 1 (NPC1L1) [66, 67], or by blocking cholesterol acyl-CoA:cholesterol acyltransferase 2 (ACAT2)-driven cholesterol esterification [68]. Both conditions are expected to cause the accumulation of free cholesterol in the liver, but these excess free cholesterol will be repackaged into new apoB-containing lipoproteins. These lipoproteins are then secreted from the liver into the circulation and are recognized by the proximal small intestine through lipoprotein receptors such as LDLR [69]. Since TICE can still occur in LDLR −/− mice, there may be other mechanisms contribute to it, but SR-BI is not included in them considering the current results [68, 69]. The transport route of cholesterol within the intestinal enterocyte is not well understood in TICE. However, as apoB-containing lipoproteins are the main particles participating in TICE, endosomal or lysosomal compartments are probably to be involved [65]. After efflux from TICE associated lipoproteins, this cholesterol can be transported by ATP binding cassette transporters ABCG5/ABCG8 and ABCB1a/b [69–71].

When evaluating the relative contribution of non-biliary routes to RCT, it is important to clear whether in normal physiology conditions or not. Under normal physiological conditions, the biliary pathway mainly contributes to the RCT efflux, while the non-biliary route typically makes up less than 30% of the total cholesterol found in the feces [72, 73]. However, the cholesterol efflux ability of non-biliary route is highly dynamic and can be stimulated by some pathophysiologic conditions and drugs. In transgenic mouse models that lacked the ability to normally secrete cholesterol into bile, or in the case of surgical removal of the common bile duct, fecal cholesterol loss remained the same or increased in some cases [58, 65, 74]. These studies suggest that the non-biliary TICE could be a reserve to response to the decrease of fecal cholesterol loss level under the pathophysiologic condition of biliary cholesterol insufficiency (Fig. 4.2).

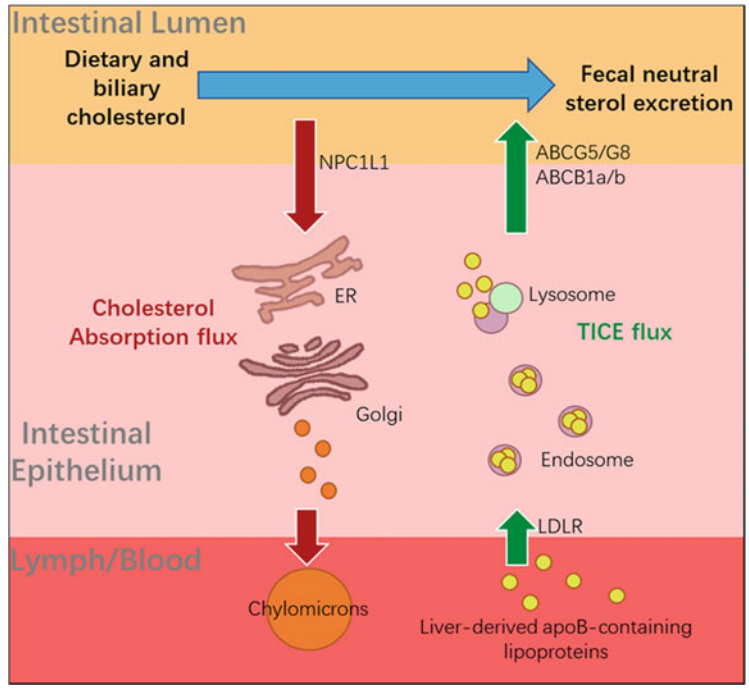

Fig. 4.2 Model for integrated biliary and non-biliary reverse cholesterol transport. Adapted from Temel, R. E. & Brown et al. [65]

4.2 Metabolism of Cholesterol Is Essential to Cell and Life

Cholesterol plays a role in many essential biochemical processes. Cholesterol is a special kind of plasma lipids for it is a precursor of steroidogenic steroids, which could regulate metabolism. And cholesterol in the form of LDL-C and HDL-C has been proven to be associated with ASCVD [23].

4.2.1 Lipid Droplets in Cells

Lipid droplets are intracellular organelles specialized for the storage of neutral lipids. Extensive evidences show that FC accumulation within cells is toxic, pro-inflammatory, and pro-atherogenic [75, 76]. It is shown that cholesterol load in macrophages leads to cholesterol crystal and the formation of NLRP3 inflammasome, which then produce pro-inflammatory mediators such as IL-1β [77]. The conversion of excess FC to CE by ACAT is thought to represent a protective mechanism against the toxic effects of excess FC in cells [78]. CE droplets are usually found in fat store tissues, but in fact the formation of droplets can be induced in any cell type when cholesterol is overloaded [79]. However, CE accumulation could also cause cell damage. For instance, the accumulation of CE in the central nervous system is related to neurodegeneration and the accumulation of β-amyloid peptide in Alzheimer's disease [80]. Although ACAT inhibition indirectly enhances the movement of the nascent amyloid precursor protein molecules into the early secretory pathway [52, 81], the amyloid plaque load in mouse model is decreased and the cognitive function is improved [82].

Moreover, some evidences suggest that CE rich lipid droplets are dynamic rather than passive inert structures and can be pro-inflammatory. In leukocytes these lipid bodies consist of a neutral lipid core, which is surrounded by a phospholipid monolayer [83]. These lipid droplets are found to be metabolically active since the CE in droplets undergoes a continual cycle of hydrolysis and re-esterification to release FC for membrane lipid raft maintenance and efflux [84]. There are

also proteins found in lipid droplets of not only adipocytes but also all cells, such as the ancient ubiquitous proteins which play roles in the degradation of HMGCoA reductase [85]. Recent studies suggest that lipid bodies can be formed in response to inflammation and inflammatory cell activation. Leukocyte lipid droplet formation has been observed following infectious by Hepatitis C, *Trypanasoma cruzi*, and exposure to various bacterial products, though whether blocking the formation of lipid body in leukocytes can change the progression of disease remains to be shown [52, 86, 87].

4.2.2 Membrane Cholesterol and Lipid Raft Microdomains

FC, together with glycerophospholipid (GPL) and sphingomyelin form a highly ordered 5–500 nm diameter structure, called lipid rafts in the plasma membrane [88]. These rafts are detergent-resistant membrane complexes that can organize and separate many different protein components. The FC content of these structures is usually 3–5 times that of the surrounding membrane. These FC can help stabilize the raft through their hydrophobic combination with other components [89]. A number of critical enzymes and signaling systems are active when concentrated within these microstructures, modulating cell activation and function, such as eNOS, SR-B1, Ras, CD36, Rho, MAP kinase, G-protein coupled receptors, and Ca2+ regulatory proteins [52]. In addition, although lipid rafts are typically studied at the cell membrane, similar structure can also be found in organelles containing membrane components, such as the Golgi, mitochondria, lysosomes, and lipid droplets [52, 90, 91].

The cholesterol required for the formation and maintenance of lipid rafts can come from exogenous sources, such as lipoproteins or from cell synthesis, through the mevalonate pathway in the ER and then transport to the plasma membrane [76, 92]. Another source of cholesterol are intracellular lipid droplets [93]. Extrinsic signals which promote CE hydrolysis can lead to the cholesterol efflux from lipid droplet. FC can also be moved to the substrate pool to be exported through ABCA1. ABCA1 is the uniquely sensitive master controller of membrane cholesterol that regulates lipid raft composition [52], which is under the control of the liver X receptor (LXR) [94]. Further studies showed that cholesterol efflux and lipid raft cholesterol maintenance were the same process, and the lipid composition of nascent HDL was similar to that typically found in microdomains from cell membranes [95, 96].

The addition of β-cyclodextrin can consume membrane cholesterol, while squalene replenishes it. By this way, the importance of cholesterol and lipid raft to cell activation and polarization has been extensively studied in many different conditions [97, 98]. Especially in the bone marrow, lipid rafts have been proven to regulate the retention and quiescence of hematopoietic stem cell in bone marrow niches and further participate in regulating their mobilization and homing [52, 99, 100]. Therefore, the regulation of the formation, composition, and decomposition of lipid rafts in cells is of great significance and can be applied in the field of cardiovascular disease.

4.3 HDL and Other Bioactive Lipids

For many years, phosphatidylcholine and sphingomyelin, along with small amounts of phosphoglycerol, phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol, have been considered the main components of the HDL surface. Later, several other classes of glycosphingolipids were found, such as galactosylceramide, glucosylceramide, lactoseceramide, sulfatides, globulins, and gangliosides. Subsequently, phospholipid lysoderivatives were identified and soluble phospholipase A2 was found in HDL [101]. Sphingosine 1 phosphate (S1P), as a kind of lysosphingolipid, was found to be mostly carried by HDL and also positively correlated with HDL-C, apoA-I and apoA-II levels [102].

4.3.1 HDL and S1P

Moreover, HDL-related S1P is now considered to be the main determinant of S1P concentration in plasma. The source of S1P in circulation remained uncertain. Sphingosine kinase is the main enzyme that phosphorylates sphingosine to produce S1P. It is expressed in platelets and various peripheral blood cells, including red blood cells, neutrophils, and monocytes [103]. Platelets could store a large amount of S1P and release them under the stimulation of thrombin or calcium, but other studies have shown that S1P derived from red blood cells accounts for the largest proportion in the blood [104, 105]. Although erythrocytes cannot produce sphingosine and display relatively low levels of sphingosine kinase activity, they efficiently convert exogenous sphingosine to S1P [106]. Lack of S1P-degrading enzymes leads to the accumulation of S1P in erythrocytes. S1P may transport from erythrocytes to HDL through ATP-binding cassette transporters. Although the association with HDL seems to explain the atherosclerotic protective effect of S1P, it is not clear whether this effect also depends on the morphology of HDL and the ratio of apoA-I and apoA-II. A recent report indicated that S1P was enriched in small and dense HDL3 particles which contained apoA-I [107]. The main plasma apolipoprotein that S1P physically binds is apolipoprotein M (apoM), most of which are contained in HDL [108]. Only the apoM-containing fraction of human HDL carries S1P, and apoM-deficient mouse HDL contains almost no S1P, indicating that the presence of apoM determines HDL-S1P [109]. However, there is no correlation between apoM and S1P in human plasma or HDL [110], which suggests that there may be other molecules besides apoM involved in the relationship between S1P and HDL [111]. Interestingly, there is recent evidence that S1P may perform different biological functions, depending on whether it functions in an HDL-related form or an albumin-related form. In cultured endothelial cells, it was found that HDL-S1P helped more in reducing S1P internalization though had the similar half-life, which means HDL-S1P was more effective than albumin-S1P in maintaining endothelial function [112]. The function of HDL-S1P was shown to have changed in human cardiovascular, kidney, and metabolic diseases. A number of studies have linked plasma and HDL-S1P to the incidence of coronary artery disease [113–115].

4.3.2 HDL and Ox-PL

Phospholipids contain polyunsaturated fatty acids that are easily peroxidized. Ox-PL is involved in cell signaling and is associated with a variety of inflammatory processes, as well as atherosclerosis. Plasma levels of ox-PC have been found to be associated with increased risk of cardiovascular disease. Oxidized-PL in plasma is mainly associated with apoB100-containing lipoproteins, including the low-density lipoprotein variant Lp (a). The role played by HDL in oxidative-PC metabolism is unknown, but given the anti-inflammatory potential of HDL, it is expected to be beneficial [116]. Based on this, Gharavi et al. [117] have reported that HDL inhibited the proinflammatory pathway induced by ox-PL signaling in human endothelial cells, possibly by reducing superoxide production. This suggests an additional mechanism for the anti-atherosclerotic function of HDL.

4.4 Conclusions

HDL is of great significance to lipid metabolism, especially cholesterol metabolism. Mediating RCT is the most classic function of HDL. RCT includes the efflux, transport, and excrete of cholesterol. ABCA1 and ABCG1 mediate the efflux of cholesterol from cells to HDL, especially in vascular smooth muscle cells and macrophages. After cholesterol transfer to HDL particles, the next step is the esterification of cholesterol to form cholesterol ester, which depends on LCAT. The combined HDL-C is transported through lymph and circulation. CE in the HDL core can be transferred to triglyceride-rich lipoproteins by

CETP or be selectively taken up via SR-B1 to enter the cells again. Synthesis and excretion of bile acids comprise the major cholesterol catabolism pathway in mammals. This process is mainly carried out through the liver, but transintestinal cholesterol excretion is equally important, especially under certain pathological conditions. As cholesterol is a component of lipid rafts and lipid droplets in cells, HDL and RCT can influence cell activity. Problems in RCT are closely related to immune cells and atherosclerosis. HDL has also been shown to be related to the metabolism of some other biological lipids, such as S1P and ox-PL. Although some clinical experiments of using HDL-C concentration as a direct target failed, the importance of HDL in lipid metabolism and its potential clinical value are significant.

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